Pergamon

PII: S0003-4878(01)00041-2

Ann. occup. Hyg., Vol. 45, No. 8, pp. 677–687, 2001

Printed in Great Britain.
0003-4878/01/$20.00

Heterogeneity in Sources of Exposure Variability Among Groups of Workers Exposed to Inorganic Mercury

ELAINE SYMANSKI†*, GERD SÄLLSTEN‡, WENYAW CHAN† and LARS BARREGÅRD‡

†The University of Texas School of Public Health, Houston, TX 77030, USA; ‡Department of Occupational Medicine, Sahlgrenska University Hospital, Göteborg, Sweden

Many exposure assessment strategies rely on the occupational group as the unit of analysis in which workers are classified on the basis of job title, location, or on other characteristics related to the workplace or the job. Although statistical methods that combine exposure data collected on workers from different occupational groups are more efficient, the underlying assumption that the degree of variation over time and among workers is the same for all groups has yet to be fully investigated. Given the utility of different modeling approaches when assessing exposures, we investigated assumptions of homogeneity of variance within and between workers using both random- and mixed-effects models. In our study of four groups of workers exposed to inorganic mercury (Hg) at a chloralkali plant, there was no evidence of significant heterogeneity in the levels of variation over time or between workers for air Hg levels. For the biological monitoring data, however, our findings indicate that groups did not share common levels of variability and that it was not appropriate to pool the data and obtain single estimates of the within- and between-worker variance components. Classification of job group as a random or fixed effect had no effect on the results and yielded the same conclusions when the models were compared. To illustrate effects related to the proper specification of a model, the likelihood of exceeding certain levels (which is a function of the parameters of the underlying distribution of the natural log-transformed exposures) was evaluated using the results obtained from the different models. Although the probability that workers' mean exposures exceeded occupational exposure limits for air, urine and blood Hg was generally low (<10%) for all groups except maintenance workers, the estimated values sometimes varied depending upon the particular model that was applied. Given the growing use of random- and mixed-effects models that combine data across occupational groups, additional studies are warranted to evaluate whether it is reasonable to assume common variances and covariances among measurements collected on workers from different groups.

Keywords: mixed-effects models; exposure assessment methods; inorganic mercury; chloralkali industry; overexposure

INTRODUCTION

Exposure assessment strategies may focus either on individual workers or on groups of workers who perform similar job tasks in common locations. The individual-based approach requires that measurements are available on all workers under investigation, which are then used to generate estimates of workers' exposure levels. When relationships between exposure and a continuous outcome are examined in a simple linear regression analysis, it is desirable to maximize differences between individuals' exposure levels relative to the variation that occurs from day-to-day to reduce the measurement error and the attendant bias in the estimated slope coefficient (Liu *et al.*, 1978). Assuming that the regression model adequately describes the exposure–response relation,

Received 9 October 2000; in final form 5 March 2001.
*Author to whom correspondence should be addressed. Tel: +1-713-500-9238; fax: +1-713-500-9249; e-mail: esymanski@sph.uth.tmc.edu

the bias can be expressed as a function of the magnitude of the within- and between-worker sources of variation and the number of repeated measurements collected on each individual. Suitable data have been available to examine likely effects on regression results for workers exposed to styrene in the reinforced plastics industry (Rappaport *et al*., 1995a; Symanski *et al*., 2001a), mercury in the chloralkali industry (Symanski *et al*., 2000), dust in the carbon black manufacturing industry (van Tongeren *et al*., 1997) and a variety of different contaminants arising in various industries (Tielemans *et al*., 1998).

In the more common situation where measurements are not collected on the entire workforce, the occupational group becomes the unit of analysis in which workers are classified on the basis of job title, location, or other characteristics related to the workplace or job function. Relying on representative measurements that are collected on some, but not necessarily all, individuals, the average exposure for the group is estimated and assigned to all members (Heederik *et al*., 1996; Seixas and Sheppard, 1996; Tielemans *et al*., 1998). Numerous studies have relied on the one-way random-effects model to evaluate variability in exposure from day-to-day and between workers who comprise an occupational group (Kromhout *et al*., 1987, 1993, 1995; Spear *et al*., 1987; Heederik *et al*., 1991; Kromhout and Heederik, 1995; Nieuwenhuijsen *et al*., 1995; Kumagai *et al*., 1996; Milton *et al*., 1996; Houba *et al*., 1997; Lagorio *et al*., 1997). In these applications, it is assumed that workers selected for monitoring represent random samples from a larger population of workers and that the days of sampling are representative of the period over which inferences are to be drawn. In addition to obtaining estimates of the group's average exposure, information about the magnitude of the variance components can be used to assess homogeneity in exposure levels (Rappaport *et al*., 1993), determine the probabilities of overexposure relative to exposure limits (Rappaport *et al*., 1995b, 1999; Lyles *et al*., 1997; Tornero-Velez *et al*., 1997; van Tongeren *et al*., 2000), and evaluate the utility of different exposure measures (Rappaport *et al*.; 1995a; Symanski *et al*., 2000, 2001a).

Investigators have also expanded their examination of exposure variability to investigate variation among different occupational groups of workers. Most commonly, a two-way random-effects model has been applied (Kromhout and Heederik, 1995; Nieuwenhuijsen *et al*., 1995; Kromhout *et al*., 1996; Houba *et al*., 1997; van Tongeren *et al*., 1997; van Wijngaarden *et al*., 1999), in which occupational groups are assumed to have come from a population and thus account for another source of random variation (between-group variability) in the exposure data. The two-way random-effects model has been used to evaluate the utility of grouping workers using different classification schemes by relying on relationships that depend upon the relative magnitude of the between-group, between-worker, and within-worker variances (Kromhout *et al*., 1995, 1996; Tielemans *et al*., 1998). In addition, mixed-effects models have been applied that evaluate the occupational group to which the worker belongs as a fixed (rather than random) effect (Rappaport *et al*., 1999; Symanski *et al*., 2001a). While random effects associated with the variation between and within workers are still included in the model, inferences are focused in these applications on differences in the mean values for those (and only those) groups represented in the data.

Specification of 'occupational group' as either a fixed or random-effect will depend partly on the manner of data collection, the structure of the data, and on the nature of the inferences to be drawn (Symanski *et al*., 2001b). However, both types of variance component models typically assume common between- and within-worker variances across groups. It is important to check whether this assumption is correct since the mean exposures for workers within a given group (which are viewed as random variables in both types of models) may well differ in variability from those in other groups. Likewise, the degree to which shift-long exposures vary for each worker may differ across groups as well. With the exception of one study that compared models with different variance structures when evaluating aerosol exposures among four groups of construction workers (Rappaport *et al*., 1999), little attention has focused on the validity of the assumption that the variances and covariances of measurements are the same for all occupational groups. Thus, we undertook this study to explicitly evaluate whether the within- and between-worker sources of variation were common among groups of workers exposed to inorganic mercury at a chloralkali plant. Given the utility of different modeling approaches when assessing exposures, analyses are presented that evaluated job group as either a random or a fixed effect in separate models. To illustrate effects related to the proper specification of a model, a secondary objective was to evaluate the probabilities of exceeding occupational exposure limits using the results obtained from the mixed models that make different assumptions about the variance–covariance structure of measurements across occupational groups.

MATERIALS AND METHODS

As part of a previous investigation (Symanski *et al*., 2000), air and biological monitoring data that had been collected routinely at a chloralkali plant in Sweden were compiled from laboratory records. Nearly the entire workforce participated in the biomonitoring program with each worker typically providing one blood sample and two urine samples each year. The sampling campaign was normally conducted in late winter and spring (February through

April) and then again later in the year during the months of July through November. Whereas approximately equal numbers of urine samples were collected during both campaigns, a greater number of blood samples was generally collected in the spring than in the autumn period.

Blood was collected by venipuncture in metal-free heparinized vacutainers at the health-care center of the plant. First-morning urine samples were collected at home in metal-free polyethylene bottles. Determinations of mercury in biological samples were made using cold vapor atomic absorption spectrophotometry (Einarsson *et al*., 1984) and reported in units of nanomoles per liter (nmol/l). The limit of detection for urinary and blood mercury was 10 nmol/l through 1992 and 5 nmol/l thereafter. From 1988 onwards, urinary creatinine was analyzed with a modified kinetic Jaffé method and used to express mercury concentration in units of μg Hg/g creatinine.

Unlike the biological monitoring program in which almost all workers provided urine and blood samples, only one-half of the workforce had been selected for personal sampling over the study period. Although personal monitoring had been conducted periodically throughout each year, measurements on the same worker were typically collected during two- or three-day campaigns. To evaluate personal exposures in the breathing zone of the workers, active sampling on Hydrar tubes was conducted during the full work shift and the samples analyzed using standard methods (NIOSH, 1989). The detection limit for airborne mercury was 0.5 μg/m^3 throughout the entire study period.

Since urinary creatinine was analyzed from 1988 onwards, the database for this investigation was restricted to the period 1988–1997 to facilitate comparisons among all exposure measures. Biological measurements on workers exposed to mercury vapor for less than one year were excluded since their exposure regimen was not sufficiently long enough to reasonably assume steady-state conditions. Urine samples that were either too dilute (<0.5 g creatinine/l) or too concentrated (>3 g creatinine/l) were also omitted (Alessio *et al*., 1985). A standard procedure was adopted for air, blood, and urinary mercury levels below the limit of detection (Hornung and Reed, 1990) — such measurements were assigned a level of two-thirds the value of the reported detection limit.

The job titles of the workers were assigned to four broad occupational categories: (1) shift workers, (2) cell hall maintenance workers, (3) cell hall production workers and (4) non-cell hall workers. The cell hall production workers and the cell hall maintenance workers perform the majority of their tasks in the cell hall whereas the non-cell hall workers typically spend less than 10% of their time in the cell hall. The shift workers run the process for 24 h, which requires that they perform numerous tasks in the control room, salt solution hall, and cell hall. Additional details about the study population and the exposure-monitoring database have been previously reported (Symanski *et al*., 2000), but we note that the database analyzed in the present study extends over a slightly longer interval (1988–1997) than that presented earlier (1990–1997).

In preliminary analyses, scatter plots of the annual mean levels of the natural logarithms of the data were inspected. While no trends were apparent in the air monitoring data, there was a downward shift in urinary and blood mercury levels in 1994 (and thereafter) that was likely due to a change in laboratory for the biological samples that occurred in June of 1994 (Symanski *et al*., 2000). Because this downward shift in biological levels made it difficult to discern whether trends were present over the entire monitoring period, time trends were formally evaluated in the mixed-models that were applied. In these analyses, the year the measurement was collected (1988–1997) was re-scaled from 0 to 9.

Specification of job group as a fixed effect in a mixed-effects linear model

To evaluate fixed effects on exposure related to job group, a mixed-effects linear model was applied and is specified as follows:

$$Y_{ijk} = \ln(X_{ijk}) = \mu_Y + \delta t + \alpha_i + \beta_{j(i)} + \varepsilon_{ijk} \quad (1)$$

for $i = 1, ..., 4$ job groups,
$j = 1,2, ...,$ b workers,
$k = 1,...,n_{j(i)}$ measurements of the jth worker in the ith job, group collected in year t,
and where

X_{ijk}	the *k*th measurement of the exposure concentration for the *j*th worker in the *i*th job group,
Y_{ijk}	the natural logarithm of the exposure concentration,
μ_Y	the overall mean of Y_{ijk} at time=0,
δ	the slope for the annual time trend,
α_i	the fixed effect due to the *i*th job group,
$\beta_{j(i)}$	the random effect of the *j*th worker in the *i*th job group, and
ε_{ijk}	the random error of the *k*th measurement collected on the *j*th worker in the *i*th job group.

It is assumed under model (1) that $\beta_{j(i)} \sim N(0,\sigma^2_{B,i})$, $\varepsilon_{ijk} \sim N(0,\sigma^2_{W,i})$ and that $\beta_{j(i)}$'s and ε_{ijk}'s are statistically independent. Thus, $\sigma^2_{B,i}$ and $\sigma^2_{W,i}$ represent the between- and within-worker components of variance for the *i*th job group. It directly follows that $Y_{ijk} \sim N(\mu_Y + \delta t + \alpha_i, \sigma^2_{Y,i})$ where $\sigma^2_{Y,i} = \sigma^2_{B,i} + \sigma^2_{W,i}$ and that $\mathrm{cov}(Y_{ijk}, Y_{ijk'}) = \sigma^2_{B,i}$ for $i = i$, $j = j$, and $k \neq k'$. For the untransformed exposure concentration

(X_{ijk}) which is assumed to follow a lognormal distribution, the mean ($\mu_{X,i}$) and variance ($\sigma^2_{X,i}$) can be expressed as functions of the mean and variance of the normally-distributed log-transformed exposures, i.e., $\mu_{X,i} = \exp(\mu_Y + \delta t + \alpha_i + 0.5\sigma^2_{Y,i})$ and $\sigma^2_{X,i} = \mu^2_{X,i}[\exp(\sigma^2_{Y,i})-1]$. As noted above, a systematic change in urinary and blood mercury levels was detected in mid-1994 arising from a change in laboratory for the biological samples (Symanski *et al.*, 2000). Thus, a fixed (period) effect was added to model 1 when the biomonitoring data were analyzed (period 1: 1988–June 1994 and period 2: July 1994–1997).

Specification of job group as a random effect in a mixed-effects linear model

To evaluate random effects related to job group, a two-way random-effects model was applied and is specified as follows:

$$Y_{ijk} = \ln(X_{ijk}) = \mu_Y + \delta t + \alpha^*_i + \beta_{j(i)} + \varepsilon_{ijk} \quad (2)$$

Model (2) differs from model (1) in its specification of job group (α^*_i) as a random effect; thus, μ_Y represents a common mean for all job groups. All other terms are defined as for model (1). Here, it is assumed that α^*_i, $\beta_{j(i)}$ and ε_{ijk} are independent normal random variables with zero means and variances σ^2_G, $\sigma^2_{B,i}$, and $\sigma^2_{W,i}$, respectively, which represent the between-group, between-worker, and within-worker variance components. It directly follows that $\mathrm{cov}(Y_{ijk},Y_{ij'k'}) = \sigma^2_G + \sigma^2_{B,i}$ for $i = i$, $j = j'$, and $k \neq k'$ and that $\mathrm{cov}(Y_{ijk},Y_{ij'k'}) = \sigma^2_G$ for $i = i$, $j \neq j'$, and $k \neq k'$. As in model (1), a period (fixed) effect was added to the model when evaluating the urinary and blood mercury data.

Under models (1) and (2), three different sets of assumptions were evaluated regarding the variances and covariances of measurements within each occupational group: (a) $\sigma^2_{B,i}$ and $\sigma^2_{W,i}$ were the same for all job groups [hereafter referred to as model 1.1 or 2.1], (b) $\sigma^2_{B,i}$ was different for all job groups and $\sigma^2_{W,i}$ was the same for all job groups [model 1.2 or 2.2], and (c) $\sigma^2_{B,i}$ and $\sigma^2_{W,i}$ were different for all job groups [model 1.3 or 2.3]. Thus, model 1.1 or 2.1 represents the most parsimonious model and model 1.3 or 2.3 the most complex model. In the current investigation, we assume a common covariance for all pairs of measurements collected on the same worker irrespective of the time interval separating them (this structure is referred to as compound symmetry). To evaluate whether it was appropriate to pool the variance components across groups in model (1) or model (2), likelihood ratio tests and the Akaike's Information Criterion (AIC) were used to compare the following sets of models:

1. The model with different between-worker variances, but a common within-worker variance across groups was compared to the model with a common between and within-worker variance across groups. This comparison tests the hypothesis that H_0:$\sigma^2_{B,1} = \ldots = \sigma^2_{B,4}$ and compares model 1.2 to 1.1 (or model 2.2 to 2.1).
2. The model with distinct between and within-worker variances was compared to the model with different between-worker variances, but a common within-worker variance. This comparison tests the hypothesis that H_0:$\sigma^2_{W,1} = \ldots = \sigma^2_{W,4}$ and compares model 1.3 to 1.2 (or model 2.3 to 2.2).

To apply the likelihood ratio test, a test statistic was computed as the difference in the -2 log likelihood values between the two models. This statistic is approximately distributed as a chi-squared variate with degrees of freedom specified by the difference in the number of parameters estimated between the two models and was evaluated at a significance level of 0.05. The AIC, which is defined as the maximized (restricted) log likelihood minus the number of parameters in the covariance matrix, was also used to compare models. In making comparisons using the AIC, selection was based on the model with the smallest value. All model parameters were estimated using the method of restricted maximum likelihood (REML) implemented with the PROC MIXED procedure from the SAS System Software (Version 8.01, Cary, NC, USA).

Evaluation of exposures relative to occupational exposure limits

Given that exposures vary both within and between workers in an occupational group, the 'exceedance' [i.e., the probability that a single measurement obtained from a randomly-selected worker in the *i*th group on a randomly-selected day exceeds an occupational exposure limit (OEL)] can be expressed as a function of the mean and variance components of the underlying distribution of the natural log-transformed exposures for the *i*th job group (Rappaport *et al.*, 1999). In our application, the exceedance probability [$\gamma_i(t)$] can be represented as follows:

$$\gamma_i(t) = P\{X_{ijk}>\mathrm{OEL}\} = 1-\Phi\left\{\frac{\ln(\mathrm{OEL})-\mu_{Y,i}(t)}{\sqrt{\sigma^2_{B,i} + \sigma^2_{W,i}}}\right\} \quad (3)$$

In Eq. (3), X_{ijk} represents the *k*th measurement randomly collected on the *j*th worker from the *i*th job group at time *t*, $\mu_{Y,i}(t)$ represents the mean value of the logged exposures for the *i*th job group at time *t* (i.e. $\mu_{Y,i}(t) = \mu_Y + \delta t + \alpha_i$) and $\sigma^2_{B,i}$ and $\sigma^2_{W,i}$ represent the between- and within-worker variance components of the logged-exposures for the *i*th job group, respectively. $\Phi\{z\}$ denotes the probability that a standard normal variate falls below the value of *z*.

To ensure mathematical correctness, we define 'overexposure' as the probability that the *conditional* mean exposure for a randomly selected worker exceeds an occupational exposure limit. Our definition presents a different probability statement than what has been published previously (Rappaport *et al.*, 1999), but the computational formula remains the same. Using our definition, the probability of 'overexposure' [$\theta_i(t)$] can be represented as follows:

$$\begin{aligned}\theta_i(t) &= P\{E(\bar{X}_{j(i)}|\beta_{j(i)}) > \mathrm{OEL}\} \\ &= P\{E(X_{ijk}|\beta_{j(i)}) > \mathrm{OEL}\} \\ &= P\{\exp(\mu_{Y,i}(t) + \beta_{j(i)} + 0.5\sigma^2_{\mathrm{W},i}) > \mathrm{OEL}\} \\ &= 1 - \Phi\left\{\frac{\ln(\mathrm{OEL}) - \mu_{Y,i}(t) - 0.5\sigma^2_{\mathrm{W},i}}{\sigma_{\mathrm{B},i}}\right\}\end{aligned} \tag{4}$$

In Eq. (4), $\bar{X}_{j(i)}$ represents a method of moments estimator for the mean exposure of the jth worker in the ith job group at time t and X_{ijk}, $\mu_{Y,i}(t)$, $\beta_{j(i)}$, $\sigma^2_{\mathrm{B},i}$ and $\sigma^2_{\mathrm{W},i}$ are defined as before. Here, we note that $E(X_1|X_2)$ represents the conditional expectation of X_1 given X_2, and is a function of the random variable X_2. In our application, we focus on the expectation of a worker's mean conditional on the random effect associated with a particular individual who belongs to the ith group (i.e. $E[\bar{X}_{j(i)}|\beta_{j(i)}]$). The 3rd equality in Eq. (4) arises from $E[X_{ijk}|\beta_{j(i)}] = \exp(\mu_{Y,i}(t) + \beta_{j(i)} + 0.5\sigma^2_{W,i})$ since $X_{ijk}|\beta_{j(i)}$ is lognormally distributed with parameters $\mu_{Y,i}(t) + \beta_{j(i)}$ and $\sigma^2_{\mathrm{W},i}$. We are ultimately interested in the probability that this conditional expectation (a random variable) exceeds an occupational exposure limit.

Using the invariance principle for restricted maximum likelihood (see, for example, Bartoszynski and Niewiadomska-Bugaj, 1996), the probabilities of exceedance and overexposure relative to an occupational exposure limit were estimated based on $\hat{\mu}_{Y,i}(t)$, $\hat{\sigma}^2_{\mathrm{B},i}$ and $\hat{\sigma}^2_{\mathrm{W},i}$ obtained from models 1.1, 1.2, or 1.3. Threshold limit values and biological exposure indices (ACGIH, 1999) of 25 μg/m^3, 75 nmol/l and 35 μg/g creatinine were chosen as the exposure limits for air, blood, and urinary mercury, respectively.

RESULTS

Table 1 provides a breakdown of the air and biological monitoring data that were evaluated. In total, there were 325 airborne mercury measurements, 847 blood mercury measurements and 1165 urinary mercury measurements. Most workers participated in shift work or were involved in maintenance activities. Over 80% of workers in all job groups contributed more than one measurement. Taken together, there were few blood (<7%) and no urinary or air (0%) measurements below the limit of detection.

Results from the analyses of the air, blood, and urinary mercury data that applied models (1) and (2) with different variance structures appear in Tables 2 and 3, respectively. In comparing the model with common variances (1.1 or 2.1) to the model with distinct variances (1.3 or 2.3), we observed a greater range across job groups in the point estimates of the between-worker variance compared to the within-worker variance for all three exposure measures. For example, model 1.1 generated estimates of the between- and within-worker variance components of 0.168 and 0.701 for air mercury. In comparison, the point estimate of the between-worker variance from the model with distinct variance components (model 1.3) varied from 0.098 for maintenance workers to 0.470 for non-cell hall workers. In contrast, the estimates of the within-worker variance ranged from 0.349 for cell hall production workers to 0.785 for cell hall maintenance workers. Although the underlying construct of the models that evaluate job group as a fixed (model 1) or random (model 2) effect are quite different, the point estimates of the between- and within-worker variance components were nearly the same in both sets of models that were applied.

Table 4 summarizes the results for the evaluation of trends in the air and biological monitoring data. While trends in exposure were not detected in either the air or blood Hg data, urinary mercury levels declined slightly ($P<0.05$) at a rate of approximately 3% per year. In evaluating effects related to a change in laboratory for the biological monitoring data, there was a significant shift towards lower levels for both the urinary and blood Hg data in all models that were applied ($P<0.05$, results not shown).

Table 5 summarizes the comparisons between models that were made using either Akaike's Information Criterion (AIC) or the likelihood ratio test (LRT) statistic. Similar conclusions are reached irrespective of the classification of job group as a fixed or random effect. Based on both indices, our results suggest that there was no advantage in assuming heterogeneity in the between- or within-worker variances across groups for the airborne mercury data. For blood mercury, the AIC selects the model with distinct between- and within-worker variances whereas the likelihood ratio test selects the model with a common within-worker variance but distinct between-worker variances. For urinary mercury, the model with distinct between- and within-worker variances appears to offer the best fit based upon both selection criteria.

The estimated probabilities of exceedance [$\hat{\gamma}_i(t)$] for 1988 ($t = 0$), which rely on parameter estimates that were generated under models 1.1, 1.2, and 1.3 for air, blood, and urinary mercury, appear in Table 6. The likelihood that a single randomly-collected air measurement would exceed 25 μg/m^3 ranged considerably across the four groups with the highest values observed for maintenance workers (~40%) who are involved in activities that give rise to extremely variable exposures. For this same group of workers, two- and four-fold differences in the exceedance probabilitites for blood and urinary Hg, respectively, were observed across models. Table 6

Table 1. Breakdown of the database of airborne, blood, and urinary mercury data collected on workers at a Swedish chloralkali plant

	N[a]	b[a]	Median number of measurements per worker	% of workers with >1 measurement	% of measurements < LOD
Airborne Hg (µg/m³)					
Shift workers	62	20	3	90	0
Cell hall production workers	26	6	4	100	0
Cell hall maintenance workers	205	18	9	100	0
Non-cell hall workers	32	8	3	88	0
Blood Hg (nmol/l)					
Shift workers	248	44	6	90	7
Cell hall production workers	98	7	11	100	3
Cell hall maintenance workers	214	20	7	85	4
Non-cell hall workers	287	34	7	91	9
Urinary Hg (µg/g creatinine)					
Shift workers	585	47	14	94	0
Cell hall production workers	63	7	7	86	0
Cell hall maintenance workers	155	19	5	84	0
Non-cell hall workers	362	33	10	94	0

[a]N: number of measurements; b: number of workers.

Table 2. Results from the mixed-effects models with a *fixed* effect due to occupational group under different assumptions regarding homogeneity in the between- and within-worker variance components ($\sigma^2_{B,i}$ and $\sigma^2_{W,i}$) among groups of workers exposed to inorganic mercury at a chloralkali plant

	Model 1.1[a]				Model 1.2[a]				Model 1.3[a]			
	$\hat{\sigma}^2_{B,i}$	$\hat{\sigma}^2_{W,i}$	$\hat{\mu}_{Y,i}$[b]	$\hat{\mu}_{X,i}$[b]	$\hat{\sigma}^2_{B,i}$	$\hat{\sigma}^2_{W,i}$	$\hat{\mu}_{Y,i}$[b]	$\hat{\mu}_{X,i}$[b]	$\hat{\sigma}^2_{B,i}$	$\hat{\sigma}^2_{W,i}$	$\hat{\mu}_{Y,i}$[b]	$\hat{\mu}_{X,i}$[b]
Airborne Hg (µg/m³)												
Shift workers	0.168	0.701	2.34	16.1	0.087	0.702	2.33	15.3	0.118	0.615	2.39	15.7
Production workers	0.168	0.701	2.33	15.9	0.279	0.702	2.35	17.2	0.437	0.349	2.43	16.8
Maintenance workers	0.168	0.701	2.94	29.3	0.112	0.702	2.98	29.7	0.098	0.785	3.03	32.2
Non-cell hall workers	0.168	0.701	1.54	7.21	0.455	0.702	1.56	8.45	0.470	0.521	1.63	8.39
Blood Hg (nmol/l)												
Shift workers	0.190	0.223	3.00	24.7	0.055	0.224	3.00	23.2	0.056	0.223	3.00	23.0
Production workers	0.190	0.223	3.28	32.6	0.126	0.224	3.30	32.3	0.127	0.171	3.29	31.2
Maintenance workers	0.190	0.223	3.48	40.0	0.201	0.224	3.47	39.9	0.204	0.203	3.46	39.1
Non-cell hall workers	0.190	0.223	3.11	27.5	0.351	0.224	3.09	29.3	0.344	0.261	3.08	29.6
Urinary Hg (µg/g creatinine)												
Shift workers	0.161	0.159	2.23	10.9	0.059	0.160	2.21	10.1	0.062	0.141	2.21	10.1
Production workers	0.161	0.159	2.59	15.6	0	0.160	2.55	13.9	0	0.113	2.58	13.9
Maintenance workers	0.161	0.159	3.10	26.0	0.151	0.160	3.16	27.5	0.151	0.158	3.16	27.5
Non-cell hall workers	0.161	0.159	2.09	9.51	0.319	0.160	2.04	9.80	0.312	0.201	2.05	10.0

[a]Model 1.1: Common $\sigma^2_{B,i}$ and $\sigma^2_{W,i}$; Model 1.2: Common $\sigma^2_{W,i}$, different $\sigma^2_{B,i}$; Model 1.3: Different $\sigma^2_{B,i}$ and $\sigma^2_{W,i}$.
[b]$\hat{\mu}_{Y,i}$ represents an estimate of the mean exposure of the logged data for the ith job at the start of the monitoring period in 1988; $\hat{\mu}_{X,i}$ represents the estimated mean exposure of the untransformed data for the ith job in 1988; ($\hat{\mu}_{X,i} = \exp[\hat{\mu}_{Y,i} + 0.5(\hat{\sigma}^2_{B,i} + \hat{\sigma}^2_{W,i})]$).

also reports the values of $\hat{\theta}_i(t)$ for 1988 estimated under the three mixed-effects models. As with the exceedance probabilities, there were differences (in some cases) when comparing the results obtained from different models.

DISCUSSION

The application of random- and mixed-effects models to evaluate sources of variation in exposure to workplace contaminants is growing in the occu-

Table 3. Results from the two-way mixed-effect models with a *random* effect due to occupational group under different assumptions regarding homogeneity in the within- and between-worker variance components among groups of workers exposed to inorganic mercury at a chloralkali plant

	Model 2.1[a]			Model 2.2[a]			Model 2.3[a]		
	$\hat{\sigma}^2_{G}$	$\hat{\sigma}^2_{B,i}$	$\hat{\sigma}^2_{W,i}$	$\hat{\sigma}^2_{G}$	$\hat{\sigma}^2_{B,i}$	$\hat{\sigma}^2_{W,i}$	$\hat{\sigma}^2_{G}$	$\hat{\sigma}^2_{B,i}$	$\hat{\sigma}^2_{W,i}$
Airborne Hg (µg/m³)									
Shift workers	0.297	0.167	0.701	0.285	0.086	0.702	0.278	0.119	0.610
Production workers	0.297	0.167	0.701	0.285	0.263	0.702	0.278	0.418	0.348
Maintenance workers	0.297	0.167	0.701	0.285	0.111	0.702	0.278	0.097	0.787
Non-cell hall workers	0.297	0.167	0.701	0.285	0.466	0.702	0.278	0.479	0.522
Blood Hg (nmol/l)									
Shift workers	0.041	0.190	0.223	0.038	0.055	0.224	0.037	0.056	0.223
Production workers	0.041	0.190	0.223	0.038	0.122	0.224	0.037	0.123	0.171
Maintenance workers	0.041	0.190	0.223	0.038	0.208	0.224	0.037	0.211	0.202
Non-cell hall workers	0.041	0.190	0.223	0.038	0.349	0.224	0.037	0.342	0.261
Urinary Hg (µg/g creatinine)									
Shift workers	0.198	0.161	0.160	0.231	0.059	0.160	0.232	0.062	0.141
Production workers	0.198	0.161	0.160	0.231	0	0.160	0.232	0	0.113
Maintenance workers	0.198	0.161	0.160	0.231	0.153	0.160	0.232	0.154	0.158
Non-cell hall workers	0.198	0.161	0.160	0.231	0.318	0.160	0.232	0.312	0.201

[a]Model 2.1: Common $\sigma^2_{B,i}$ and $\sigma^2_{W,i}$; Model 2.2: Common $\sigma^2_{W,i}$, different $\sigma^2_{B,i}$; Model 2.3: Different $\sigma^2_{B,i}$ and $\sigma^2_{W,i}$.

Table 4. Estimates of the annual linear trends in the log-transformed air and biological monitoring data [$\hat{\delta}$ (SE)] among a series of mixed models with different covariance structures that specify job group as either a fixed (model 1) or random (model 2) effect

	$\hat{\delta}$ (SE)		
Model[a]	Airborne Hg (µg/m³)	Blood Hg (nmol/l)	Urinary Hg (µg/g creatinine)
1.1	−0.016 (0.022)	−0.009 (0.01)	−0.030 (0.008)
1.2	−0.019 (0.022)	−0.011 (0.01)	−0.029 (0.008)
1.3	−0.029 (0.022)	−0.009 (0.01)	−0.030 (0.007)
2.1	−0.019 (0.022)	−0.009 (0.01)	−0.030 (0.008)
2.2	−0.022 (0.021)	−0.011 (0.01)	−0.029 (0.008)
2.3	−0.033 (0.022)	−0.009 (0.01)	−0.030 (0.007)

[a]Model 1.1 or 2.1: Common $\sigma^2_{B,i}$ and $\sigma^2_{W,i}$; Model 1.2 or 2.2: Common $\sigma^2_{W,i}$, different $\sigma^2_{B,i}$; Model 1.3 or 2.3: Different $\sigma^2_{B,i}$ and $\sigma^2_{W,i}$.

pational arena. One of the distinctive characteristics of random-effects models is that they accommodate the correlation among measurements collected on the same individual or in the same location (Symanski *et al.*, 2001b). Mixed-effects models provide an additional advantage because they can be used to evaluate determinants of exposure (e.g., effects due to type of work, ventilation controls, or changes in the process), while incorporating the covariation among certain measurements. Since the occupational group to which a worker belongs may distinguish workers on the basis of what work is performed and in which location tasks are carried out, it serves as a surrogate for the combined effects of various determinants of exposure and can easily be evaluated as a fixed effect to detect differences in exposure levels among groups of workers (Rappaport *et al.*, 1999; Symanski *et al.*, 2001a). Of course, significant between-worker variability within an occupational group has been well documented (Kromhout *et al.*, 1993; Rappaport *et al.*, 1993) and it is clear that work practices and other factors vary within an occupational category and contribute to the variation in exposure levels among workers who share the same job title.

In the application of random- or mixed-effects models to data collected on workers from several occupational groups, it is statistically advantageous to pool information across groups because more precise estimates of the variance components are obtained, which in turn lead to smaller standard errors associated with the fixed effects (Sullivan *et al.*, 1999). Decisions to pool data should be based, in part, upon whether it is reasonable to expect that the degree of variation among measurements is similar across groups. While qualitative evaluations regarding likely differences in the magnitude of variability between and within workers across groups represent a useful first step, the statistical methods applied herein provide a more rigorous approach in making such an evaluation. For the biological exposure indices, our

Table 5. Comparisons among models applied to the airborne, blood, and urinary mercury (Hg) data with different variance structures using Akaike's Information Criterion (AIC) and the Likelihood Ratio Test Statistic (LRT)

Model[a]	No. of parameters	AIC	−2 log likelihood	LRT	$P>\chi^2_3$
Airborne Hg (μg/m³)					
1.1	2	858.9	854.9		
1.2	5	862.6	852.6	2.3	0.5135
1.3	8	862.4	846.4	6.2	0.1023
2.1	2	867.5	861.5		
2.2	5	871.2	859.2	2.3	0.5125
2.3	8	871.0	853.0	6.2	0.1023
Blood Hg (nmol/l)					
1.1	2	1339.7	1335.7		
1.2	5	1334.9	1324.9	10.8	0.0129
1.3	8	1334.0	1318.0	6.9	0.0752
2.1	2	1342.3	1336.3		
2.2	5	1337.7	1325.7	10.6	0.0141
2.3	8	1336.7	1318.7	7.0	0.0719
Urinary Hg (μg/g creatinine)					
1.1	2	1417.9	1413.9		
1.2	5	1399.1	1391.2	22.7	<0.0001
1.3	8	1389.1	1373.1	18.1	0.0004
2.1	2	1427.9	1421.9		
2.2	5	1406.8	1396.8	25.1	<0.0001
2.3	8	1396.7	1378.7	18.1	0.0004

[a]Model 1.1: Common $\sigma^2_{B,i}$ and $\sigma^2_{W,i}$; Model 1.2: Common $\sigma^2_{W,i}$, different $\sigma^2_{B,i}$; Model 1.3: Different $\sigma^2_{B,i}$ and $\sigma^2_{W,i}$. Two-way random-effects models: Model 2.1: Common $\sigma^2_{B,i}$ and $\sigma^2_{W,i}$; Model 2.2: Common $\sigma^2_{W,i}$, different $\sigma^2_{B,i}$; Model 2.3: Different $\sigma^2_{B,i}$ and $\sigma^2_{W,i}$.

Table 6. Probabilities of exceedance ($\hat{\gamma}_i$) and over-exposure ($\hat{\theta}_i$) estimated for 1988 under a mixed-effects model with different assumptions regarding homogeneity in the within- and between-worker variance components (Models 1.1, 1.2, and 1.3)[a]

Job group	Exceedance probability ($\hat{\gamma}_i$)			Overexposure probability ($\hat{\theta}_i$)		
	1.1	1.2	1.3	1.1	1.2	1.3
Airborne Hg (μg/m³)						
Shift workers	0.173	0.160	0.166	0.010	0.035	0.063
Production workers	0.171	0.191	0.186	0.010	0.165	0.175
Maintenance workers	0.384	0.398	0.421	0.573	0.636	0.745
Non-cell hall workers	0.036	0.061	0.055	<0.001	0.026	0.026
Blood Hg (nmol/l)						
Shift workers	0.020	0.006	0.006	0.003	<0.001	<0.001
Production workers	0.053	0.043	0.030	0.017	0.005	0.004
Maintenance workers	0.097	0.098	0.090	0.048	0.052	0.048
Non-cell hall workers	0.030	0.053	0.056	0.006	0.030	0.030
Urinary Hg (μg/g creatinine)						
Shift workers	0.010	0.002	0.001	<0.001	<0.001	<0.001
Production workers	0.044	0.006	0.002	0.013	–[b]	–[b]
Maintenance workers	0.209	0.238	0.239	0.173	0.207	0.208
Non-cell hall workers	0.005	0.014	0.018	<0.001	0.006	0.006

[a]Model 1.1: Common $\sigma^2_{B,i}$ and $\sigma^2_{W,i}$; Model 1.2: Common $\sigma^2_{W,i}$, different $\sigma^2_{B,i}$; Model 1.3: Different $\sigma^2_{B,i}$ and $\sigma^2_{W,i}$.
[b]$\hat{\theta}_i$ is undefined because $\hat{\sigma}^2_{B,i} = 0$.

findings indicate that groups did not share common levels of variability. Thus, it would not be appropriate to pool the urinary or blood mercury data to generate single estimates of the within- and between-worker variances. On the other hand, we found that there was no evidence of significant heterogeneity in the degree of variation within or between workers for air mercury levels. The inability to detect significant heterogeneity in the degree of variation in airborne mercury among the four groups of chloralkali plant workers may be due to insufficient sample size although a previous study detected differences in the between-worker variance among workers exposed to manganese and total particulates with far fewer data (Rappaport *et al.*, 1999). Another possible explanation for our equivocal findings relates to differences in the sampling strategy employed for collection of the airborne and biological monitoring data. In the former case, only a portion of the workforce was selected for monitoring and repeated measurements were commonly collected within a few days. In contrast, nearly all workers contributed at least one blood and two urine samples each year. Thus, for airborne Hg, we may have underestimated the extent of variation from day-to-day because the sampling strategy was not conducted over the full range of exposures experienced by workers within each group, thereby making the within-worker variances appear more homogenous than they actually were.

According to company personnel, there were no major changes in the workplace during the period over which the monitoring data had been collected and inspection of the records for the amount of mercury emitted to the air from the cell room (kg/yr) suggested that levels remained relatively constant from 1988 through 1997. Nonetheless, it is possible that exposures declined as evidenced by our result for urinary Hg and that our inconsistent trend results may be due to the greater number of measurements that was available for the urine samples ($N = 1165$) compared to either the blood ($N = 847$) or air ($N = 325$) samples. Given our findings of a highly insignificant trend in both the air and blood Hg levels, we applied mixed models without a trend component to the data and observed (as expected) little differences when comparisons in the estimated variance components were made (results not shown).

There was little variation in the estimates of the mean values of the logged exposures that were obtained from the different models for each job group, which suggests that improperly specifying the variance structure does not affect the estimation of the fixed effects portion of the model. On the other hand, estimates of the groups' arithmetic mean exposures, which are functions of the estimated values of the variance components, may vary considerably depending on which model is applied (Rappaport *et al.*, 1999). However, such differences appeared to be small in the current investigation (see Table 2).

Valuable information is contained in the variance components, which can be used to evaluate the utility of different grouping schemes, assess the bias in measures of effect in health effects studies, and estimate probabilities that exposures exceed occupational exposure limits. However, important errors can be made when assumptions regarding homogeneity in the degree of variation within and between workers across groups are not met. To illustrate effects related to the particular specification of the variance–covariance structure in a mixed-model, we calculated the probabilities that workers were exposed at levels exceeding occupational exposure limits using the results obtained from models that assumed common or distinct within- and between-worker variances. While exposures are generally below acceptable levels for all groups except for maintenance workers, we detected moderate to large differences in the exceedance and overexposure probabilities across models in some cases. Such differences are of little consequence when the probabilities are low ($\ll$5%), but could become more important when values begin to fall within the range of unacceptable levels. For airborne mercury, it is interesting to note that the estimated probabilities of overexposure [$\hat{\theta}_i(t)$] compared to the probabilities of exceedance [$\hat{\gamma}_i(t)$] were lower for shift workers, production workers, and non-cell hall workers, but considerably higher for maintenance workers. These results confirm previous findings that the probability that a randomly-collected measurement exceeds an exposure limit compared to the probability that the mean exposure for a randomly-selected worker exceeds that same limit may not be equal, and that the exceedance probability is not necessarily higher than the probability of overexposure (Tornero-Velez *et al.*, 1997).

Focusing again on maintenance workers, important questions are raised regarding the equivocal conclusions that would be drawn based on the three exposure indices. For air mercury, the probabilities of exceedance (which ranged from 38 to 42% depending on the model that was applied) and overexposure (which ranged from 57 to 75%) were considerably higher than the corresponding values for blood or urine mercury. Given that air measurements were commonly collected in 2- or 3-day campaigns, it is possible that worst-case exposures were targeted and that the air-monitoring data are not representative of the full-range of exposures experienced by workers. The possible lack of representative data point, once again, to the limited utility of biased data in making meaningful statements about exposure (Symanski *et al.*, 1998). In comparison to the air-monitoring program, however, the blood and urinary samples were collected routinely on nearly the entire workforce over the 10-yr period. Yet, the exceedance and overexposure probabilities in maintenance workers were two to four times greater for urine mercury than blood mercury. These differences could be partly explained by the fact that the average ratio between urine mercury and blood mercury in reality is higher (see Table 2) than the ratio between limit values given by the ACGIH (1999) (35 μg/g creatinine and 75 nmol/l, respectively). In establishing the biological exposure indices (BEI) for inorganic mercury in urine and blood, the ACGIH BEI committee stated that the recommended level for urinary mercury did not include a safety factor and that no significant health effects had been observed at a level of 75 nmol/l for blood mercury (BEI Committee, 1990). Moreover, they noted that urine to blood mercury ratios varied considerably across studies. Nevertheless, our results open the question as to which measure might be more suitable to evaluate whether exposure levels fall within an acceptable range. Owing to kinetic differences, peak airborne exposures are dampened in urinary mercury but more easily detected using blood mercury. A comparatively higher 'limit of exceedance' for blood mercury versus urine mercury could therefore be interpreted in light of the emphasis placed on average rather than peak exposures, in line with differences between shift-long and short-term exposure limits for air contaminants.

As noted earlier, a characteristic feature of random- and mixed-effects models is that they account for correlation among the data. However, there are many covariance patterns available and choosing the most appropriate one is not always straightforward. In the present study, we assumed that a compound symmetry (CS) structure, in which the correlation between measurements collected on the same worker is the same irrespective of the interval separating them, adequately fit the data. There is, however, a wide range of covariance structures that could be modeled to account for a more complex pattern of repeated measurements. For example, in the most general 'unstructured' pattern (although relatively inefficient because of the number of parameters involved), the variances of observations differ for each time period and the covariance varies for pairs of measurements separated by different intervals. A simpler approach might apply a first-order autoregressive [AR (1)] structure that models the covariance as an exponentially decreasing function of the time interval between measurements. Such a structure was applied in a recent study (Symanski *et al*., 2001b) that applied an hierarchical linear mixed model to evaluate long-term trends in exposures to nickel aerosols and was found to provide a better fit (compared to CS) in some of the data that were analyzed. While more complex covariance structures can only be evaluated on relatively large datasets with fair numbers of repeated observations, investigators are urged to consider the broad array of variance–covariance specifications that are available (provided the data support such applications) to ensure that the most appropriate model is applied. Given a suitable variance–covariance structure, studies should also be conducted to determine whether it is reasonable to assume common variances and covariances among measurements collected on different groups of workers.

Acknowledgements—This research was supported by grant KO1 OH00166 from the National Institute for Occupational Safety and Health, the Swedish Medical Research Council in Stockholm, and by the Wallenberg Foundation and the Medical Faculty at Göteborg University.

REFERENCES

ACGIH. Documentation of the threshold limit values and biological exposure indices. Cincinnati (OH): American Conference of Governmental Industrial Hygienists, 1999.

BEI (Biological Exposure Index) Committee. Mercury — elemental and inorganic. Appl Occup Envir Hyg 1990;5:545–52.

Alessio L, Berlin A, Dell'Orto A, Toffoletto F, Ghezzi I. Reliability of urinary creatinine as a parameter used to adjust values of urinary biological indicators. Int Arch Occup Envir Hlth 1985;55:99–106.

Bartoszynski R, Niewiadomska-Bugaj M. Probability and statistical inference. New York: John Wiley and Sons, 1996.

Einarsson Ö, Lindstedt B, Bergström T. A computerized automatic apparatus for determination of mercury in biological samples. J Autom Chem 1984;6:74–9.

Heederik D, Boleij JSM, Kromhout H, Smid T. Use and analysis of exposure monitoring data in occupational epidemiology: an example of an epidemiological study in the Dutch animal food industry. Appl Occup Envir Hyg 1991;6:458–64.

Heederik D, Kromhout H, Braun W. The influence of random exposure estimation error on the exposure response relationship when grouping into homogeneous exposure categories. Occup Hyg 1996;3:229–41.

Hornung RW, Reed LD. Estimation of average concentration in the presence of nondetectable values. Appl Occup Envir Hyg 1990;5:46–51.

Houba R, Heederik D, Kromhout H. Grouping strategies for exposure to inhalable dust, wheat allergens and α-amylase allergens in bakeries. Ann Occup Hyg 1997;41:287–96.

Kromhout H, Oostendorp Y, Heederik D, Boleij JSM. Agreement between qualitative exposure estimates and quantitative exposure measurements. Am J Ind Med 1987;12:551–62.

Kromhout H, Heederik D. Occupational epidemiology in the rubber industry: Implications of exposure variability. Am J Ind Med 1995;27:171–85.

Kromhout H, Loomis DP, Mihlan GJ, Peipins LA, Kleckner RC, Iriye R, Savitz D. Assessment and grouping of occupational magnetic field exposure in five electric utility companies. Scand J Work Envir Hlth 1995;21:43–50.

Kromhout H, Symanski E, Rappaport SM. A comprehensive evaluation of within- and between-worker components of occupational exposure to chemical agents. Ann Occup Hyg 1993;37:253–70.

Kromhout H, Tielemans E, Preller L, Heederik D. Estimates of individual dose from current measurements of exposure. Occup Hyg 1996;3:23–39.

Kumagai S, Kusaka Y, Goto S. Cobalt exposure level and variability in the hard metal industry of Japan. Am Ind Hyg Assoc J 1996;57:365–9.

Lagorio S, Iavarone I, Iacovella N, Proietto AR, Fuselli S, Baldassarri LT, Carere A. Variability of benzene exposure among filling station attendants. Occup Hyg 1997;4:15–30.

Liu K, Stamler J, Dyer A, McKeever J, McKeever P. Statistical methods to assess and minimize the role of intra-individual variability in obscuring the relationship between dietary lipids and serum cholesterol. J Chron Dis 1978;31:399–418.

Lyles RH, Kupper LL, Rappaport SM. Assessing regulatory compliance of occupational exposures via the balanced one-way random effects ANOVA model. J Agric Biol Envir Stat 1997;2:64–86.

Milton DK, Walters MD, Hammond K, Evans JS. Worker exposure to endotoxin, phenolic compounds, and formaldehyde in a fiberglass insulation manufacturing plant. Am Ind Hyg Assoc J 1996;57:889–96.

Nieuwenhuijsen MJ, Lowson D, Venables KM, Newman Taylor AJ. Flour dust exposure variability in flour mills and bakeries. Ann Occup Hyg 1995;39:299–305.

NIOSH. Inorganic mercury, NIOSH method 6009, NIOSH manual of analytical methods, 3rd ed. Cincinnati (OH): National Institute for Occupational Safety and Health, 1989.

Rappaport SM, Kromhout H, Symanski E. Variation in exposure between workers in homogeneous exposure groups. Am Ind Hyg Assoc J 1993;54:654–62.

Rappaport SM, Lyles RH, Kupper LL. An exposure-assessment strategy accounting for within-and between-worker sources of variability. Ann Occup Hyg 1995b;39:69–495.

Rappaport SM, Symanski E, Yager JW, Kupper LL. The relationship between environmental monitoring and biological markers in exposure assessment. Envir Hlth Perspect 1995a;103(Suppl 3):49–54.

Rappaport SM, Weaver M, Taylor D, Kupper L, Susi P. Application of mixed models to assess exposures monitored by construction workers during hot processes. Ann Occup Hyg 1999;43:457–69.

Seixas NS, Sheppard L. Maximizing accuracy and precision using individual and grouped exposure assessments. Scand J Work Envir Hlth 1996;22:94–101.

Spear RC, Selvin S, Schulman J, Francis M. Benzene exposure in the petroleum refining industry. Appl Ind Hyg 1987;2:155–63.

Sullivan LC, Dukes KA, Losina E. An introduction to hierarchical linear modelling. Stat Med 1999;18:855–88.

Symanski E, Bergamasch E, Mutti A. Inter- and intra-individual sources of variation in levels of urinary styrene metabolites. Int Arch Occup Envir Hlth 2001a;74:336–44.

Symanski E, Chan W, Chang C. Mixed-effects models for the evaluation of long-term trends in exposure levels with an example from the nickel industry. Ann Occup Hyg 2001b;45:71–81.

Symanski E, Kupper LL, Rappaport SM. Comprehensive evaluation of long term trends in occupational exposure: part 1. Description of the database. Occup Envir Med 1998;55:300–9.

Symanski E, Sällsten G, Barregård L. Variability in airborne and biological measures of exposure to mercury in the chloralkali industry: implications for epidemiologic studies. Envir Hlth Perspect 2000;108:569–73.

Tielemans E, Kupper LL, Kromhout H, Heederik D, Houba R. Individual-based and group-based occupational exposure assessment strategies: some equations to evaluate different strategies. Ann Occup Hyg 1998;42:115–9.

Tornero-Velez R, Symanski E, Kromhout H, Yu RC, Rappaport SM. Compliance versus risk in assessing occupational exposures. Risk Anal 1997;17:279–92.

van Tongeren M, Gardiner K, Calvert I, Kromhout H, Harrington JM. Efficiency of different grouping schemes for dust exposure in the European carbon black respiratory morbidity study. Occup Envir Med 1997;54:714–9.

van Tongeren MJA, Kromhout H, Gardiner K. Trends in levels of inhalable dust exposure, exceedance and overexposure in the European carbon black manufacturing industry. Ann Occup Hyg 2000;44:271–80.

van Wijngaarden E, Savitz DA, Kleckner RC, Mihlan G, Nylander-French LA, Dufort V, Cai J, Loomis D, Kromhout H. Refinements in magnetic field exposure assignment for a case-cohort study of electrical utility workers. Ann Occup Hyg 1999;43:485–92.