Variability in Airborne and Biological Measures of Exposure to Mercury in the Chloralkali Industry: Implications for Epidemiologic Studies

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Exposure assessment is a critical component of epidemiologic studies, and more sophisticated approaches require that variation in exposure be considered. We examined the intra- and interindividual sources of variation in exposure to mercury vapor as measured in air, blood, and urine among four groups of workers during 1990–1997 at a Swedish chloralkali plant. Consistent with the underlying kinetics of mercury in the body, the variability of biological measures was dampened considerably relative to the variation in airborne levels. Owing to the effects of intraindividual variation, estimating workers' exposures from a few measurements can attenuate measures of effect. To examine such effects on studies relating long-term exposure to a continuous health outcome, we evaluated the utility of each exposure measure by comparing the necessary sample sizes required for accurate estimation of a slope coefficient obtained from a regression analysis. No single measure outperformed the others for all groups of workers. However, when workers were evaluated together, creatinine-corrected urinary mercury better discriminated workers' exposures than airborne or blood mercury levels. Thus, pilot studies should be conducted to examine variability in both air and biomonitoring data because quantitative information about the relative magnitude of the intra- and interindividual sources of variation feeds directly into our efforts to design an optimal sampling strategy when evaluating health risks associated with occupational or environmental contaminants. *Key words*: **biological markers, exposure variability, mercury, variance components.** *Environ Health Perspect* **108:569–573 (2000). [Online 5 May 2000]**
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Of critical importance when assessing the utility of an exposure measure are questions related to exposure variability. Two major components of exposure variability are the variation that occurs from day-to-day (intraindividual variation) and the variation that occurs among workers (interindividual variation). For airborne measures of exposure, intraindividual variation occurs as a result of myriad factors related to the process and the work environment or it may be due, to a lesser extent, to measurement errors associated with sampling and analysis (*1*). Interindividual variation in airborne contaminant levels among workers has been attributed to differences in job tasks or work practices (*2*).

Intraindividual variation in the external exposure is transmitted, at least to some degree, to biological levels of the contaminant or its metabolite in body fluids. In addition, sources of biological variability are likely to induce fluctuations in contaminant concentrations in urine or blood over time. Such variability in biomarker levels associated with occupational exposure has been restricted thus far to a single investigation (*3*), but some endogenous constituents in blood and urine are marked by considerable intraindividual variation (*4–7*), and the same physiologic parameters are likely to exert similar effects on body burdens of contaminants. Moreover, the variation between workers in exposure levels would contribute to interindividual variability in biomarker levels. Ethnicity, sex, age, anthropometric and lifestyle factors, and physiologic differences in the rates of uptake, metabolism, and elimination are also likely to play a role.

Intraindividual variability in exposure can induce error in exposure assessment and thereby can adversely affect epidemiologic studies by reducing the power to detect associations and by diminishing measures of effect (*8–13*). To assess the magnitude of the error in an exposure measure, the well-established techniques of analysis of variance can be applied (when repeated measurements on study subjects are available) to estimate the magnitude of the intra- and interindividual sources of variation. Information contained in the estimated variance components can then be used to assess the bias in measures of effect and to optimize study design in terms of the number of workers to be studied and the number of samples to collect.

In the chloralkali industry, exposure to mercury vapor (Hg^0) can occur during the production of chlorine through the electrolysis of a brine solution in mercury cells (*14*). Exposure can be monitored by measuring mercury in the breathing zone of exposed workers using either active or passive personal sampling techniques (*15*) or by biomonitoring mercury in urine or whole blood. The primary aim of the present study was to examine the intra- and interindividual sources of variation in levels of mercury in the air, urine, and blood among workers at a Swedish chloralkali plant during the 1990s. Using information about exposure variability, a secondary objective was to investigate whether airborne or biological measures of exposure might be more suitable for use in an epidemiologic study by comparing the minimum sample sizes necessary to minimize the attenuation of regression results when health-effects studies are carried out.

Materials and Methods

Compilation of the database. During the period 1990–1997, no major changes in production were implemented at the chloralkali plant involved in the current investigation. Review of the company's data on annual emissions of mercury from the cell hall revealed that the output remained relatively constant over the study period. To evaluate workers' exposures to mercury, both air and biological monitoring were conducted. One blood sample and two urine samples were typically collected on each worker per year. First-morning urine samples were collected at home in metal-free polyethylene bottles, and blood was collected by venipuncture in metal-free heparinized vacutainers at the health-care center of the plant. Personal exposures were evaluated during the full work shift by active sampling on Hydrar tubes (*16*). Nearly all workers participated in the biomonitoring program, but approximately one-half of the workforce was monitored by personal sampling.

We analyzed air samples using standard methods (*16*); determinations of mercury in biological samples were made using cold vapor atomic absorption spectrophotometry (*17*). To correct for urinary flow rate, mercury concentrations in urine were adjusted for creatinine, which was analyzed with a modified kinetic Jaffé method (*18*). There

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was a change in the laboratory responsible for the analysis of the biomonitoring data in 1994. Quality assurance has been presented elsewhere for the analyses before 1994 (*19*). From 1996 onward, analyses of external reference samples showed acceptable results (Centre de Toxicologie du Québec, Sainte-Foy, Québec, Canada; interlaboratory comparison). The detection limit for airborne mercury was 0.5 μg/m^3. For urinary and blood mercury, the limit of detection was 10 nmol/L through 1992 and 5 nmol/L thereafter.

We used laboratory reports for 1990–1997, provided by the company's health and personnel unit, to compile a database of both air and biological monitoring measurements. Before the data were entered, they were inspected to identify outliers, which were subsequently investigated to ascertain possible coding errors. In the absence of any errors, the original data were left intact. Blood, urinary, and air mercury values were recorded in units of nanomoles per liter, micrograms per gram creatinine, and micrograms per cubic meter, respectively. Uncorrected urinary values (nanomoles per liter) were compiled as well. For the biomonitoring database, measurements on workers exposed to mercury vapor for < 1 year were excluded because their exposure regimen was not sufficiently long to reasonably assume steady-state conditions. We omitted urine samples that were either too dilute (< 0.5 g creatinine/L) or too concentrated (> 3 g creatinine/L) (*20*). Very few urinary (< 1%) and blood (5%) mercury measurements were below the limit of detection; all such measurements were flagged and assigned a level of two-thirds the value of the reported detection limit (*21*). There were no undetectable air mercury values.

With assistance from company personnel, we ascertained the job titles of the workers. We created four broad occupational categories based on the following classifications: *a*) shift workers; *b*) cell cleaners, basement flushers, and mercury-pump repairmen (hereafter referred to as "cell hall maintenance workers"); *c*) cell hall foremen, "egalisators" (voltage regulators of the mercury cells), and cell switchers (hereafter referred to as "cell hall production workers"); and *d*) instrument technicians, mechanical workshop workers and foremen, staff electricians, operating engineers, plastic workshop workers, and laboratory workers (hereafter referred to as "non-cell hall workers"). Both the cell hall production workers and the cell hall maintenance workers typically spend the majority of their time in the cell hall, whereas the non-cell hall workers spend < 10% of their time in the cell hall. Shift workers run the process for 24 hr, rotate between day and night shifts, and perform numerous tasks in the control room, salt solution hall, and cell hall. Due to small sample sizes and the irregularity of the work performed, data collected on workers who spend no time in the cell hall (e.g., washers or storeroom workers) and external workers (e.g., painters or electricians) were not evaluated.

We examined temporal effects by visually inspecting graphs of the annual mean levels for the air and biological monitoring data collected over the period 1990–1997. Although the air mercury levels appeared to fluctuate erratically above and below the mean value for the entire period, a shift in exposure levels in 1994 was apparent for the biological monitoring data, especially urinary mercury. Thus, a systematic change in the urinary and blood mercury levels was evaluated when sources of exposure variability were examined. Also, histograms of the air, blood, and urinary measurements suggested that the data were approximately lognormally distributed; as such, the natural logarithms of the data were used in subsequent analyses.

Intra- and interindividual sources of variation in exposure levels. To assess the intra- and interindividual sources of variation in airborne measures of exposure to mercury, we applied a one-way random-effects model (*22*). For the biological monitoring data, we applied a mixed-effects model to evaluate possible differences that may have arisen from a change in laboratories in mid-1994. Briefly, the mixed model is specified as follows:

$$Y_{ijk} = \ln(X_{ijk}) = \mu_Y + \alpha_i + \beta_j + \varepsilon_{ijk} \qquad [1]$$

for i = 1 (1990–June 1994) or 2 (July 1994–1997) time periods, j = 1,2, …, b workers, k = 1, …, n_j measurements per worker, and where

X_{ijk} = the exposure concentration for the jth worker on the kth day during the ith period,

Y_{ijk} = the natural logarithm of the exposure concentration,

μ_Y =the overall mean (mean of Y_{ijk}),

α_i = the fixed effect due to the measurement having been collected during the ith period,

β_j = the random effect measuring the deviation of the jth worker's true exposure from ($\mu_Y + \alpha_i$), and

ε_{ijk} = the random effect measuring the deviation of the jth worker's exposure from ($\mu_Y + \alpha_i + \beta_j$) on the kth day during the ith period.

It is assumed that the α_i values sum to zero and thus have a population variance defined as

$$\sum_{i=1}^{a} \alpha_i^2 / a - 1$$

where a = 2 in our two-period situation. It is further assumed that β_j and ε_{ijk} are mutually independent and normally distributed with zero means and variances σ_B^2 and σ_W^2, respectively. Thus, σ_B^2 and σ_W^2 represent the interindividual and intraindividual variance components. It follows that

$E(Y_{ijk}) = \mu_Y + \alpha_i$ for all i, j, k;

$\mathrm{Var}(Y_{ijk}) = \sigma_B^2 + \sigma_W^2$ for all i, j, k;

and

$\mathrm{Cov}(Y_{ijk}, Y_{ijk'}) = \sigma_B^2$ for $k \neq k'$ and for all i, and j.

For the air, blood, and urinary mercury data, analyses were run separately on each occupational group of workers and on all workers combined. Restricted maximum likelihood estimates of the variance components were obtained using PROC MIXED available with SAS software (SAS Institute, Cary, NC).

Effects of measurement error on accurate estimation of regression coefficients. To assess the influence of measurement error in air or biological levels of mercury, we constructed a hypothetical scenario in which estimates of average levels of the log-transformed mercury values in air, blood, or urine for each worker were used to examine the relation with a continuous health outcome measure (e.g., neuropsychologic deficits or changes in renal function). It was further assumed that there were no other explanatory variables to consider as covariates in the linear model; as such, a simple linear regression model could be applied to examine the exposure–response relation.

Under the standard assumptions that underlie simple (unweighted) linear regression analysis (*23*), the expected value of the observed slope coefficient $E(\hat{\beta})$ can be expressed as follows (*24*):

$$E\left(\hat{\beta}\right) = \beta\left(\frac{1}{1 + \lambda/n}\right), \qquad [2]$$

where β is the true slope coefficient, λ is the ratio of the intra- and interindividual variance components for the exposure variable (i.e., $\lambda = \sigma_W^2/\sigma_B^2$), and n is the number of measurements obtained from each worker. Except in instances when the intraindividual variance component is zero, the observed slope coefficient (under expectation) is smaller than the true coefficient [i.e., $E(\hat{\beta})/\beta < 1$]. For example, if only single measurements were available for each worker, the observed slope obtained from a regression analysis would be one-half as large as the true slope when the intra- and interindividual variances are equal to one another (λ = 1). Following algebraic manipulation, Equation 2 can be easily rearranged to estimate samples sizes (n) that would be necessary to minimize the attenuation of an observed slope coefficient [$E(\hat{\beta})/\beta$] to specified levels.

Effects of measurement error on accurate estimation of regression coefficients. Relying on estimates of the variance components

obtained from the models ($\hat{\sigma}^2_W$ and $\hat{\sigma}^2_B$), sample sizes were estimated to minimize the attenuation of an observed slope coefficient to 90%, 75%, and 60% of the true value. Assessments were made separately for mercury in air, blood, and urine for each group, as well as for all workers across job categories. All statistical analyses were performed using SAS software (SAS Institute).

Results

Compilation of the database. Although information on lifestyle factors was not available, there were relatively few differences in the mean age of workers across job groups in our study (data not shown). During this period, 282 air measurements were collected on 42 workers. Far greater numbers of blood (n = 646) and urine samples (n = 955) were collected. Among all workers, the median number of repeated measurements was 4 air samples, 6 blood samples, and 13 urine samples. The arithmetic means ± 1 SD for air, blood, and urinary mercury levels during this 7-year period were 22 ± 35 μg/m^3, 30 ± 23 nmol/L, and 10 ± 9 μg/g creatinine [79 ± 66 nmol/L], respectively. Correspondingly, the geometric means (geometric SD) were 12 μg/m^3 (2.8) for airborne mercury, 24 nmol/L (2.8) for blood mercury, and 8 μg/g creatinine (2.1) [59 nmol/L (2.2)] for urinary mercury. Nearly 62% of the air measurements were performed for maintenance workers, whereas most blood and urine mercury samples were collected from shift workers, cell hall maintenance workers, and non-cell hall workers. When workers were classified by occupational category, the highest and lowest exposures were typically observed for the cell hall maintenance workers and shift workers, respectively.

Intra- and interindividual sources of variation in exposure levels. Point estimates of the variance components in the log-transformed air, blood, and urinary mercury data are shown in Table 1. For airborne mercury, the proportion of the total variability attributable to the intraindividual source of variation differed among groups. Cell hall maintenance workers and shift workers were characterized by extreme day-to-day variability; little variation was detected between workers. There appeared to be as much or greater variation among individuals compared to variation across shifts in both the cell hall production workers and non-cell hall workers. There was greater variation between, rather than within, workers for the biomonitoring data when all workers were combined, whereas equivocal results were obtained when the analyses were conducted by occupational group. Based on the mixed-model analyses, exposure levels appeared to decrease in the latter period (mid-1994 onward), especially for urinary mercury levels (data not shown).

Table 2 shows the estimates of the number of repeated measurements per worker required to minimize the attenuation of an observed slope coefficient to 90%, 75%, and 60% of its true value for air, blood, and urinary measures. When workers were evaluated together irrespective of occupational category, the sampling requirements were reduced for mercury measured in blood or urine as compared to those for air. Across occupational groups, the sampling demands varied, and in some instances sizeable differences were noted.

Discussion

Effects related to intraindividual variation have long been recognized in the statistical and epidemiologic literature (*10,11*). However, the quantification of the inter- and intraindividual sources of exposure variability in the occupational arena has focused primarily on airborne contaminant levels (*22,25–27*). Similar investigations of variation in biological measures of exposure to workplace contaminants have, to our knowledge, been restricted to a single study of workers exposed to styrene at a boat manufacturing plant (*3*). In our study we found that a substantial percentage of the variability in airborne mercury levels was due to day-to-day variation, which was nearly 50% or higher in all groups of workers. This finding is in agreement with an investigation of variability in airborne contaminants across a broad cross-section of workplaces worldwide (*22*). Our results also confirm that fluctuations of daily airborne mercury levels are smoothed in both the body burdens of mercury in blood and, to a greater extent, to that in urine. Given that the damping of variability in air exposures is highly dependent on the contaminant's half-life in the body (*28*), these results are consistent with the underlying kinetics of mercury in blood and in urine, with slow elimination phases of several weeks and 2–3 months (*29–31*), respectively.

Based on kinetic considerations alone, urinary mercury may be deemed a superior measure relative to blood mercury because exposures are integrated over longer periods (*32*). Yet our results for the entire group of chloralkali plant workers indicate that similar numbers of measurements would be required if blood or uncorrected urinary mercury were used to estimate individual workers' mean levels in a regression analysis (Table 2). Because variations in urinary flow rate (e.g., due to variable water intake) increase the variability in urinary mercury concentrations in spot samples (*33*), creatinine-corrected urinary mercury produced less variable results and thus yielded the expected benefits when compared to mercury in blood. Nevertheless, in situations when the primary aim of biological monitoring is to detect temporary peak exposures rather than to assess the long-term body burden of mercury, mercury in blood would be a superior measure, owing to the damping of such peaks in urinary levels.

Table 1. Inter- and intraindividual sources of variation ($\hat{\sigma}^2_B$ and $\hat{\sigma}^2_W$) for log-transformed air, blood, and urinary mercury data collected on Swedish chloralkali plant workers during 1990–1997.

	n	b[a]	Median n_j	$\hat{\sigma}^2_B$	$\hat{\sigma}^2_W$	$\hat{\lambda}$[b]
Airborne Hg (μg/m^3)						
Shift workers	56	17	4	0.09	0.70	7.9
Cell hall production workers	19	4	4	0.56	0.46	0.83
Cell hall maintenance workers	174	15	9	0.06	0.82	13
Non-cell hall workers	33	8	3	0.50	0.50	1.00
All workers	282	42	4	0.39	0.74	1.9
Blood Hg (nmol/L)						
Shift workers	185	38	5	0.06	0.23	4.16
Cell hall production workers	76	6	13	0.13	0.10	0.81
Cell hall maintenance workers	176	18	7	0.14	0.17	1.27
Non-cell hall workers	209	30	7	0.36	0.23	0.65
All workers	646	87	6	0.23	0.20	0.87
Urinary Hg (nmol/L)[c]						
Shift workers	472	41	14	0.08	0.18	2.41
Cell hall production workers	49	6	8	0.04	0.11	2.95
Cell hall maintenance workers	130	17	4	0.05	0.23	4.33
Non-cell hall workers	296	30	9	0.31	0.31	1.01
All workers	947	88	13	0.32	0.23	0.73
Urinary Hg (μg/g creatinine)						
Shift workers	474	41	14	0.05	0.11	2.2
Cell hall production workers	49	6	8	0	0.08	–
Cell hall maintenance workers	130	17	4	0.08	0.12	1.6
Non-cell hall workers	302	30	8	0.32	0.19	0.59
All workers	955	88	13	0.32	0.14	0.45

Abbreviations: n, total number of measurements; b, number of workers; n_j, number of repeated measurements per worker. [a]A few workers held more than one job title over the study period. [b]$\hat{\lambda} = \hat{\sigma}^2_W / \hat{\sigma}^2_B$. [c]In a few instances, the lab reports indicated urinary mercury levels only in units of micrograms per gram creatinine. Thus, there were slightly fewer uncorrected measurements (nanomoles per liter) compared to the creatinine-corrected values.

The proportion of the intraindividual variability to the total variance generally decreased in levels of mercury in blood or urine when compared to air mercury levels. A notable exception was the group of shift workers for which the percentage of variation attributable to intraindividual variability was higher in biological levels (especially in blood mercury) as compared to airborne levels. In this group, the geometric mean level of blood mercury (reflecting both inorganic and organic mercury exposure) was 18 nmol/L, which is only slightly higher than that found in the general Swedish population (*34,35*). It is likely that the greater intraindividual variation relative to the total variability in blood mercury levels in shift workers is due to fluctuations in exposures from nonoccupational sources (primarily from contaminated fish and amalgam fillings) (*35*), which play a bigger role in influencing body burdens of contaminants when workplace exposures are low.

Relying on quantitative estimates of the intra- and interindividual sources of variation in exposure to mercury as measured in the air, blood, and urine among workers at a Swedish chloralkali plant, we also evaluated effects on regression results should such data be used to examine long-term health effects associated with mercury exposure. As shown in Figure 1, our results suggest that the underestimation of the regression coefficient can be substantial when limited numbers of measurements are collected (although the benefits of collecting additional measurements diminish with increasing sample size). Although requisite sample sizes are not the only factor to consider when evaluating exposure measures, estimating the distribution of measurement errors and quantifying differences among measures provide invaluable information that can be used to plan future investigations.

Although random and mixed-effects models offer clear advantages when evaluating the nature of workplace exposures, important questions must be addressed related to the variance–covariance structure of the data. In the statistical models that were applied, we assumed that the covariance between measurements collected on the same worker was the same regardless of the interval separating them. Shift-long airborne samples were often collected repeatedly on the same worker over the course of a few days, but studies have indicated relatively little serial correlation in air monitoring data (*36–38*). Biological monitoring data may lack independence; however, the extent to which such data are autocorrelated will be a function of both the half-life of the contaminant in the body and the timing of sampling. In our study, when the interval between measurements for each individual was computed, we found that only 10% of the urinary data were < 4 months apart. Likewise, only 1% of the blood measurements was collected at intervals of ≤ 1 month. Thus, errors associated with an improper specification of the variance–covariance structure are unlikely to have affected our results.

Another issue related to the proper specification of the model when data across occupational groups are combined stems from the assumption that the intraindividual variance was the same for all groups of workers. Based on our stratified analyses, it appears that the magnitude of the intraindividual variance varies by occupational group. Thus, the assumption of variance homogeneity may be violated when data across groups are combined. Although some effects related to the misspecification of variance components models have been evaluated (*39*), the robustness of such models when underlying assumptions are violated warrants further investigation.

Finally, our investigation focused on an exposure assessment strategy that relies on an individual-based approach in which each individual worker's exposure is evaluated. Should a group-based approach be adopted instead, study questions may be focused either on evaluating the individual group mean exposure levels (in which case the mixed-effects model would evaluate job group as a fixed effect) or on assessing the degree of variability across groups (in which case the mixed-effects model would evaluate job group as a random effect). Questions related to the relative merits of both approaches are being evaluated in another investigation.

Whether biological monitoring offers advantages compared to air monitoring depends on kinetic factors as well as on the relative magnitude of the inter- and intraindividual sources of variation in each exposure measure. It is interesting to note that Rappaport et al. (*3*) found that personal sampling measurements of airborne styrene

Table 2. The number of measurements per worker that would be required to obtain an observed slope coefficient that is 90, 75, and 60% of the true value.[a]

	90%	75%	60%
Airborne Hg (μg/m^3)			
Shift workers	71	24	12
Cell hall production workers	7	2	1
Cell hall maintenance workers	119	40	20
Non-cell hall workers	9	3	1
All workers	17	6	3
Blood Hg (nmol/L)			
Shift workers	37	12	6
Cell hall production workers	7	2	1
Cell hall maintenance workers	11	4	2
Non-cell hall workers	6	2	1
All workers	8	3	1
Urinary Hg (nmol/L)			
Shift workers	22	7	4
Cell hall production workers	27	9	4
Cell hall maintenance workers	39	13	7
Non-cell hall workers	9	3	2
All workers	7	2	1
Urinary Hg (μg/g creatinine)			
Shift workers	20	7	3
Cell hall production workers[b]	–	–	–
Cell hall maintenance workers	15	5	2
Non-cell hall workers	5	2	1
All workers	4	1	1

[a]Slope coefficient estimated from a simple linear regression relating mercury exposure to a continuous health outcome. [b]No calculation was possible given that $\hat{\sigma}^2_B = 0$.

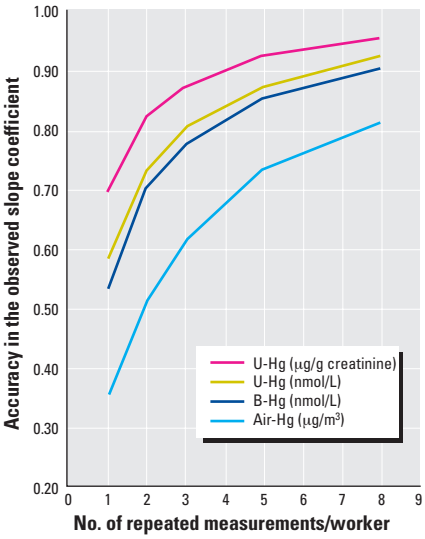

Figure 1. Accuracy in the observed slope coefficient as a function of the number of measurements collected on each worker for the log-transformed air (Air-Hg), blood (B-Hg), and urinary mercury (U-Hg) data collected on Swedish chloralkali workers during 1990–1997 (see Equation 2 in text). The estimated ratio of the intra- to interindividual variance component ($\hat{\lambda}$) was 1.9 for Air-Hg, 0.87 for B-Hg, 0.73 for uncorrected U-Hg, and 0.45 for creatinine-corrected U-Hg.

yielded the least biased measure when compared to measurements of styrene in exhaled air among boat-manufacturing workers, whereas one of the biological measures of exposure performed the most efficiently in the current investigation. In any case, our investigation demonstrates that quantitative information about intra- and interindividual sources of variation in exposure can be used to design efficient sampling strategies when evaluating health risks associated with workplace or environmental contaminants.

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