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Assessment of Variability in Biomonitoring Data Using a Large Database of Biological Measures of Exposure

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Although intra- and interindividual sources of variation in airborne exposures have been extensively studied, similar investigations examining variability in biological measures of exposure have been limited. Following a review of the world's published literature, biological monitoring data were abstracted from 53 studies that examined workers' exposures to metals, solvents, polycyclic aromatic hydrocarbons, and pesticides. Approximately 40% of the studies also reported personal sampling results, which were compiled as well. In this study, the authors evaluated the intra- and interindividual sources of variation in biological measures of exposure collected on workers employed at the same plant. In 60% of the data sets, there was more variation among workers than variation from day to day. Approximately one-fourth of the data were homogeneous with small differences among workers' mean exposure levels. However, an almost equal number of data sets exhibited moderate to extreme levels of heterogeneity in exposures among workers at the same facility. In addition, the relative magnitude of the intra- to interindividual source of variation was larger for biomarkers with short compared to long half-lives, which suggests that biomarkers with half-lives of 7 days or longer exhibit physiologic dampening of fluctuations in external levels of the workplace contaminant and thereby may offer advantages when compared to short-lived biomarkers or exposures assessed by air monitoring. The use of biological indices of exposure, however, places an additional burden on the strategy used to evaluate exposures, because data may be serially correlated as evidenced in this study, which could result in biased estimates of the variance components if autocorrelation is undetected or ignored in the statistical analyses.

Keywords: biomarkers, exposure variability, interindividual source of variation, intraindividual source of variation, variance components

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In making comparisons between air and biological monitoring, biomonitoring offers distinct advantages. Biological measures integrate exposure due to all routes of entry, account for individual differences in the underlying kinetics of the contaminant and reflect both nonoccupational and occupational sources of exposure.[1] Notwithstanding these advantages, biomarkers are invasive, may be expensive to collect and analyze, and may lack specificity for exposure to a single contaminant. In contrast to airborne contaminants, which have been the focus of numerous investigations,[2–15] fewer studies have examined the intra- and interindividual sources of variability in biological measures of exposure.[1,16–20] This lack of information about the degree to which biological levels of contaminants or their metabolites vary over time and among workers limits the overall comparison that can be made between air and biological monitoring.

In general, the variation in levels of contaminants or their metabolites in bodily fluids is affected by fluctuations in airborne exposures and

by physiologic factors related to the uptake, distribution, and elimination of the contaminant.[20] Although air levels of contaminants are often characterized by extreme variation over time,[5] the extent to which the variation in the external exposure is transmitted to levels of the contaminant in the body depends on its half-life.[21] As compared with the variation in air levels, fluctuations in levels of biomarkers with short half-lives predominantly reflect environmental variation over time, whereas there is physiological dampening of variability in biomarkers with longer half-lives.[20] However, biological variation plays a role as well, which may become important when external levels of airborne contaminants vary little from day to day or when there is considerable smoothing of variability as is the case for biomarkers with long half-lives. With respect to interindividual variability in biomarker levels, differences in the external exposure received by workers; effects due to ethnicity, gender, and age; anthropometric and lifestyle factors; and physiologic differences in the rates of uptake, distribution, and elimination are all likely to play a role.

Although the relative magnitude of the intra- and interindividual sources of variation in exposure provides valuable information that can be used for a multitude of purposes,[2] the implications of variability depend on the approach that is used to assess workers' exposures. On the one hand, if exposures were to be evaluated for each worker, it is desirable to select an exposure measure in which the interindividual source of variation is (much) greater than the intraindividual source of variation. In this way, differences among workers' exposure levels are maximized relative to the variation that occurs from day to day, which would minimize effects of intraindividual variation on measures of effect.[22] Thus, it is expected that biomarkers with longer half-lives would perform more efficiently because fewer measurements would be required to reliably estimate workers' exposures due to the physiologic dampening of variability in external levels of the contaminant. On the other hand, if exposures were to be evaluated on a group-by-group basis, it is desirable to minimize the heterogeneity in exposure levels among workers (relative to the degree of variability from day to day), so that the mean exposure for the group reasonably estimates exposures for all members of the group. Although homogeneity in exposure among workers in an occupational group (however classified) has been investigated in studies that have relied on personal sampling data,[2,6,8,9,11,14,23–25] this matter also warrants investigation when biological monitoring is used to assess workers' exposures.

Another issue that merits consideration in developing exposure assessment strategies that rely on biomonitoring data are questions that relate to autocorrelation. Because biological measurements on the same worker that are collected closer together in time may be more highly correlated than those collected further apart,[18] additional demands are placed on the analytical strategy to determine whether the data are serially dependent. Although accounting for serial correlation adds some complexity to an exposure assessment, it enhances the ability to make meaningful statements about workers' exposures.[26]

Due to the scarcity of studies that have examined variability in biological measures of exposure to workplace contaminants, this investigation was conducted to develop a database of biological measurements that had been collected repeatedly on groups of workers who share common work environments and to quantify the intra- and interindividual sources of variation in each group. A secondary objective was to evaluate the degree of homogeneity in exposure among workers employed at the same plant. Given that biomarkers with longer half-lives average external exposures received over time and that repeated measurements of biomarkers may be serially correlated, a final objective was to assess the influence of half-life on the relative magnitude of the sources of variation and to evaluate autocorrelation in the biological monitoring data.

METHODS

Compilation of the Database

To compile a database of repeated biological measurements collected on different groups of workers from a broad cross-section of industries worldwide, a comprehensive review of primary journals in the occupational hygiene and occupational medicine fields was undertaken. Seven journals were searched from their inception through March 2000 to identify published sources of raw data: *American Industrial Hygiene Association Journal*; *American Journal of Industrial Medicine*; *The Annals of Occupational Hygiene*; *Applied Industrial Hygiene* (now *Applied Occupational and Environmental Hygiene*); *British Journal of Industrial Medicine* (now *Occupational and Environmental Medicine*); *International Archives of Occupational and Environmental Health*; and *Scandinavian Journal of Work Environment and Health*. Additional journals in related fields were searched through December 1998: *Archives of Environmental Health, Environmental Health Perspectives, Journal of Occupational Medicine* (now *Journal of Occupational and Environmental Medicine*), and *The Journal of the Society of Occupational Medicine* (now *Occupational Medicine*). References of studies used to compile the database or otherwise identified in the literature review were evaluated to identify additional publications that might have reported suitable data.

To be included in the database, at least 10 measurements collected on a minimum of five workers employed at the same plant had to be available. Exceptions were made for a few studies that provided extensive data on four workers each.[27–31] Data in either graphical or tabular formats were acceptable. If personal shift-long sampling results were reported, the air measurements were compiled if they met the same restriction criteria as those applied to the biological monitoring data. One exception was made for a data set that contained short-term personal sampling measurements collected simultaneously with exhaled air measurements.[32] The limit of detection (LOD) for the monitoring data was abstracted if reported in the individual studies. Data sets that had more than one-third of the measurements less than the LOD were excluded. All nondetectable measurements were assigned a value equivalent to $1/\sqrt{2}$ of the LOD, as recommended by Hornung and Reed.[33]

In addition to the exposure measurements, details about the industry, the airborne contaminant, the sampling protocol, and the worker were abstracted from the individual studies (Table I). Some information was coded for all data sets, including unique identifiers for data set, worker, industry, and plant, as well as details about the airborne exposure and the biological measurements that had been collected. Industry was classified by International Standard Industrial Classification (ISIC) coding,[34] which was later collapsed into five categories: chemical manufacturing, coke/petroleum manufacturing, other manufacturing, agriculture/forestry, and miscellaneous industries. Country of origin was coded for each data set and used to define four broad geographical locations: Scandinavia, United States, Western Europe, and all other countries. The level of detail regarding when measurements were collected varied widely, with some studies reporting the exact date or year and others giving the day without respect to calendar time (e.g., Day 1, Day 2, Day 3). The duration of personal sampling

TABLE I. Information Related to the Industry, Facility, Exposure Measure, Sampling Protocol, and Worker That is Included in the Biological and Air Monitoring Database

Variable	Description
Industry/Facility	
Set	unique data set number
Industry	description of industry
Industrial classification	International Standard Industrial Classification (ISIC) code
Country	country of origin where the data were collected
Plant	plant description
Plant code	plant code
Building	building description
Building code	building code
Biological/Airborne Measure	
Workplace contaminant	airborne exposure (agent)
Type of airborne exposure	gas; vapor; aerosol; liquid; combination
Agent measured	airborne or biological contaminant measured in the study
Type of exposure measure	biological measure; airborne measure
Half-life	estimated half-life of the measured contaminant in the body
Concentration	measured concentration
Units	concentration units (e.g., ppm)
Limit of detection	below detection limit; at or above detection limit
Analytical method	information about the analytical method used
Sampling Protocol	
Length	duration of airborne measurement (hours)
Time	time of measurement: preshift; postshift; during shift; etc.
Weekday	day of the week (Monday, Tuesday, etc.)
Date	date of measurement
Day	day number (1, 2, . . .)
Shift	shift number (1, 2, . . .)
Week	week number (1, 2, . . .)
Month	January, February etc. or 1, 2, . . ., if name of month not given
Season	preseason; Season 1; Season 2
Year	year of measurement
Worker Information	
Worker ID	unique identifier for each worker
Job title	job title of worker
Age	age of worker
Gender	female; male
Smoking habits	number of cigarettes smoked per day
Smoker status	nonsmoker; smoker
Respiratory protection	use of respiratory protection: no; yes

(hours) and the time of day the biological samples were collected (preshift, during shift, end-shift or postshift) were also added to the database. To the extent that data were available, information about the worker's job title, age, gender, smoking status, and respirator use was coded when provided in the original studies. Data were input into the spreadsheet program MS Excel® (Microsoft Corp., Redmond, WA) and then combined into one large SAS (SAS Institute, Inc., Cary, NC) database.

The half-lives for the biomarkers represented in the database were abstracted from the original studies, where available, or obtained from the literature (using MEDLINE, the IARC Monograph series,[35–41] the ATSDR Toxicological Profile series,[42–52] and references in the original studies). Information was available for all biomarkers except for urinary s-methylcysteine and sister-chromatid exchanges. In a preliminary analysis, the data were stratified into three categories on the basis of half-life (less than 7 days, 7 days–4 weeks, and greater than 4 weeks). Because many more groups had been monitored using biomarkers with half-lives of less than 1 week (n=71 sets) compared with either of the other classifications (n=30 and 17, respectively), the latter two categories were collapsed. Thus, for the stratified analyses in the current study, the biomarkers were classified on the basis of either a "short" (less than 7 days) or "long" (7 days or longer) half-life (see Appendix A). For a majority of biomarkers, one-compartment models had been used to describe the toxicokinetics of the contaminants (or their metabolites) in the body, which provided estimates of the half-lives that were subsequently classified as either "short" or "long." When both one- and multicompartment models had been applied, using a multicompartment model instead of a one-compartment model resulted in the same classification of the half-life for all contaminants except urinary chromium. Estimates of the half- life for this contaminant under a one-compartment model (4–10 hours[44] or 15–41 hours[53]) appeared to reflect only the fast phase of elimination; the three-compartment model for urinary chromium yielded half-life estimates of 7 hours, 15–30 days, and 3–5 years.[53] Because 60% of the chromium is eliminated in the latter two compartments of the three-compartment model,[53] urinary chromium was categorized as having a "long" half-life. When only multicompartment models had been applied, the categorization of the half-life was straightforward with one exception. For mercury in the blood, 50% of the mercury is attributed to the fast phase of elimination and 50% to the slow phase, with half-lives of 3.8 and 45 days, respectively.[46] As such, the half-life for blood mercury was classified as "long."

Evaluation of Intra- and Interindividual Sources of Variation in Exposure

Although the database contains both air and biological monitoring data, the evaluation of the sources of variation in exposure in the current investigation was restricted to the biological measurements. In preliminary analyses, lognormality was assessed visually by examining the histograms of the biological measurements for each data set. The majority of the data appeared to be approximately lognormally distributed; thus, all subsequent analyses were run on the natural logarithms of the biomarker concentrations. To evaluate stationarity in the mean exposure levels over the period during which workers were monitored,[54] the plots of the concentration values versus time were inspected for sets of data collected over three or more time points, of which only 12 were collected over a 1-year or longer period. In addition, the original studies were reviewed to determine whether evidence was provided that exposure levels had changed over time. Based on both assessments, the majority of the data appeared to be stationary. For 17 cases in which exposure levels may have changed over time, such changes could not be formally evaluated in the models that were applied because of insufficient data.

To quantify the intra- and interindividual sources of variation in exposure, a one-way random-effects model was applied to the

biological measurements collected on each group of workers. This model has been well described in the literature both for air[5] and biological[18] monitoring data. Using previous notation[18] where Y_{ij} represents the concentration of the biological measurement (on a logarithmic scale) for worker i collected on day j, the total variation in exposure (σ_Y^2) is partitioned into a component of variation in mean exposure levels among workers (σ_B^2, the between-worker variance component), and a component of variation in exposures from one time period to the next (σ_W^2, the within-worker variance component). In this study two covariance structures for measurements collected on the same individual were considered: (1) a compound symmetric error structure and (2) a first-order autoregressive [AR(1)] error structure. Under compound symmetry (CS), it is assumed that the correlation between measurements collected on the same worker is the same irrespective of the time interval separating them. Thus, $\mathrm{Cov}(Y_{ij}, Y_{ij'}) = \sigma_B^2$ and $\mathrm{Corr}(Y_{ij}, Y_{ij'}) = \sigma_B^2/\sigma_Y^2$ for $i = i$ and $j \neq j'$. With an AR(1) error structure, on the other hand, the correlation between measurements collected on the same individual is a function of the interval separating them.[18] Here, the correlation function decays exponentially as the interval between measurements increases (i.e., $\rho^\tau = \alpha^\tau$, where τ is the number of time units between measurements). Thus, $\mathrm{Cov}(Y_{ij}, Y_{ij'}) = \sigma_B^2 + \rho^\tau\sigma_W^2$ and $\mathrm{Corr}(Y_{ij}, Y_{ij'}) = (\sigma_B^2 + \rho^\tau\sigma_W^2)/\sigma_Y^2$ for $i = i$ and $j \neq j'$.

To identify data that were possibly serially correlated, the average interval between all pairs of measurements collected on the same worker was calculated for each set. A random-effects model with an AR(1) error structure was then applied to data sets that met the following criteria: (1) biological monitoring of five or more workers had occurred on a minimum of five occasions and (2) the average interval between measurements (computed first by individual and then across all workers in the group) was less than the estimated half-life for the biomarker. PROC MIXED from the SAS system software (SAS Institute, Inc.) was used to obtain restricted maximum likelihood estimates of the within- and between-worker variance components ($\hat{\sigma}_W^2$ and $\hat{\sigma}_B^2$) under both error structures and the autocorrelation parameter ($\hat{\rho}^\tau$), which was evaluated at a significance level of 0.05.

Homogeneity of Exposure Within Groups

Relying on estimates of the between-worker variance component ($\hat{\sigma}_B^2$), the ${}_BR_{0.95}$ value,[23] which is defined as the ratio of the 97.5th to the 2.5th percentile of the distribution of individual workers' mean exposures [i.e., ${}_BR_{0.95} = \exp(3.92 \times \hat{\sigma}_B]$, was computed for each group. As recommended by Rappaport,[23] a cut point of 2 was used to define a group of workers with homogeneous exposures.

RESULTS

Compilation of the Database

In total, the literature review yielded 53 articles that were published from 1963–2000 (Table II). The majority of studies were published in the *International Archives of Occupational and Environmental Health* (9 articles), *The Annals of Occupational Hygiene* (6 articles), *American Industrial Hygiene Association Journal* (5 articles), *Archives of Environmental Health* (5 articles), *Occupational and Environmental Medicine* (or *British Journal of Industrial Medicine*) (5 articles), *Scandinavian Journal of Work Environment and Health* (4 articles), and *Journal of Occupational Medicine* (3 articles). In a couple of studies that did not report the raw data therein,[80,98] the biological measurements had been obtained previously in the compilation of a large database of personal exposure measurements.[5]

The basic characteristics of the database are summarized in Table III. More than 4000 measurements collected on 577 workers in 55 workplaces are contained in the biological database alone, which represents a wide range of biomarkers collected in blood, urine, and exhaled air. In some workplaces more than one biomarker was used to evaluate exposure in the same group of workers and, in several instances, the same biomarker was evaluated at different times during the course of a day (e.g., pre- and postshift)

TABLE II. Airborne Contaminants and Corresponding Biomarkers Represented in the Database

Airborne Contaminant	Biomarker(s)
Allyl chloride[55]	urinary allylmercapturic acid (ALMA)
Arsenic[56,57]	urinary arsenic (As), methylarsonic acid (MMA), dimethylarsinic acid (DMA), trimethylarsenic compounds
Arsenic trioxide[58]	urinary inorganic As + MMA + DMA
Cadmium[59,60]	urinary cadmium, blood cadmium
Carbon black[61]	urinary 1-hydroxypyrene
Carbon disulfide[62]	urinary 2-thiothiazolidine-4-carboxylic acid (TTCA)
Chlorinated phenolic sapstain[63]	urinary tetrachlorophenol (TCP), pentachlorophenol (PCP)
Chromic acid[64]	urinary chromium
Chromium[65-67]	urinary chromium, sister-chromatid exchanges (SCEs), blood chromium
DDT[68]	urinary dichlorodiphenylacetic acid (DDA)
Dimethylarsinic acid[69]	urinary arsenic, blood arsenic
Ethylene oxide[32]	ethylene oxide in blood and alveolar air
Lead[70–78]	urinary lead, urinary δ-aminolevulinic acid (ALA), blood lead, erythrocyte protoporphyrin (EP), ALA dehydratase (ALAD)
Inorganic mercury[27,28,79–81]	blood mercury, urinary mercury
Methyl chloride[82]	urinary S-methylcysteine
4,4′-methylenedianiline[83]	urinary 4,4′-methylenedianiline (MDA)
Nickel[84–85]	urinary nickel
Nickel sulfate and chloride[30]	urinary nickel; plasma nickel
Parathion[86]	plasma cholinesterase, red blood cell cholinesterase, urinary p-nitrophenol
Polycyclic aromatic hydrocarbons[31,87–92]	urinary 1-hydroxypyrene, urinary 1,2-dihydroxy-1,2-dihydropyrene, various urinary phenanthrenes
Styrene[93–97]	alveolar air styrene; blood styrene; urinary mandelic acid (MA), phenylglyoxylic acid (PGA), MA + PGA; O^6-styrene-guanine lymphocyte adducts
Tetrachloroethylene (PERC)[98]	mixed exhaled air PERC
Toluene[29,99]	alveolar air toluene, blood toluene, urinary hippuric acid
Toluene diisocyanate[100,101]	plasma 2,4-toluenediamine (TDA), plasma 2,6-toluenediamine

TABLE III. Characteristics of the Air and Biological Monitoring Database

	Air Monitoring Data	Biological Monitoring Data
Number of studies	23	53
Number of occupational groups	23	55
Number of data sets[A]	43	121
Number of workers	192	577
Number of agents (air contaminants)	14	24
Number of total measurements	1847	4327
Number of measurements less than the LOD	11	43
Number of data sets containing LOD values	2	13
Range in the number of workers per group	4–20	4–44
Range in the number of measurements per worker	1–40	1–36
Range in the number of measurements per group	10–592	10–226

[A]Because some groups of workers were monitored with multiple measures of exposure or, in the case of the biological monitoring data, with the same biomarker collected at different times of the day or expressed in different concentration units, the number of data sets exceeds the number of groups.

TABLE IV. Number of Data Sets (%) in the Database Stratified on the Basis of Industry, Geographical Location, Type of Exposure, and Characteristics Related to the Sampling Regimen

	Airborne (n = 43)	Biological (n = 121)
Industry		
Agriculture and forestry	0	11 (9.1%)
Coke and petroleum manufacturing	22 (51.2%)	16 (13.2%)
Chemical manufacturing	7 (16.3%)	30 (24.8%)
Other manufacturing	9 (20.9%)	46 (38.0%)
Miscellaneous industries	5 (11.6%)	18 (14.9%)
Geographical Location		
Western Europe	26 (60.5%)	44 (36.4%)
Scandinavia	8 (18.6%)	33 (27.3%)
United States	7 (16.3%)	31 (25.6%)
Other (Eastern Europe, Chile, Japan, West Indies)	2 (4.7%)	13 (10.7%)
Type of Exposure		
Gases/vapors	13 (30.3%)	36 (29.8%)
Aerosols	7 (16.3%)	56 (46.3%)
Liquid (dermal)/combination	23 (53.5%)	29 (24.0%)
Survey Length		
≤1 month	35 (81.4%)	74 (61.2%)
>1 month to 12 months	8 (18.6%)	33 (27.3%)
>1 year	0	14 (11.6%)
No. of workers		
≤7 workers	31 (72.1%)	61 (50.4%)
>7 workers	12 (27.9%)	60 (49.6%)
Measurements per Group		
≤25 measurements	30 (69.8%)	63 (52.1%)
>25 measurements	13 (30.2%)	58 (47.9%)
Average no. of Measurements per Worker		
≤3 measurements	11 (25.6%)	52 (43.0%)
>3 measurements	32 (74.4%)	69 (57.0%)

Note: Percentages do not always add up to 100 due to rounding.

or expressed in different concentration units (e.g., micrograms per liter and micrograms per gram creatinine). Thus, 121 sets of data, which were collected on 55 groups of workers, are contained in the biological monitoring database. Because studies reporting the biological measurements did not always include personal sampling results, the air-monitoring database contains fewer measurements (1847) collected on a smaller number of workers (192). In some workplaces personal sampling was conducted for more than one contaminant. Thus, the air-monitoring database is comprised of 43 data sets, which were collected on 23 groups of workers. Altogether, the database contains 6174 measurements collected on 577 workers. Of these data only 54 measurements in 15 data sets had values below the LOD, which constitute a small fraction of the entire database (<1%).

Table IV displays a breakdown of the database stratified by industry, geographical location, type of exposure, and by characteristics related to the sampling regimen. The majority of the biological monitoring data arose in the manufacturing sector (13% from coke and petroleum manufacturing, 25% from chemical manufacturing, and 38% from other types of manufacturing) and originated in workplaces in Western Europe (36%), Scandinavia (27%), or the United States (26%). Although type of industry and geographical location were reported in all studies, far less information about the workers on whom measurements were collected was available. In the biological monitoring database, age was reported in 27 sets (22%), gender in 64 sets (53%), smoking status in 12 sets (10%), smoking habits in 21 sets (17%), and respirator use in 37 sets (31%) (data not shown).

Evaluation of the Intra- and Interindividual Sources of Variation in Exposure

Estimates of the geometric mean and the variance components obtained from the one-way random-effects model with a compound symmetric error structure for each of the biological data sets are listed in Appendix A. Nearly two-thirds of the data (73/121 data sets) exhibited more variation among workers than variation from day to day ($\hat{\sigma}_B^2 > \hat{\sigma}_W^2$). For biological contaminants with "long" half-lives, 34 of the 47 data sets (72%) were characterized by more variation among workers than variation from day to day compared with 37 out of 71 data sets (52%) for biomarkers with "short" half-lives.

In comparing the heterogeneity among workers employed at the same plant, it was found that 26% of the data sets were homogeneous, having a ${}_BR_{0.95}$ value ≤2 (data not shown). However, an almost equal number of data sets exhibited rather heterogeneous exposures among workers at each location with ${}_BR_{0.95}$ values of 20 or higher. Notably, extremely large differences in exposures among workers (i.e., ${}_BR_{0.95} \geq 111$) were observed in 5% of the data sets.

Evaluation of Serial Correlation

Table V compiles the results from the random-effects model with AR(1) error structure that was applied to 25 data sets. Evidence of serial correlation ($p<0.05$) was provided in 72% of the data. Among these data sets, point estimates of the autocorrelation parameter ranged from 0.25 to 0.99, which suggests moderate to substantial levels of serial correlation. In comparing the results of the random-effects model with compound symmetry (see Appendix A) to the model with an autocorrelated error structure, the differences suggest that ignoring serial correlation underestimates the within-worker variance, but overestimates the between-worker

TABLE V. Results from the One-Way Random-Effects Model With an AR(1) Error Structure Applied to a Subset of the Biological Monitoring Data

Group	Biomarker	First-Order Autocorrelation Coefficient (τ = 1 day)	$\hat{\sigma}^2_W$	$\hat{\sigma}^2_B$
4	plasma cholinesterase	0.85[A]	0.004	0.029
	red blood cell cholinesterase	0.97[A]	0.021	0.004
5	plasma cholinesterase	0.99[A]	0.057	0.043
	red blood cell cholinesterase	0.90[A]	0.007	0.003
6	plasma cholinesterase	0.87[A]	0.004	0.051
	red blood cell cholinesterase	0.95[A]	0.009	0.001
22	urinary arsenic	0.09	0.754	0.001
23	mixed exhaled air tetrachloroethylene	0.13	0.124	1.200
24	blood mercury	0.93[A]	0.336	0
26	urinary mercury	0.46	0.024	0.328
	blood lead	0.75[A]	0.011	0.034
	urinary lead	0.25[A]	0.091	0.139
	urinary δ-aminolevulinic acid	0.34[A]	0.249	0.242
28	urinary 1-hydroxypyrene	0.76[A]	0.504	~0
33	urinary chromium (7:00 a.m.)	0.62[A]	0.138	0.237
	urinary chromium (11:00 a.m.)	0.12	0.064	0.315
	urinary chromium (4:00 p.m.)	0.33	0.104	0.486
37	urinary 1-hydroxypyrene (preshift)	0.57[A]	0.374	~0
	urinary 1-hydroxypyrene (postshift)	0.54	0.422	0.352
38	plasma 2,4-toluenediamine	0.93[A]	0.079	0.088
	plasma 2,6-toluenediamine	0.98[A]	0.224	0
41	urinary 1-hydroxypyrene (preshift)	0.79[A]	1.348	~0
	urinary 1-hydroxypyrene (postshift)	0.14	0.315	1.168
46	urinary 1-hydroxypyrene	0.58[A]	1.257	0
49	blood mercury	0.69[A]	0.032	0.117

Note: Model applied to data sets consisting of measurements collected on five or more workers over a minimum of five occasions and where the average interval between measurements collected on the same individual was less than the estimated half-life for the biomarker.
[A]$p < 0.05$.

variance. These findings confirm previous results[18] and are consistent with known consequences of positively autocorrelated processes.[102]

DISCUSSION

The database compiled for this study is unique in that it represents a wide range of repeated biological measures of exposure to different airborne contaminants in a broad cross-section of industries worldwide. As such, the database provided an opportunity to quantify the intra- and interindividual sources of variation in workers' exposures as assessed by biological monitoring. The findings indicate that, in general, there was more variation among workers at the same plant than variation from day to day. In contrast, a majority of studies that have examined variability in airborne measures of exposure reported that the variation within workers was greater than that between workers. However, many of these earlier studies grouped workers by job title[4,12] or by both job title (or work area) and location[5,7,10,11,54] and it would be expected that workers who share the same job have more similar exposures than workers at the same location but with different jobs. Nonetheless, in those investigations (of airborne exposures) that grouped workers at the plant level, a larger between-worker variance component relative to the within-worker variance was reported in some,[1,3,8] but not all,[11,13,17,23] studies. Thus, differences in the classification schemes used to group workers offer only a partial explanation for the equivocal findings.

To facilitate comparisons with the one study[5] in which a sizable database of airborne exposure measurements was evaluated after classifying workers by job title and location, 54 sets of data in the database were evaluated that had information about workers' job titles. When a random-effects model with a compound symmetric error structure was applied to these data, 28 job groups (52%) were characterized by more variation among workers than variation from day to day. In contrast, the results from the air-monitoring database[4] indicated a much smaller percentage of groups [35 out of 165 groups (21%)] with a similar pattern of variability. In the current study the authors also stratified the data on the basis of half-life and determined that 15 of the 24 job groups (63%) that had been monitored with biomarkers with "long" half-lives exhibited more variation in exposure among workers than variation from day to day. This finding is consistent with the results obtained on the entire database (using "plant" to classify workers) in which 72% of the data sets comprised of biomarkers with half-lives of 7 days or more were characterized by greater variation between than within workers. Although these results suggest that the dampening of exposure variability in external levels of the contaminant depends on the half-life of the contaminant in the body, this issue will be more adequately addressed in a future investigation of sources of variability in air and biological monitoring data collected simultaneously on the same group of workers.

Although it is advantageous to maximize differences among workers' exposure levels in assessment strategies that estimate exposures for workers one by one, a group-based approach seeks to

minimize the differences in workers' exposure levels relative to the variation over time. It was found that a majority of groups (three-fourths) were heterogeneous ($_{B}R_{0.95,} \geq 2$), with approximately one-fourth of the data exhibiting 20-fold differences or greater among workers' mean exposure levels. The lack of homogeneity in exposure in a considerable proportion of groups is consistent with results reported previously for the large database of airborne exposure measurements.[5] Findings of the current study also support the view that observational approaches that rely on job titles or on common work environments may not necessarily establish groups of workers with similar exposures[2,24] and that quantitative methods are needed to evaluate the degree of homogeneity of exposures irrespective of whether the assessment relies on personal or biological monitoring.

Biological monitoring may place an additional burden on the sampling strategy or on the selection of the statistical model applied, because data may be serially correlated as evidenced in this study. Should autocorrelation go undetected or be ignored in the statistical analyses, the potential for biased estimates of the variance components raises the possibility of making important errors of inference about the relative magnitude of the sources of variation in exposure and thereby could hinder the ability to accurately assess exposure. Thus, investigators are encouraged to consider the potential for autocorrelation either in the design of a sampling strategy (in terms of the timing of measurements relative to the half-life of the contaminant or its metabolite in the body) or in the analyses of biological monitoring data that allow for comparisons of model results with different error structures.[18,22]

CONCLUSIONS

In summary, this study represents the first comprehensive evaluation of the intra- and interindividual sources of variability in biological monitoring data. In general, the results suggest that biological measures of exposure are characterized by more variability among workers employed at the same facility as compared with variability from day to day. However, the relative magnitude of the within- and between-worker variance components varied considerably across groups in that variability in some data sets was attributable almost entirely to differences among workers and, in other sets, the variability was largely due to random fluctuations from one time period to the next. Such findings underscore the importance of quantifying the within- and between-worker sources of variation in exposure to workplace contaminants, especially given the implications of variability when designing sampling strategies to assess workers' exposures.

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APPENDIX A. Estimates of the Geometric Mean and the Within- and Between-Worker Variance Components for 55 Groups of Workers Based on Results From the One-Way Random-Effects Model With a Compound Symmetric Error Structure

Group	Industry/Type of Plant	Biomarker[A]	Half-Life[B]	Time of Sampling	k[C]	N[D]	$\hat{\sigma}^2_B$	$\hat{\sigma}^2_W$	Geometric Mean[E]
1	copper smelting	U-arsenic	short		7	14	0.000	0.479	115 μg/l
2	copper smelting	Bl-lead	long		10	30	0.000	0.224	24.5 μg/100 ml
3	copper smelting	U-inorganic arsenic	short	postshift	11	22	0.176	0.035	53.4 μg/l
		U-methylarsonic acid	short	postshift	11	22	0.066	0.071	33.8 μg/l
		U-dimethylarsinic acid	short	postshift	11	22	0.028	0.040	140 μg/l
		U-trimethylarsenic compounds	short	postshift	11	22	1.153	0.303	14.9 μg/l
4	tobacco farm (#1)	plasma cholinesterase	long	p.m.	22	106	0.029	0.003	5.37 μmol/ml/min
		red blood cell cholinesterase	long	p.m.	22	160	0.013	0.013	11.0 μmol/ml/min
		U-p-nitrophenol	short	p.m.	10	28	0.842	1.271	0.032 μg/ml
5	tobacco farm (#2)	plasma cholinesterase	long	p.m.	11	55	0.091	0.009	5.55 μmol/ml/min
		red blood cell cholinesterase	long	p.m.	11	55	0.004	0.006	10.7 μmol/ml/min
		U-p-nitrophenol	short	p.m.	8	24	1.812	1.212	0.062 μg/ml
6	tobacco farm (#3)	plasma cholinesterase	long	p.m.	14	62	0.052	0.004	4.73 μmol/ml/min
		red blood cell cholinesterase	long	p.m.	14	62	0.003	0.006	12.0 μmol/ml/min
		U-p-nitrophenol	short	p.m.	8	21	0.000	1.733	0.037 μg/ml
7	printing	alveolar air toluene	short	postshift	11	28	0.000	0.706	7.11 μg/l
		Bl-toluene	short	postshift	11	28	0.000	0.528	0.103 mg/kg
		U-hippuric acid	short	postshift	11	32	0.049	0.065	1.55 g/l
8	hospital sterilizer unit	Bl-ethylene oxide	short	postshift	9	27	0.000	5.289	10.9 μg/l
		alveolar ethylene oxide	short	postshift	9	27	0.000	1.561	1.12 mg/m^3
9	DDT formulating plant	U-DDA (DDT equivalent)	long	postshift	15	26	1.014	0.190	0.172 ppm
10	hydroelectric power plant	U-MDA	short	24-hour sample	7	21	0.985	0.265	0.155 μmol/24 hrs
11	lead-acid storage battery manufacturing plant	Bl-lead	long		13	106	0.035	0.032	37.8 μg/100 g
12	manufacture of cadmium stabilizers and pigments	U-cadmium	long		13	39	0.037	0.295	25.07 μg/l
		Bl-cadmium	long		13	32	0.118	0.125	1.90 μg/100ml
13	sawmill	U-tetrachlorophenol	short		44	124	1.217	0.899	66.5 ppb
		U-pentachlorophenol	long		44	124	0.418	0.400	51.3 ppb
14	plastic boat factory	U-mandelic acid + phenylglyoxylic acid	short	4:00 p.m.	11	19	0.605	0.513	0.077 mmol/h
14		U-mandelic acid + phenylglyoxylic acid	short	9:00 p.m.	11	20	0.000	0.947	0.054 mmol/h
15	chromium plating	U-chromium	long	during shift	12	66	0.669	0.247	12.5 μg/g creatinine
		SCEs		during shift	12	66	0.022	0.009	7.75 SCEs/cell
16	manufacture of polyurethane foam	plasma 2,4-TDA	long	3:30 p.m.	6	12	0.463	0.028	0.798 ng/ml
		plasma 2,6-TDA	long	3:30 p.m.	6	12	0.881	0.002	2.28 ng/ml
17	coal liquefaction plant	U-1-hydroxypyrene	short	postshift	5	20	0.071	0.364	6.35 μmol/mol creatinine
18	coal liquefaction plant	U-1-hydroxypyrene	short	postshift	12	45	0.858	0.176	4.55 μmol/mol creatinine
19	electroplating factory	U-chromium	long	postshift	16	57	0.161	0.278	13.1 μg/g creatinine
20	police firing range	Bl-lead	long		7	18	0.000	0.055	2.04 nmol/l
21	bridge demolition	Bl-lead	long		9	32	0.027	0.021	4.02 μmol/l
22	forest service	Bl-arsenic	short	postshift	5	40	0.000	1.064	0.067 ppm
		U-arsenic	short	24-hour sample	5	40	0.001	0.754	92.5 μg/24 hrs
23	dry cleaning	mixed exhaled air PERC	short	postshift	13	57	2.004	0.116	1.50 ppm
24	dry alkaline battery plant	Bl-mercury	long	2 p.m.	10	42	0.297	0.045	1.60 μg/100 ml
		U-mercury	long	2 p.m.	10	46	0.338	0.018	39.0 μg/g creatinine
25	production of lead alkyl compounds	U-lead	long	during shift	5	30	0.016	0.080	0.165 mg/l
		U-ALA	long	during shift	5	30	0.238	0.286	0.119 mg/100 ml
26	alkyl lead manufacturing	Bl-lead	long	during shift	6	36	0.038	0.010	38.4 μg/100 g
		U-lead	long	during shift	6	181	0.143	0.089	65.5 μg/l
		U-ALA	long	during shift	6	181	0.241	0.244	0.273 mg/100 ml

APPENDIX A. Continued

Group	Industry/Type of Plant	Biomarker[A]	Half-Life[B]	Time of Sampling	k[C]	N[D]	$\hat{\sigma}_B^2$	$\hat{\sigma}_W^2$	Geometric Mean[E]
27	fiberglass boat plant	alveolar styrene	short	postshift	5	24	0.000	0.167	3.75 ppm
28	carbon black manufacturing	U-1-hydroxypyrene	short	postshift	5	22	0.346	0.208	0.243 μmol/mol creatinine
29	acid-lead battery plant	Bl-lead	long	during shift	20	40	0.450	0.027	20.2 μg/100 ml
30	manufacture of cadmium pigments	U-cadmium	long	24-hour sample	12	24	0.685	0.451	38.4 μg/24 hrs
31	coke plant	U-1-hydroxypyrene	short	postshift	10	20	0.223	0.335	15.8 ng/ml
32	coke plant	U-1-hydroxypyrene	short	postshift	8	16	0.341	0.195	3.58 ng/ml
33	manufacture of pulp and paper machines	U-chromium	long	7:00 a.m.	5	30	0.312	0.091	31.1 μg/g creatinine
		U-chromium	long	11:00 a.m.	5	25	0.325	0.060	43.4 μg/g creatinine
		U-chromium	long	4:00 p.m.	5	30	0.523	0.092	47.0 μg/g creatinine
		Bl-chromium	long	7:00 a.m.	5	10	0.211	0.020	2.68 μg/100 ml
34	polyester resin boat plant	Bl-styrene	short	postshift	11	22	0.307	0.589	0.597 mg/l
		U-mandelic acid	short	postshift	11	39	0.114	0.279	1013 mg/g creatinine
		U-phenylglyoxylic acid	short	postshift	11	39	0.000	0.343	246 mg/g creatinine
35	metal smelter	U-inorganic As + MMA + DMA	short	preshift	5	10	0.569	0.038	119 μg/g creatinine
		U-inorganic As + MMA + DMA	short	postshift	5	10	0.636	0.035	115 μg/g creatinine
		U-inorganic As + MMA + DMA	short	preshift	5	10	0.584	0.111	171 μg/l
36	chemical plant	U-S-methylcysteine		preshift	6	38	0.776	0.184	197 mmol/mol creatinine
		U-S-methylcysteine		postshift	6	37	0.913	0.094	196 mmol/mol creatinine
37	aluminum plant	U-1-hydroxypyrene	short	preshift	5	25	0.091	0.255	1.55 μmol/mol creatinine
		U-1-hydroxypyrene	short	postshift	5	23	0.430	0.289	3.97 μmol/mol creatinine
38	manufacture of polyurethane foam	plasma 2,4-TDA	long		5	13	0.118	0.039	0.758 ng/ml
		plasma 2,6-TDA	long		5	13	0.178	0.035	2.84 ng/ml
39	manufacture of polyurethane foam	plasma 2,4-TDA	long		6	22	0.797	0.072	11.2 ng/ml
		plasma 2,6-TDA	long		6	22	0.095	0.066	14.6 ng/ml
40	electroplating	U-nickel	short	preshift	8	23	0.285	0.337	24.4 μg/l
		U-nickel	short	midshift	8	23	0.042	0.634	42.9 μg/l
		U-nickel	short	postshift	7	21	0.180	0.428	34.8 μg/l
41	carbon anode plant	U-1-hydroxypyrene	short	preshift	6	30	0.946	0.504	2.12 μmol/mol creatinine
		U-1-hydroxypyrene	short	postshift	6	30	1.190	0.295	4.31 μmol/mol creatinine
42	organochlorine production plant	U-ALMA	short	preshift	16	30	0.000	1.977	87.3 μg/g creatinine
		U-ALMA	short	postshift	16	30	0.669	0.926	215 μg/g creatinine
43	viscose rayon plant	U-TTCA	short	postshift	6	18	3.039	1.348	0.251 mg/g creatinine
44	abrasive blasting	Bl-lead	long		21	83	0.284	0.205	28.1 μg/100 ml
45	lead pigment production plant	Bl-lead	long		32	59	0.033	0.043	1.63 μmol/l
		EP	long		32	59	0.197	0.098	2.02 μmol/L erythrocytes
		ALAD	long		32	59	0.011	0.107	24.6 U/L erythrocytes
46	creosote impregnation plant	U-1-hydroxypyrene	short	preshift	6	34	0.300	0.903	38.6 μmol/mol creatinine
		U-1-hydroxypyrene	short	midshift	6	18	0.154	0.776	30.4 μmol/mol creatinine
		U-1-hydroxypyrene	short	end of shift	6	18	0.233	0.235	53.3 μmol/mol creatinine
		U-1-hydroxypyrene	short	postshift	6	21	0.390	0.084	88.9 μmol/mol creatinine
47	reinforced plastics plant	Bl-styrene	short	midshift	9	25	0.214	0.294	0.617 mg/l
		U-mandelic acid	short	postshift	9	23	0.289	0.375	161 mmol/mol creatinine
		O^6-styrene-guanine lymphocyte adducts	long	midshift	9	18	0.214	0.165	4.73 adducts/10^8 normal nucleotides
48	electrolytic nickel refinery	U-nickel	short	preshift	8	31	0.439	0.058	0.438 μmol/l
		U-nickel	short	postshift	8	32	0.486	0.223	0.611 μmol/l
		U-nickel	short	preshift	8	31	0.358	0.048	31.6 mmol/mol creatinine
		U-nickel	short	postshift	8	32	0.355	0.227	46.9 mmol/mol creatinine
49	chloralkali plant	Bl-mercury	long	postshift	16	226	0.119	0.029	86.0 nmol/l
50	coke plant	U-4-hydroxyphenanthrene	short	24-hour sample	4	16	1.032	0.287	0.431 μg/24 hrs
		U-9-hydroxyphenanthrene	short	24-hour sample	4	15	0.442	0.453	0.446 μg/24 hrs
		U-1-hydroxyphenanthrene	short	24-hour sample	4	16	0.641	0.134	3.23 μg/24 hrs
		U-3-hydroxyphenanthrene	short	24-hour sample	4	16	0.817	0.147	6.51 μg/24 hrs

APPENDIX A. Continued

Group	Industry/Type of Plant	Biomarker[A]	Half-Life[B]	Time of Sampling	k[C]	N[D]	$\hat{\sigma}_B^2$	$\hat{\sigma}_W^2$	Geometric Mean[E]
		U-2-hydroxyphenanthrene	short	24-hour sample	4	16	0.756	0.144	2.60 μg/24 hrs
		U-1,2-dihydroxy-1,2-dihydrophenanthrene	short	24-hour sample	4	16	1.740	0.154	31.4 μg/24 hrs
		U-3,4-dihydroxy-3,4-dihydrophenanthrene	short	24-hour sample	4	16	2.119	0.083	7.82 μg/24 hrs
		U-9,10-dihydroxy-9,10-dihydrophenanthrene	short	24-hour sample	4	16	1.373	0.144	11.0 μg/24 hrs
		U-1-hydroxypyrene	short	24-hour sample	4	16	1.039	0.102	13.4 μg/24 hrs
		U-1,2-dihydroxy-1,2-dihydropyrene	short	24-hour sample	4	16	2.488	0.355	4.37 μg/24 hrs
		total phenanthrene metabolites	short	24-hour sample	4	16	1.441	0.098	66.12 μg/24 hrs
		total pyrene metabolites	short	24-hour sample	4	16	1.269	0.133	18.8 μg/24 hrs
51	electroplating shop	U-nickel	short	7:00 a.m.	4	20	0.308	0.086	35.2 μg/l
		U-nickel	short	4:00 p.m.	4	18	0.171	0.053	62.0 μg/l
		plasma nickel	short	7:00 a.m.	4	20	0.253	0.173	3.74 μg/l
		plasma nickel	short	4:00 p.m.	4	18	0.317	0.055	6.70 μg/l
52	printing plant	Bl-toluene	short	postshift	4	31	0.000	0.357	0.656 mg/kg
53	manufacture of chlorine	U-mercury	long	16-hour sample	4	15	0.305	0.213	0.074 mg/l
		U-mercury	long	7:05 a.m.	4	16	0.399	0.182	0.136 mg/l
		U-mercury	long	16-hour sample	4	15	0.281	0.036	0.127 mg/l (sp g)
		U-mercury	long	7:05 a.m.	4	16	0.250	0.151	0.158 mg/l (sp g)
54	chemical plant	Bl-mercury	long		20	30	0.228	0.276	60.1 μg/l
		U-mercury	long		21	30	0.641	0.153	154 μg/g creatinine
55	artificial target shooting factory	U-1-hydroxypyrene	short	preshift	5	20	0.141	0.337	2.62 μmol/mol creatinine
		U-1-hydroxypyrene	short	postshift	5	20	0.046	0.063	6.84 μmol/mol creatinine

[A]U = urine, Bl = blood; see Table II for description of acronyms.
[B]Short = half-life less than 7 days; long = Half-life 7 days or longer.
[C]k = number of workers.
[D]N = number of measurements.
[E]Note that the arithmetic mean can be estimated as $exp[lnGM + 0.5(\hat{\sigma}_B^2 + \hat{\sigma}_W^2)]$ and the geometric standard deviation as $exp(\sqrt{\hat{\sigma}_B^2 + \hat{\sigma}_W^2})$.