Bivariate left-censored measurements in biomonitoring: A Bayesian model for the determination of Biological Limit Values based on Occupational Exposure Limits

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Bivariate left-censored measurements in biomonitoring: a Bayesian model for the determination of Biological Limit Values based on Occupational Exposure Limits.

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Biomonitoring, Biological Limit Values, Limit of Detection, Occupational Exposure Limit, Bayesian model, left-censored data

ABSTRACT

Biological Limit Values (BLV) are often determined from the occupational exposure limits (OEL) in modelling biological data obtained on a number of exposed subjects based on measurements of air exposure. In order to obtain such BLVs, biomonitoring studies are conducted collecting simultaneously biological and airborne measurements to these substances in exposed workers.

One obstacle in the modelling of such data is the often large number of values below the Limit of Detection (LOD) for both biological and airborne measurements (left censored measurements). A second difficulty, which is also a strength, is that multiple measurements are obtained for the same workers, leading to non-independence of the data.

In this paper, we propose a statistical method based on Bayesian theory making use of measurements below the LOD for both dependent (biological) and independent (air exposure) data, and taking into account multiple measurements on the same worker.

This method relies on the modelling of the airborne exposure measurements using standard random effect models adapted for values below LOD and the simultaneous modelling of the biological measurements assumed to be linearly (on the log scale) related to the airborne exposure while accounting for between worker variability.

This method is validated by a simulation study in which up to 50% of the measurements are censored for both variables in realistic settings. This simulation study shows that the proposed method is uniformly more efficient than the candidate alternative we considered (MLE method) that did not make use of a data with airborne measurements below the LOD.

When the method is applied on a real biomonitoring data set among electroplating workers exposed to chromium with 54% censored airborne measurements and 20% censored urinary measurements, the slope is steeper when incorporating these data using the proposed Bayesian method leading to different BLV estimations depending on the OEL used.

INTRODUCTION

According to the CDC, biomonitoring is defined as a method for assessing human exposure to chemicals by measuring the chemicals and/or their metabolites in human tissues or specimens, such as blood or urine. In occupational settings, its ultimate objective is to be able to propose suitable measures (improvement of technical, organisational and personal prevention) in order to reduce the exposure and its potential impact on health. For many hazardous substances, in particular when entry paths are multiple, the individual exposure sustained can only be quantified, and therefore assessed, by means of biomonitoring. One means of ensuring that workers are adequately protected is by setting Biological Limit Values (BLVs) which are not to be exceeded. Ideally, as for instance for Cadmium and Lead, BLVs are based on the relation between the internal exposure and its health effects observed in human studies. This is however only rarely the case.

For substances for which the main entry is inhalation, in particular when the exposure is to fumes or aerosols, the Biological Limit Values (BLV) can be derived from Occupational Exposure Limit values (OELs). The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) states for instance that (our translation) “in absence of such (health-based) data, for substances with a no-effect level, the BLV will be computed from the expected biological concentration, when the worker is exposed at the 8 hour OEL”. Estimating such an expected biological concentration relies on the statistical modelling on the biological concentration among exposed workers as a function of simultaneously measured airborne exposure concentrations (Lison et al. 1994) (Pierre et al. 1995) (Pierre, Diebold, and Baruthio 2008). Such studies typically include a limited number of workers for which repeated measurements are obtained. A relationship is usually documented (ACGIH 2015) by establishing a linear relationship between log transformed atmospheric exposure and biological exposure using simple linear regression with air concentrations as independent variable and biological concentrations as dependent variable. Log-transformation is used because the statistical distributions of both air and biological data are highly skewed. The logarithmic transformation has the consequence to make the distribution more symmetric.

There are a series of issues with such linear regression of log-transformed data, which need to be accounted for by specific statistical methods.

First, a majority of these data are repeated measurements on the same workers, leading to the non-independence of the data. Indeed, the elimination rates in different workers may differ significantly (between-worker variability in biological measurements) even with the same airborne exposure. On the other hand, as has been shown some time ago (Kromhout,

Symanski, and Rappaport 1993) the airborne concentrations may also exhibit a between-worker variability in excess of the day-to-day variability.

Second, although analytical methods are increasingly sensitive, the improvement of worker protection and collective protection leads to lower concentration levels and increasing numbers of exposure measurements are below the Limit Of Detection (LOD) that in the statistical jargon are referred to as left-censored data. Note that sometimes exposure measurements are reported as below the Limit of Quantification (LOQ) rather than LOD.

Up to now, in the industrial hygiene context, methods of data censored treatment have mainly focused on the univariate analysis of the airborne exposure measurements (Helsel 2005) (Hewett and Ganser 2007) (Ganser and Hewett 2010) (Huynh et al. 2014) (Huynh et al. 2016). In this context, (Jin et al. 2011) performed a simulation study comparing different approaches to take account of up to 80% left-censored measurements while at the same time acknowledging a between-worker variability. Their study compared the widely used substitution method, replacing data below the LOD for the independent variable by LOD/2 or LOD/sqrt(2), with mixed-effects models (based on Maximum Likelihood Estimation, MLE) to log-normally distributed occupational exposure data. They found that the substitution methods led to large biases (underestimation or overestimation) of geometric means and standard deviations, especially when the proportion of censored measurements was large, but that this was not the case with the MLE methods.

However, we know of no paper in the context of industrial hygiene that takes into account of censoring for both biological and airborne concentrations. In the context of modelling the relation between biological concentrations as a function of airborne concentrations, censored data for the independent variable, i.e. the airborne concentrations, can only be ignored, leading to a loss of information, loss of statistical power, and loss of precision of the relation assessment or substituted by LOD/2 or LOD/sqrt(2) leading to bias (see for instance (Ong et al. 1996) or (Ghittori et al. 1995)).

The purpose of the present paper is to present a statistical method making use of left-censored measurements for both dependent (biological) and independent (airborne) concentrations while accounting for between-worker variability both for airborne and biological measurements in order to improve the precision of their relation. Such an improved method would yield a BLV that better corresponds to the OEL.

METHODS

In this paper, we propose a statistical method based on Bayesian theory to use bivariate left-censored data, that is data with measurements below the LOD for both dependent (biological) and independent (air exposure) data. This is done by modelling simultaneously the two variables.

This proposed method is validated in a simulation study contrasting its performance to that of standard methods (based on MLE) that ignore all data corresponding to atmospheric data below the LOD.

Finally the proposed Bayesian method is applied to a real data set of chromium measurements among electrolytic platers.

Description of the data structure

We assume that we measured repeatedly the occupational airborne exposure as well as the biological exposure (e.g. in urine) for a series of workers. We assumed that these workers belong to the same Homogeneous Exposure Group i.e. a group of workers with one geometric mean airborne exposure – the difference between workers being characterized by a between-worker geometric standard deviation.

Both types of measurements are assumed to follow log-normal distributions and for both, there are within and between variance components. While the between worker variance component for air exposure is mainly due to differences in work practices, the between-worker variance component for biologic exposure is due to intrinsic between-worker differences in metabolism.

Finally, both measurements are measured with a certain precision and have therefore LODs and the biologic exposure measurement is assumed to depend, for any given worker, only on its atmospheric exposure.

The log-transformed airborne measurements are denoted by X and the log-transformed biological measurements are denoted by Y. The corresponding respective limits of detection (on the log scale) are denoted by $\mathrm{LOD_X}$ and $\mathrm{LOD_Y}$.

In a first data pattern, we simulated 20 subjects each with 11 measurements for both airborne and biological measurements (balanced data). In a second data pattern, we considered 80 subjects, with 1 measurement for 50 subjects, 2 measurements for 20 subjects and 5 measurements for 10 subjects (unbalanced data).

Bayesian modelling

Let us first present the full Bayesian model ignoring censoring

Following (Kromhout, Symanski, and Rappaport 1993), the airborne exposure data X are modelled by a random effect model with a random effect representing between-worker variability and a residual error representing within-worker variability. A similar model is used for the biological data Y, with random effects for between-worker variability and a residual within-worker variability. However we assume that, given these random effects, the log biological exposure measurement depends linearly on the (log-transformed) airborne exposure measurement.

For the *j*th observation of the *i*th worker, this can be written as:

$X_{ij} \sim N(\mu_{pop}^{X} + \zeta_i^X,\ \sigma_W^X)$ with $\zeta_i^X \sim N(0, \sigma_B^X)$ (1)

$Y_{ij} \sim N(\alpha_{pop}^{Y} + \beta . X_{ij} + \xi_i^Y, \sigma_W^Y)$ with $\xi_i^Y \sim N(0, \sigma_B^Y)$ (2)

where

σ_B^{X} and $\sigma_{\mathrm{W}}^{\mathrm{X}}$ are respectively the between-worker standard deviation and the within-worker standard deviation for the airborne log exposure measurements and μ_{pop}^X the population mean log airborne exposure;

$\sigma_{\mathrm{B}}^{\mathrm{Y}}$ and $\sigma_{\mathrm{W}}^{\mathrm{Y}}$ are respectively the between-worker standard deviation and the within-worker standard deviation for log biological measurements, α_{pop}^Y is the population log biological exposure for a zero log airborne exposure (intercept), and β is the slope of the relation.

Censoring

In order to accommodate measurements below the LOD, we introduce following notation for a truncated normal distribution $(\mu, \sigma)[a, b]$, a normal distribution truncated to the interval $[a, b]$. Thus, in our model corresponding to (1), a left censored value observed for jth observation of the ith worker would be specified as $X_{ij} \sim N\left(\mu_{pop}^X + \zeta_i^X,\ \sigma_W^X\right)[-\infty, LOD_X]$. In our model corresponding to (2), a left censored value observed for *j*th observation of the *i*th worker would be specified as $Y_{ij} \sim N(\alpha_{pop}^Y + \beta . X_{ij} + \xi_i^Y, \sigma_W^Y)\ [-\infty, LOD_Y]$.

Prior distribution of the parameters

Weakly informative prior distributions of the variability parameters $\sigma_{\mathrm{W}}^{\mathrm{Y}}, \sigma_{\mathrm{B}}^{\mathrm{Y}}$, are based on inverse gamma distribution with parameters (0.001, 0.001). It was chosen as it is the conditionally conjugate distribution for the inverse-chi2 distribution and leads to less computation time.

However, in order to examine the sensitivity to these choices of priors, we also used non-informative Half-Cauchy distributions for these parameters instead of Gamma distributions in a limited set of simulations.

The prior distribution of the variability parameter σ_B^X is informative as information exists in the literature on this quantity. Following (McNally et al. 2014), we chose a lognormal with Geometric Mean GM=0.29 and Geometric Standard Deviation GSD=2.82 expressing that σ_B^X lies between 0.036 and 2.22 in 95% of the cases.

The prior distribution of the variability parameter σ_W^X is also informative as information exists in the literature on this quantity. Following (McNally et al. 2014), we chose a lognormal with Geometric Mean GM=0.92 and Geometric Standard Deviation GSD=1.64 expressing that σ_W^X lies between 0.34 and 2.38 in 95% of the cases.

Prior distributions of the parameters α_{pop}^Y , β and μ_{pop}^X are non-informative normal distributions.

Estimation of model parameters

The Bayesian model was fitted using Gibbs Sampling, a special case of Markov chain Monte Carlo (MCMC) methods (see (Wild et al. 1996) for Gibbs Sampling in the context of censored data, and (Lunn et al. 2012) for more recent general discussion of MCMC methods) that by default take the censored data into account. We used the freely available RJags software (JAGS 4.2.0 and R version 3.3.2) we compared to other freely available softwares. In the supplementary material available online, Appendix 1 contains the code of the model used, respectively in Jags, OpenBugs and WinBugs.

We ran the Gibbs Sampling algorithm for N=50000 samples, a thinning of 5, and discarded the 10000 to account for “burn-in”. Convergence was checked by running two different chains. The starting points of the parameters were based on their true value for the simulation study. When analysing the actual data, we ran three chains starting from overdispersed starting points.

Simulation Study

In order to assess the performance of the above proposed Bayesian model in comparison with previously published methods, we did a simulation study by repeatedly simulating airborne exposure measurement and biological exposure measurement in settings as realistic as possible. We thus fixed the parameters of the data generated by our simulations to values that were abstracted from the scientific literature or, when not available, from the analysis of our own biomonitoring data given rise to a series of scenarios detailed below

Data generation scenarios

Specifically, we defined the following main scenario by:

- A slope β=1 between X and Y , corresponding to the proportionality of airborne exposure measurements and the biological exposure measurement on the original (non log-transformed) scale.
- σ_B^Y = 1.25 corresponding to a GSD_B^Y=3.48, that is the median of between-worker GSD of historic urinary data of our own biomonitoring laboratory.
- σ_W^Y = 0.37 corresponding to a GSD_W^Y=1.45, that is the median of within-worker GSD of historic urinary data of our own biomonitoring laboratory.
- σ_B^X = 0.29, corresponding to a GSD_B^X=1.34, that is the median of between-worker GSD for vapours and non-vapours components, defined by (McNally et al. 2014))
- σ_W^X = 0.98, corresponding to a GSD_W^X=2.66, defined from the median of the ratio between GSD_W^X and GSD_B^X for vapours and non-vapours-components, defined by (McNally et al. 2014).
- For each combination of these parameters, we fix the theoretical probability of censoring in X and Y of 30 and 50%.

Fixing these parameters, determines (for given values of the LODs) the intercept α_{pop}^Y and the mean log-exposure μ_{pop}^X. Without any loss of generality we arbitrarily fixed the (log-transformed) LOD for atmospheric measurements to 0. The intercept of the regression can thus be interpreted as the predicted mean urinary measurement when the atmospheric measurement is at the LOD.

This main scenario was simulated for balanced and unbalanced data pattern.

Subsequently, eight scenarios were then explored only for the balanced data pattern, modifying from the main scenario one of the value of the 4 standard deviations at a time:

- σ_B^Y is then set to 0.71 and 1.6 (GSD_B^Y=2 and GSD_B^Y=4.95) , that is the minimum and the maximum of between-worker GSD of historic urinary data of our own biomonitoring laboratory.
- σ_W^Y is then set to 0.26 and 0.53 (GSD_W^Y=1.3 and GSD_W^Y=1.7) , that is the minimum and the maximum of within-worker GSD of historic urinary data of our own biomonitoring laboratory
- σ_B^X is set to 0 and 0.5 (GSD_B^X=1 and GSD_B^X=1.65)
- σ_W^X is set to 0.47 and 1.53 (GSD_W^X=1.6 and GSD_W^X=4.65), defined from the minimum and the maximum of the ratio between GSD_W^X and GSD_B^X for vapours and non-vapours-components (McNally et al. 2014).

Each selected combination of parameters was simulated N=1000 times

Data analysis

For each simulated dataset, we applied

- the full proposed model based on Bayesian approach as described above, using RJags (JAGS 4.2.0 and R version 3.3.2),
- the reference MLE model (mixed tobit model), using STATA version 14.0 (program xttobit), similar to the method described in (Jin et al. 2011). However, this last method leads to the exclusion to all data below the LOD for X.

Retained variables of interest:

- α_{pop}^{Y} : the intercept of the relation that is the predicted mean urinary measurement when the atmospheric measurement is set to the LOD
- β : the slope of the relation.
- The derived BLVs corresponding to 3 theoretical values of OEL, defined by the theoretical percentage of exceeding them (0.1%, 2.5% and 10%).

Evaluation metrics

In order to compare the two methods, we computed the method-specific biases and RMSEs (Root Mean Square Error) summarizing both bias and variance over all 1000 simulated data sets. For each scenario, for α_{pop}^{Y} and β as well as for the derived BLVs we computed the bias and the RMSE according to following formulas

$$Bias_{\theta} = mean(\widehat{\theta_{\iota}} - \theta)$$

$$RMSE_{\theta} = \sqrt{mean(\widehat{\theta_{\iota}} - \theta)^2}$$

For each parameter, we also computed the ratio between the RMSEs :

$$Ratio_{\theta} = \frac{RMSE_{\theta}(Reference\ MLE\ model)}{RMSE_{\theta}(Proposed\ Bayesian\ model)}$$

Chromium exposure in electrolytic plating workers

The proposed Bayesian method was applied to a real dataset of electrolytic plating workers exposed to chromium and contrasted with the reference MLE method.

Between 2007 and 2012, the INRS (French Institute for research and Safety), conducted a biomonitoring study to evaluate urinary chromium of workers exposed to electrolytic plating. The study was carried out on 47 male workers exposed to Cr VI during electrolytic plating process.

Workers were from 5 companies. Full shift air samples were collected, over one to 5 days, and urinary samples were collected at the end of each shift.

The measure of airborne exposure to soluble CrVI (inhalable fraction) (CrA) was obtained by personal sampling. The samples were taken by aspiration of the ambient air through a device

consisting of a 37 mm diameter filter (Whatman QMA quartz fiber) placed in a closed cassette (Millipore) at a flow rate of 2 L / min provided by a controlled flow pump (INRS 2004). The LOQ of CrA ranged between 0.16 and 1.16 µg/m^3 depending on the sampled volume. Analysis of CrA was performed by optical emission spectroscopy analysis (ICP-OES) according to the method described in the French METROPOL database (INRS 2008).

Chromium urinary analyses were performed in a controlled atmosphere room. The method consisted of the graphite tube atomization followed by detection by an atomic absorption spectrometer with Zeeman correction of the type AA220 (Varian, Melbourne Australia) (Dube 1988). The method developed and validated in the laboratory has a LOQ ranging between 0.3 and 0.83 µg/ L.

Creatinine in urine samples was determined by the Jaffe method (JAFFE 1886) using a clinical biology apparatus of the type Daytona (Randox, Crumlin, UK).

The proposed Bayesian approach was first applied as described above with the variant specifying 5 different Homogeneous Exposure Groups (HEG), one for each company. Each HEG had a different geometric mean for the airborne exposure but we assumed that the 5 HEGs had the same between and within worker GSDs.

On the basis of the current French OEL (1 µg/m^3) of CrVI (INRS 2006), and on the current American TLV® (50 µg/m^3) of soluble CrVI (ACGIH 2015), the corresponding BLVs were computed from the regression parameters estimated with the two methods.

RESULTS

Simulation study

Figure 1 shows the distribution of the slope estimations in the simulated data sets of the main scenario with balanced and unbalanced data patterns. As expected, the two methods were unbiased. However, the dispersion of the estimates increases with X-censoring but is always lower using our proposed Bayesian method, whatever censoring and data pattern. Note that for the unbalanced data pattern the dispersion is greater and the difference in dispersion between the two methods more important. See also the corresponding scatter plots in Appendix 2 of the supplementary material available online.

Table 1 shows the results of the simulations. Overall these simulations show that the RMSE is always lower when using the proposed Bayesian approach as documented by the ratios of RMSEs which are always greater than 1. This is particularly apparent for the unbalanced data.

Considering the balanced data, the mean ratio over the scenarios for the intercept is only 1.04 thus the gain in using the proposed Bayesian procedure is moderate and does not vary much according to the censoring pattern nor according the scenario.

For the slope β, the gain in using the proposed method is much more obvious (mean ratio over all scenarios 1.27), and is particularly important when the censoring is 50% in X (mean 1.37 with 30% censoring in Y and 1.35 with 50% censoring in Y). This ratio of RMSEs does not depend to a great extent on GSD_B^Y, it decreases with GSD_B^X and with GSD_W^X and increases with GSD_W^Y The maximal ratio 1.66 was obtained for scenario 4 (GSD_W^X =1.6, GSD_B^X=1.34, GSD_W^Y =1.45, GSD_B^Y= 3.49) and 50% censoring for both X and Y.

With respect to the BLVs, the gain is almost negligible when the OEL is exceeded in 10% of the airborne measurements (BLV1). The gain is more important for BLV2 (2.5% excess of OEL) and is most important for BLV3 (0.1% excess of OEL). In the latter case, the mean ratio of RMSEs is most important for 50% censoring for both X and Y (1.10). Again, scenario 4 shows the highest gain in efficiency.

We didn't observe any noteworthy differences on the posteriors when using Half-Cauchy non-informative priors compared with non-informative gamma distribution (observed on the main scenario – data not shown). Moreover, influence of the informative priors was very slight even when the prior was very different from the true values.

Chromium exposure in electrolytic plating workers

The studied dataset comprised 166 pairs of urinary and airborne chromium measurements, CrU (in µg/g creatinine) and CrA (in µg/m^3) respectively. This dataset contained a large number of measurements below the respective LOQs.

Figure 2 provides a schematic view of the distribution of these measurements. At the bottom left, the figure shows that measurements below the LOQ for both CrU and CrA represent 20% of the dataset. At the upper left, we have data below the LOQ for CrA and above LOQ for CrU, which represent 34% of the dataset. As mentioned above, 54% of airborne measurements were below LOQ and would thus have been excluded using standard statistical methods, although for many of them, urinary chromium measurements were available. Note that we considered LOQs and not LODs as the data were only available in this format.

Table 2 shows the descriptive results of our data set. One can notice that the airborne exposure is quite high, with 69 measurements (42%) above the present French OEL=1 µg/m^3 but also 4 (2%) above the American TLV®= 50 µg/m^3, which was the French OEL at the time of the study.

The two statistical methods give similar estimates for the urinary GSDs and for within-worker airborne exposure GSD but not for between-worker GSD (Table 3). It must however be noted that the analysis of the airborne exposure data were not part of the reference MLE model but were modelled independently and were therefore not influenced by the urinary data.

The main differences are however in the estimate of the slope and in the intercept (corresponding to an exposure of 1 µg/m^3 which happens to be the current OEL).

The most striking result is that incorporating the data with atmospheric measurement below the LOQ results in a significantly steeper slope. This difference in slope is illustrated in Figure 3, which includes virtual measurements below the LOQs sampled randomly from the model. Note that the estimate of the slope is not only steeper but has a smaller standard error (in relative terms) using the proposed Bayesian method while the intercept has a similar precision in both methods.

Note that if the OEL used is 1 µg/m^3 (current French OEL), the corresponding BLV is 7.0 µg/g creatinine for the reference MLE model and 5.1 µg/g creatinine for the proposed Bayesian method when using informative prior on standard deviation of airborne exposure. With non-informative prior on standard deviation of airborne exposure, the proposed Bayesian method gave a similar BLV. If we use 50 µg/m^3 TLV®, the corresponding BLV is 17.1 µg/g creatinine for the reference MLE model and 23.6 µg/g creatinine for the proposed Bayesian method with informative prior on airborne exposure standard deviation, and 25 µg/g creatinine with non-informative priors (data not shown). Very similar values were obtained although with a slightly larger confidence interval when discarding the two least exposed companies (circles and diamonds in Figure 3).

DISCUSSION

In this paper, we proposed a statistical method based on Bayesian theory making use of measurements below the LOD for both dependent (biological) and independent (airborne exposure) data, in the context of repeated measurements per worker. The simulation of realistic settings showed that the proposed method is uniformly more efficient than the candidate alternative we considered (reference MLE method) that did not make use of a data with airborne measurements below the LOD. This efficiency gain was most important for unbalanced data, it increased with the percentage of airborne measurements below the LOD. With 50% censoring on airborne measurements, the RMSE of the estimated BLV decreased by up to 31% using the proposed Bayesian method. When the method was applied on a real biomonitoring data set with 54% airborne measurements below the LOQ, the slope was steeper and had a smaller standard error when incorporating these data using the proposed Bayesian method leading to different BLV estimations depending on the OEL used.

For the slope parameter, the simulation study shows a decrease of the RMSE with the proposed Bayesian method compared to reference MLE method, whatever the level of the variability parameters. However, the results are less clear-cut for the intercept of the relation; although RMSE is always lower with proposed Bayesian method, the gap with reference MLE method is less than for the slope estimation. This might be because, with 30 or 50% censoring, the LOD is close to the middle of the airborne measurements and the intercept is thus well known in any estimation method.

Simulations were also run with lower percentage of censoring (10% - data not shown), on X and Y. In this case, there is still a gain using the proposed Bayesian method, but is not large enough to justify the added complexity of its use.

For derived BLV, the gain is lower, especially for BLV1 and BLV2, corresponding to OEL defined by the theoretical percentages 10% and 2.5% of exceeding them, respectively. The lower gain could be explained by the fact that, as for the intercept, these values of OEL correspond to observed data which lead to a better stability of response, whatever the method used. BLV3 corresponds to 0.1% excess and thus involves some extrapolation that is more sensitive to slope estimation.

We checked (data not shown) that when discarding all censored data for airborne measurements, Bayesian model and MLE method gave very similar results. We can therefore safely conclude that the observed gain in RMSE is due to the inclusion of these censored data. On the other hand, when discarding all censored data (airborne and biological), we observed a rather important bias in all estimated parameters.

Our proposed Bayesian method is a rather complex model, integrating random effects in order to quantify the variability both between and within subject. This type of model has been proposed already 20 years ago (Kromhout, Symanski, and Rappaport 1993) but we are not aware that the proposed extension to biomonitoring data has ever been used even without consideration of data censoring. Indeed, in actual biological data, while the between-subject variability is often lower than the within-subject variability, we think that this is due to differences in day-to-day within-subject exposure. For any given airborne exposure level, we think that the between-subject variability in data is greater than the within-subject variability if inhalation is the predominant route of entry into the organism. When analysing historical data for metals (mostly unpublished), collected by our laboratory in a mixed model including the airborne exposure, the variance component for subject was indeed greater than the within-worker variance component adjusted on airborne exposure. The reason might be that the subject-specific physiological parameters like height, weight, BMI and metabolism vary widely between subjects, whereas within a given subject, the urinary excretion, adjusted on creatinine, depends mostly on the airborne exposure. Thus this between-subject variability cannot be ignored when analysing biomonitoring data, involving repeated measurements by subject. On the opposite, for the airborne exposure model, within-subject variability, due to day-to-day differences is usually greater (e.g. 77% of the 165 situations considered in (Kromhout, Symanski, and Rappaport 1993)) than the between-subject variability which depends mostly on subject-specific work practices.

In our model, we did not consider subject-specific random slopes although this might be the reality. It would have added complexity to our already complex model and might not be applicable to real data because of the low number of available data per subject.

However, the proposed Bayesian method has some limitations.

First, to run this method, we need a large number of measurements, to be able to estimate the different parameters of variability.

Second, our proposed Bayesian method has been only compared with the mixed-effect tobit model fitted using MLE (Jin et al. 2011). Several analyses of left-censored occupational exposure data have been developed in literature, like substitution methods, β-substitution methods(Ganser and Hewett 2010), Kaplan-Meier methods, multiple imputation based model, even Bayesian method (Huynh et al. 2014; Huynh et al. 2016). However, while β-substitution methods have been found optimal for parameter estimation in (Huynh et al. 2014) when considering only airborne exposure measurements, none of these methods (except the Bayesian) can be directly extended for the purpose of establishing the relationship between two left-censored variables. Moreover, none of these methods (except (Jin et al. 2011)) take into account non-independence in repeated measurements by subject.

The only method that can be directly extended to this context is the mixed-effect tobit model fitted using MLE we refer to as the reference MLE model.

Third, measurements are often made on a single week, and we have to be sure that the half-life of the substance is short, (less than a few hours), to possibly interpret biological measurements to reflect the airborne exposure of the same day. In this case only, does a regression approach make sense. If the half-life of the substance were greater, the biological measurements would be autocorrelated.

Fourth the random effects model for the log transformed urinary concentrations is probably not in accordance with underlying physiological mechanisms. It is precisely at low air/urinary levels that the assumed model might provide a poor representation. In particular, the urinary concentration for many, if not most, substances will be an additive combination of occupational and non-occupational (background) sources (such as diet and environmental exposures). Thus as airborne exposures approach zero, the urinary concentrations do not, but instead approach a 'background' or non-occupationally exposed level. The assumed model on a log-scale does not share this behaviour. Additionally, in the proposed model, the between-worker random effects for the (log) biological monitoring values translate to multiplicative random effects on the natural scale. Whilst this makes sense for the portion of the between-worker effect that is biological, e.g. weight and metabolism, another component in the between- worker variation are variations in the non-occupational sources of exposure, which (on the natural scale) are additive. It was beyond the scope of this paper to include these aspects in our model or in our simulations. In our opinion, what our model most importantly adds, is that when the airborne measurements are below LOD, but the urinary measurements are quantified, we can make use of these data. Data points where both measurements are below LOD will have less influence on the results although limited simulations showed that suppressing them would lead to an attenuation of the slope between air and biological monitoring. Thus the issues mentioned in this paragraph may not predominate especially when we consider LOQs instead of LODs.

Fifth, the assumption of linearity on the log scale, between the two variables, is strong, it cannot be checked on the data below the LOD and it is possibly not realistic for all substances. This must be judged for each practical case, when trying to derive a BLV from existing OELs. An added complexity might be to acknowledge, that the slope for a single substance may differ according to the industrial process that might generate aerosols with different physical and chemical properties, which might influence the biological exposition.

Finally, our simulation study, like all simulation studies, was conducted in a simplified setting. For example, we did not consider the above-mentioned additive components and only one Homogenous Exposure Group was considered; in practice, as in our real example, this is rarely the case.

As a last point, we consider our practical example. This example was mainly illustrative, but we can discuss some specifics of this data set. The main hypotheses on which this model is based are reasonable. Indeed, the main half-life time is 4.5 hours and the linearity assumption on the log scale fits our data in the range of data above LOQ. However, one limitation could be the assumption of linearity when the airborne exposure is more than an order of magnitude lower than the LOQ. It is probably not reasonable to assume that so small airborne Cr VI exposures would imply level of urinary chromium between 0.05 and 1 µg/g creatinine. Indeed, as mentioned previously, when airborne exposures approach zero, the urinary concentrations approach a non-occupationally exposed level. This is why we commented on the reanalysis excluding the two least exposed companies. Figure 3 shows that the model fit is more reasonable in this case. So that the very similar estimation results were obtained, validate our method.

Finally, we can compare our estimated BLVs of 5.1 µg/g creatinine to the value (1.8 µg/g creatinine) published by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) on the basis of the French recommended OEL 1 µg/m^3. On the other hand, the ACGIH defined a BEI of 25 µg/L (about 18 µg/g creatinine) based on the 50 µg/m^3 TLV, which is close to our estimate of 23.6 µg/g creatinine. One point to be mentioned is that our censored data are reported as below LOQ rather than below LOD. From a statistical point of view, this does not change anything, if all we know is that some measurements are below a given value.

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DECLARATION

Funding for this project was entirely based on the core funding of the INRS which is the sole employer of the authors. The authors declare no conflict of interest relating to the material presented in this Article. Its contents, including any opinions and/or conclusions expressed, are solely those of the authors.

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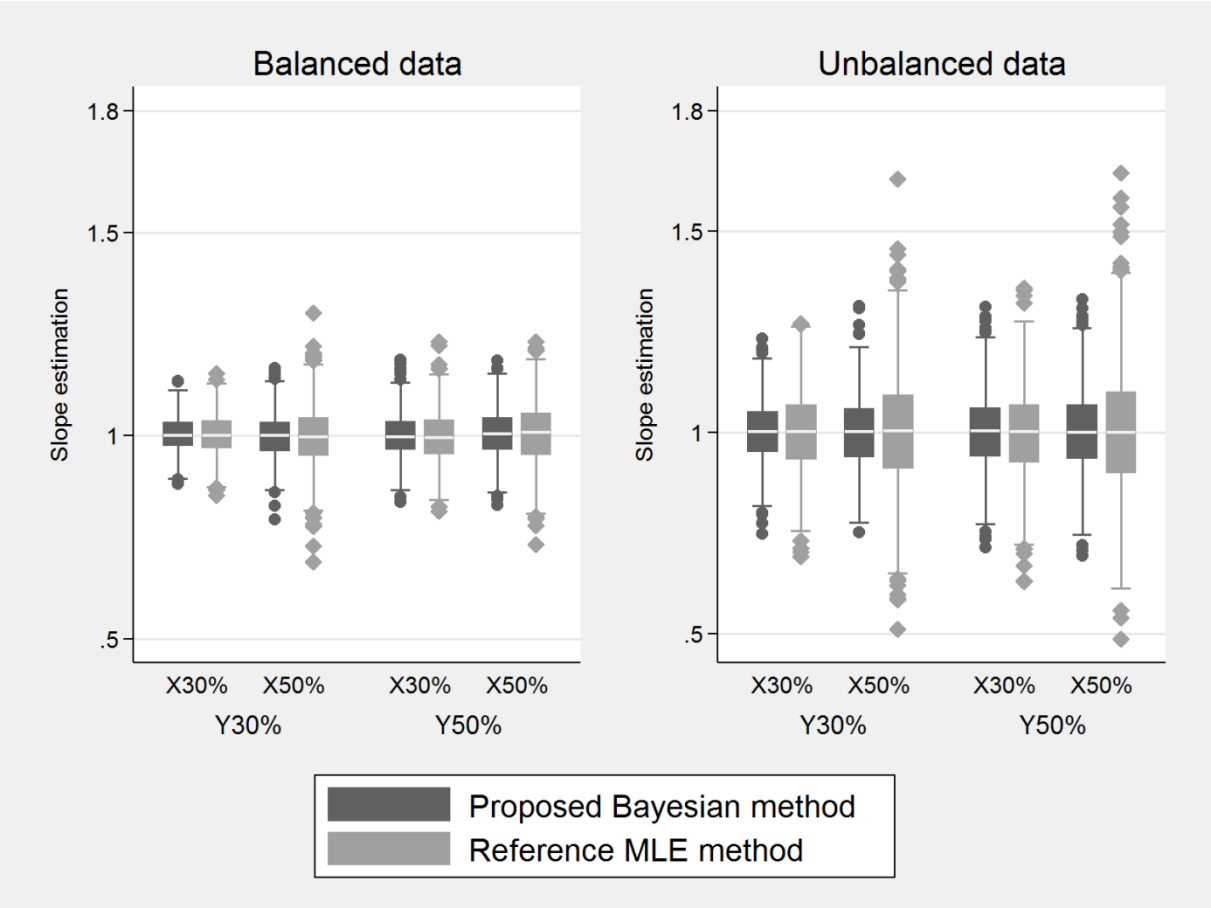

Figure 1: Distribution of the slope estimation in the simulated data sets of the main scenario, with balanced and unbalanced data patterns

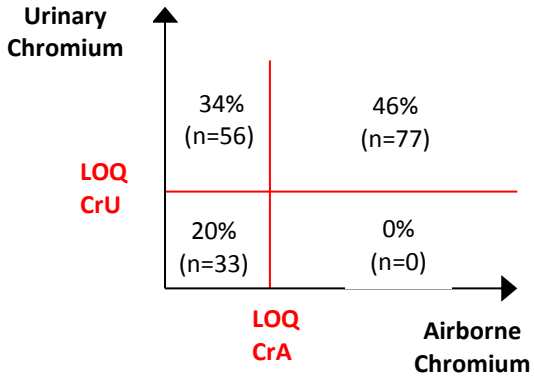

Figure 2: Schematic overview of urinary and airborne measurements in the workplace of electrolytic plating workers, above and below respective LOQ

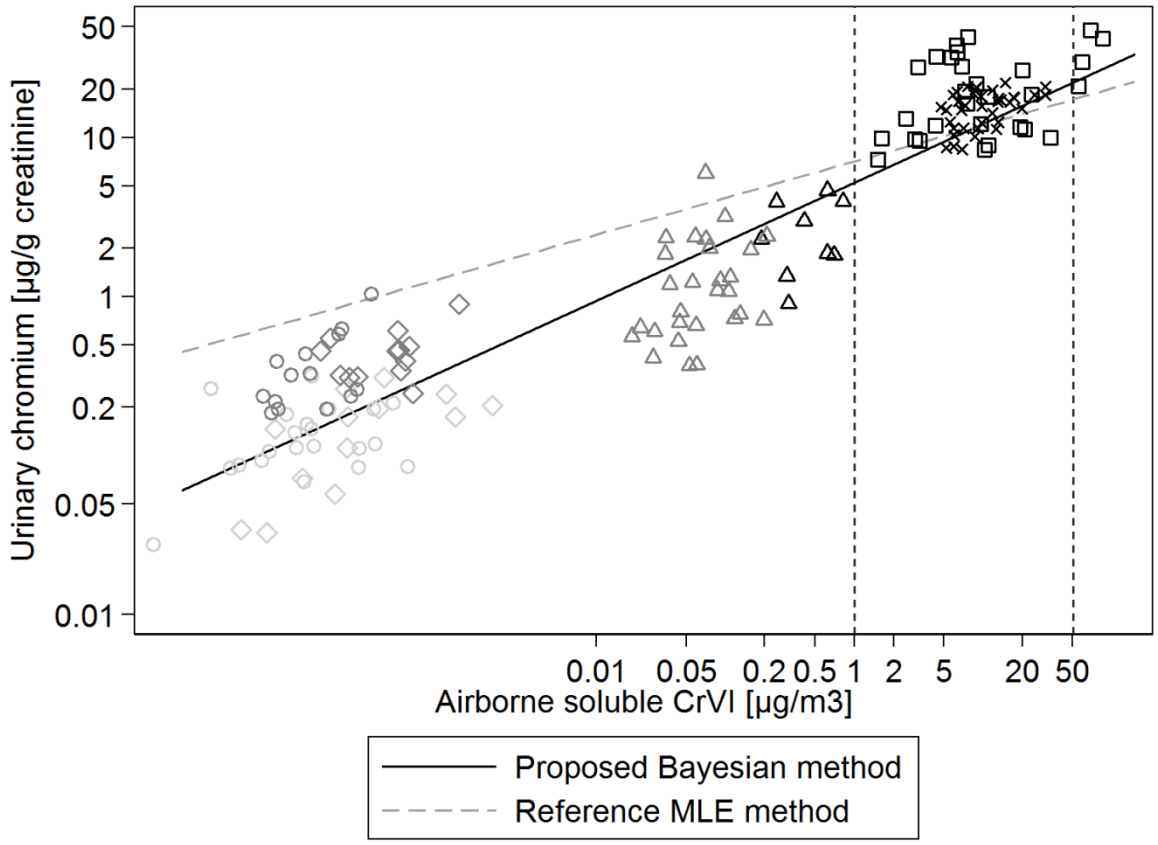

Figure 3: Scatterplot of urinary chromium vs airborne chromium measurements and regression lines for the reference and proposed methods. Black symbols represent measurements above LOQ for urinary and airborne chromium. Dark grey symbols represent urinary measurements above LOQ and model based random samples below LOQ for airborne chromium. Light grey symbols are model based random samples of measurements below LOQ for urinary and airborne chromium. Different symbols correspond to different companies. Black dashed lines correspond to the French OEL and TLV®.

SCENARIO	% Censure X	% Censure Y	GSD_B^Y	GSD_W^Y	GSD_B^X	GSD_W^X	$Ratio_{\alpha_{pop}^Y}$	$Ratio_\beta$	$Ratio_{BLV1}$	$Ratio_{BLV2}$	$Ratio_{BLV3}$
1 Balanced Data (*)	30	30	3.49	1.45	1.34	2.66	1.015	1.213	1.005	1.010	1.026
	50						1.027	1.399	1.005	1.014	1.053
	30	50					1.028	1.170	1.018	1.023	1.037
	50						1.049	1.344	1.032	1.041	1.078
1 Unbalanced Data (**)	30	30	3.49	1.45	1.34	2.66	1.177	1.305	1.057	1.090	1.153
	50						1.384	1.614	1.125	1.178	1.310
	30	50					1.193	1.249	1.089	1.105	1.145
	50						1.376	1.549	1.132	1.170	1.286
2	30	30	3.49	1.45	**1.00**	2.66	1.011	1.273	1.009	1.019	1.042
	50						1.021	1.379	1.004	1.014	1.052
	30	50					1.031	1.122	1.029	1.033	1.044
	50						1.048	1.371	1.031	1.040	1.078
3	30	30	3.49	1.45	**1.65**	2.66	1.023	1.107	1.017	1.019	1.027
	50						1.002	1.361	0.987	1.000	1.044
	30	50					1.027	1.162	1.021	1.027	1.043
	50						1.040	1.293	1.022	1.032	1.068
4	30	30	3.49	1.45	1.34	**1.60**	1.052	1.364	1.039	1.046	1.068
	50						1.051	1.547	1.035	1.049	1.097
	30	50					1.137	1.314	1.137	1.144	1.163
	50						1.130	1.665	1.121	1.139	1.194
5	30	30	3.49	1.45	1.34	**4.65**	1.005	1.124	1.000	1.004	1.016
	50						1.014	1.235	0.998	1.004	1.030
	30	50					1.003	1.050	1.004	1.007	1.015

	50						1.018	1.153	1.004	1.007	1.023
6	30	30	**2.03**	1.45	1.34	2.66	1.009	1.187	1.006	1.024	1.062
	50						1.042	1.348	1.005	1.028	1.093
	30	50					1.026	1.116	0.995	1.001	1.023
	50						1.039	1.280	0.999	1.022	1.087
7	30	30	**4.95**	1.45	1.34	2.66	1.027	1.169	1.021	1.022	1.029
	50						1.039	1.364	1.031	1.038	1.064
	30	50					1.096	1.197	1.105	1.110	1.122
	50						1.118	1.367	1.116	1.123	1.145
8	30	30	3.49	**1.3**	1.34	2.66	1.016	1.184	1.018	1.023	1.034
	50						1.028	1.239	1.019	1.021	1.033
	30	50					1.074	1.104	1.077	1.079	1.083
	50						1.088	1.222	1.091	1.097	1.111
9	30	30	3.49	**1.70**	1.34	2.66	1.014	1.286	1.004	1.020	1.059
	50						1.042	1.487	1.003	1.022	1.088
	30	50					1.017	1.190	0.994	1.004	1.036
	50						1.027	1.471	0.999	1.034	1.126

(*) Pattern with 20 subjects each with 11 measurements for both airborne and biological measurements

(**) Pattern with 80 subjects, with 1 measurement for 50 subjects, 2 measurements for 20 subjects and 5 measurements for 10 subjects

Table 1: Description of explored scenarios, (defined by censoring on X and Y, and by variability parameters), and results of the comparison between the two methods for each scenario, on variables of interest: α_{pop}^{Y} , β , BLV1, BLV2 and BLV3.

	Number of measurements	Number of measurements per workers	Median	Quartile		Measurements above LOQ	Measurements above French OEL	Measurements above TLV®
	n	*mean(min-max)*		*25th*	*75th*	*n (%)*	*n (%)*	*n (%)*
Urinary chromium [µg/g creatinine]	166	2.5 (1 – 5)	1.85	0.37	14.75	133 (80%)		
Airborne chromium [µg/m³]	166	2.5 (1 – 5)	<LOQ	<LOQ	7.23	77 (46%)	69 (42%)	4 (2%)

Table 2: Description of urinary and atmospheric chromium measurements

	Reference MLE model			Proposed Bayesian Model		
	Estimate	*95 % CI*		*Estimate*	*95 % CI*	
Intercept [µg/g creatinine]	1.95	1.63	2.26	1.62	1.41	1.85
Slope	0.23	0.10	0.36	0.39	0.29	0.49
$\mathbf{GSD_B^U}$	1.88	1.46	2.43	1.68	1.36	2.19
$\mathbf{GSD_W^U}$	1.30	1.23	1.38	1.43	1.35	1.54
$\mathbf{GSD_B^A}$	1.57	1.19	2.06	1.71	1.20	2.50
$\mathbf{GSD_W^A}$	2.03	1.77	2.34	2.1	1.85	2.50
	Estimate (95 % CI)	*Urinary measurements above BLV N (%)*		*Estimate (95 % CI)*	*Urinary measurements above BLV N (%)*	
BLV estimation [µg/g creatinine] French OEL = 1 µg/m³	7.0 (5.1-9.8)	69 (41%)		5.1 (4.1–6.4)	78 (47%)	
BLV estimation [µg/g creatinine] TLV® = 50 µg/m³	17.1 (11.4-25.9)	32 (19%)		23.6 (15.1 – 33.9)	15 (9%)	

$\boldsymbol{GSD_B^U}$ is the between-worker geometric standard deviation of urinary chromium data
$\mathbf{GSD_W^U}$ is the within-worker geometric standard deviation of urinary chromium data
$\mathbf{GSD_B^A}$ is the between-worker geometric standard deviation of airborne exposure chromium data
$\mathbf{GSD_W^A}$ is the within-worker geometric standard deviation of airborne exposure chromium data

Table 3: Estimated parameters and BLVs using French OEL or TLV® according to the two methods