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Air samples versus biomarkers for epidemiology

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Background: It has been speculated on theoretical grounds that biomarkers are superior surrogates for chemical exposures to air samples in epidemiology studies.
Methods and Results: Biomarkers were classified according to their position in the exposure-disease continuum—that is, parent compound, reactive intermediate, stable metabolite, macromolecular adduct, or measure of cellular damage. Because airborne exposures and these different biomarkers are time series that vary within and between persons in a population, they are all prone to measurement error effects when used as surrogates for true chemical exposures. It was shown that the attenuation bias in the estimated slope characterising a log exposure-log disease relation should decrease as the within- to between-person variance ratio of a given set of air or biomarker measurements decreases. To gauge the magnitudes of these variance ratios, a database of 12 077 repeated observations was constructed from 127 datasets, including air and biological measurements from either occupational or environmental settings. The within- and between-person variance components (in log scale, after controlling for fixed effects of time) and the corresponding variance ratios for each set of air and biomarker measurements were estimated. It was shown that estimated variance ratios of biomarkers decreased in the order short term (residence time $\leqslant 2$ days) > intermediate term (2 days < residence time $\leqslant 2$ months) > long term biomarkers (residence time >2 months). Overall, biomarkers had smaller variance ratios than air measurements, particularly in environmental settings. This suggests that a typical biomarker would provide a less biasing surrogate for exposure than would a typical air measurement.
Conclusion: Epidemiologists are encouraged to consider the magnitudes of variance ratios, along with other factors related to practicality and cost, in choosing among candidate surrogate measures of exposure.

A major goal of occupational and environmental epidemiology is to establish quantitative relationships between exposures to toxic chemicals and the associated risks of disease. Most studies have considered airborne exposures, where inhalation was the primary route of entry of the contaminant into the body. Investigators collected air samples to estimate concentrations inhaled by members of occupational groups or by the general population. Steady technological advances over the last 50 years have made it possible to collect large numbers of air measurements and thereby to reduce uncertainties in quantifying levels of exposure. Although the anticipated gains in sample size have not materialised,[1 2] the technology currently exists to conduct longitudinal studies of health effects from chemical exposures.

Biological monitoring has been increasingly viewed as a desirable alternative to air sampling for characterising occupational and environmental exposures. (Here we use the term "environmental exposures" to refer to chemical exposures in indoor and outdoor settings not associated with workplaces.) This technique utilises biological specimens, especially breath, urine, and blood, to quantify levels of contaminants or their products in the body.[3 4] Biological monitoring is theoretically desirable because it accounts for all possible exposure routes (for example, inhalation, ingestion, and dermal contact), it covers unexpected or accidental exposures, and it reflects interindividual differences in uptake or genetic susceptibility.[5–8]

The endpoint of biological monitoring is often referred to as a *biomarker*, defined by the US National Research Council (NRC) as "... a change induced by a contaminant in the biochemical or cellular components of a process, structure or function that can be measured in a biological system".[9] The NRC divided biomarkers into three categories, namely, *biomarkers of exposure, of effect, and of susceptibility*. Examples of biomarkers of exposure include volatile organic compounds in breath, heavy metals in blood or urine, urinary metabolites of organic compounds, and adducts of genotoxic chemicals with haemoglobin or albumin. Biomarkers of effect represent early preclinical changes thought to be related to health risk or damage. Examples include DNA adducts of genotoxic chemicals, specific gene mutations such as *hypoxanthine-guanine phosphoribosyltransferase* (HPRT), changes in serum proteins indicative of altered metabolism or function, and cytogenetic changes in peripheral lymphocytes, including chromosome aberrations and sister chromatid exchanges (SCEs). Finally, biomarkers of susceptibility relate to an individual's inherited or acquired ability to respond to a hazardous substance. Single nucleotide polymorphisms (SNPs) of important phase-I enzymes (generally bioactivating enzymes such as cytochrome P450) and phase-II enzymes (generally deactivating enzymes, such as glutathione-*S*-transferases or epoxide hydrolases) are often regarded as biomarkers of susceptibility.[10]

The relationship between exposure to a toxic substance and the many possible biomarkers is shown in fig 1, using a genotoxic carcinogen to illustrate the functional elements.[11–13] Processes leading to chronic diseases other than cancer can be described by similar schemes. The input to the model is $\{X_{ij}\}$, representing the time series of n discrete exposures to the carcinogen ($j = 1, 2, \ldots, n$) (each averaged over time unit, Δt), received by the ith person in a population. The subsequent time series $\{P_{ij}\}$, $\{R_{ij}\}$, $\{M_{ij}\}$, $\{(RY)_{ij}\}$ and $\{D_{ij}\}$ represent the corresponding time series of biomarkers (to be defined).

The chemical must first be absorbed into the body via inhalation at rate k_{0i} (designated as the uptake rate for the ith person). In some instances, the substance is intrinsically

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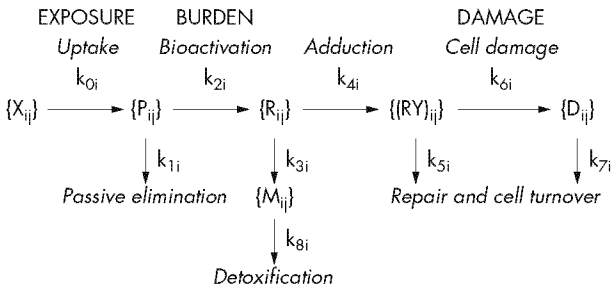

Figure 1 Kinetic processes relating exposure to a carcinogen with various biomarkers in an exposed population. Each process is represented by a time series of levels (in brackets) observed in the ith person after the jth time interval. $\{X_{ij}\}$ is the series of exposures, $\{P_{ij}\}$ is the series of the parent compound in the body, $\{R_{ij}\}$ is the series of a reactive carcinogen, $\{M_{ij}\}$ is the series of a stable metabolite, $\{(RY)_{ij}\}$ is the series of a DNA adduct, and $\{D_{ij}\}$ is the series of damaged cells; $k_{0i} - k_{8i}$ represent rate constants for the various processes.

electrophilic and capable of reacting with DNA and proteins. However, most cancer causing chemicals must first be metabolically activated to electrophiles. Thus, in fig 1, $\{P_{ij}\}$ refers to the levels of the parent compound, while $\{R_{ij}\}$ represents levels of the electrophile. The relative amounts of P_{ij} and R_{ij}, at any time, depend on competing rates of passive elimination of the parent compound (designated k_{1i}, including excretion in breath and urine), of metabolic bioactivation of P_{ij} to R_{ij} (designated k_{2i}), and of detoxification of R_{ij} (designated k_{3i}) giving rise to a stable metabolite M_{ij}, excreted at rate k_{8i}. A fraction of R_{ij} reacts at rate k_{4i} with DNA to produce a DNA adduct $(RY)_{ij}$, where Y represents a DNA base. In fig 1, molecular damage is represented as the series of adduct levels $\{(RY)_{ij}\}$, at different times. Most cells contain repair systems that remove DNA adducts and thereby protect the tissue from long term damage. Thus, the amount of $(RY)_{ij}$ depends on the relative rates of DNA adduction (that is, k_{4i}) and repair (designated k_{5i}). Cellular damage is represented by the series representing damaged cells $\{D_{ij}\}$, which depends on the rates of cell damage (given by k_{6i}), and repair and/or cell turnover (at rate k_{7i}). The magnitude of an individual's risk of cancer ultimately relates to the integration of D_{ij} over time, relative to some period of latency, and to his or her susceptibility as determined by genetic, physiological, metabolic, and lifestyle factors. Note that the rate constants $k_{0i} - k_{8i}$ are assumed to be constant for the ith individual but to vary across the population.

In the context of the NRC's definitions of biomarkers, $\{P_{ij}\}$, $\{R_{ij}\}$ and $\{M_{ij}\}$ would be biomarkers of exposure, while $\{(RY)_{ij}\}$ and $\{D_{ij}\}$ would be biomarkers of effect. Note that biomarkers of susceptibility would be measures of the variability of some rate constants (particularly $k_{2i} - k_{7i}$) across the population (analogous to effect modifiers).

Progressing from left to right in fig 1, each successive biomarker resides closer to the ultimate disease endpoint and theoretically becomes a more relevant measure of exposure for an epidemiological study than does the series of air levels $\{X_{ij}\}$. But, on the other hand, biological specimens can be more difficult to obtain and analyse than air measurements; and the particular time series of biomarker levels can be highly autocorrelated when the sampling time interval is shorter than the residence time of a biomarker, thereby adding complexity to the collection and interpretation of data. Also, in moving to the RY and D compartments, biomarkers become increasingly non-specific and subject to confounding by other agents. For example, N^2-ethenoguanine, a DNA adduct, can be produced either by exposure to ethylene or ethylene oxide, or by endogenous processes;[14] likewise, chromosome aberrations can arise from a plethora of chemical agents as well as from ionising radiation and reactive oxygen species.[15 16]

Although the above classification offers certain insights into the potential roles of biomarkers in the exposure-disease continuum, it does not differentiate with regard to the magnitudes of the key kinetic parameters that affect the variation in biomarker levels over time—that is, the rate constants k_{1i}, k_{3i}, k_{5i}, k_{7i}, and k_{8i}, each with units of time^{-1}. For example, the day-to-day fluctuations in levels of the parent compound $\{P_{ij}\}$ would be much greater for a volatile organic compound (large k_{1i}) than for a heavy metal (small k_{1i}). To consider the role that the persistence of the biomarker might play on its utility as a surrogate for exposure, it is useful to determine the in vivo residence time of each biomarker in the relevant compartment (that is, $1/k_{1i}$, $1/k_{3i}$, $1/k_{5i}$, $1/k_{7i}$, or $1/k_{8i}$ in fig 1). Here we arbitrarily assign biomarkers into three categories, namely, *short term biomarkers* with residence time $\leqslant 2$ days, *intermediate term biomarkers* with 2 days $<$ residence time $\leqslant 2$ months, and *long term biomarkers* with residence time >2 months. Under this classification scheme, short term biomarkers persist over time scales of one day to one week, intermediate term biomarkers over weeks to months, and long term biomarkers over months to years.

Aside from theoretical and practical considerations regarding the choice of air samples or biomarkers as surrogate measures of exposure, both air and biomarker concentrations vary within and between persons, thus giving rise to measurement error effects that can bias the estimation of exposure-response relationships. Indeed, the magnitudes of attenuation bias can differ among a given set of candidate biomarkers derived from the same chemical due to differences in residence time, specificity, etc. Thus, it is an open question whether a particular biomarker would be a more or less biasing surrogate for exposure than the corresponding air measurements.

The purpose of the present study is to consider the biasing potential of air and biomarker measurements in terms of attenuation in the estimated slope of a hypothetical log exposure-log response relationship. As will be shown, the biasing potential of each measure—that is, $\{X_{ij}\}$, $\{P_{ij}\}$, $\{R_{ij}\}$, $\{M_{ij}\}$ $\{(RY)_{ij}\}$, or $\{D_{ij}\}$ in fig 1, relates to its within- and between-person variance components. Thus, we compile data from occupational and environmental studies that obtained repeated measurements of both air and biological levels from representative persons. Then, we estimate the within- and between-person variance components of air and biological measurements for each study population, after controlling (when necessary) for particular fixed effects of time. Next, we compare these estimated variance components for air samples and for biomarkers classified by residence time (short term, intermediate term, and long term). Finally, we consider the biasing potential of each surrogate measure for estimating a hypothetical exposure-response relationship and comment on strategies for assessing exposures in epidemiological studies.

METHODS

Compilation of the database

The database was compiled from published and unpublished longitudinal studies involving air measurements and/or biomarkers; these studies are summarised in Appendices A and B, for environmental and occupational populations, respectively (see *OEM* website: http://www.occenvmed.com/supplemental). Because studies were dissimilar in terms of numbers of subjects and numbers of measurements per

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subject, only studies having at least five subjects with at least two repeated measurements per subject were included in the database, and subjects with single measurements were excluded. Particular attention was paid to data from studies containing repeated measurements of both air levels and biomarkers in a given population. However, due to the paucity of longitudinal studies involving biomarkers, we included some additional sets of biomarker data even when there were no corresponding air measurements. Because inhalation was the primary route of exposure in most studies, personal-air or breathing-zone samples were used. Since we were interested in exposures obtained during normal circumstances, data collected in response to an accidental release or other unusual exposure event were excluded. All data were expressed in the same concentration units as in the original studies. For reference, we point to the compilations of air measurements by Kromhout and colleagues[17] and biomarker measurements by Symanski and Greeson.[18] All human data obtained from non-published sources had been obtained with subjects' informed consent under protocols approved by the University of California, Berkeley and the University of North Carolina.

Estimation of variance components

Between- and within-person variance components were estimated using mixed-effects linear models, after natural logarithmic transformation of the air or biomarker measurements to achieve approximate normality and homogeneity of variances, and after adjustment for particular time effects. The following model was used:

$$Y_{ij} = \ln(X_{ij}) = \gamma_0 + \gamma_{ij}(\underline{\delta}) + \beta_i + \varepsilon_{ij} \qquad (1)$$

for the jth of n_i observations on the ith subject ($i = 1, 2, \ldots, k$; $j = 1, 2, \ldots, n_i$; $n_i \geqslant 2$), where X_{ij} is the (air or biomarker) concentration, Y_{ij} is the natural logarithm of X_{ij}, γ_0 is the intercept, $\gamma_{ij}(\underline{\delta})$ represents the fixed time effect (that is, for season, weekday, or linear trend), β_i is the random effect for the ith person, and ε_{ij} is the random-error effect for the jth observation on the ith person. Here, $\beta_i \sim N(0, \sigma_B^2)$, $\varepsilon_{ij} \sim N(0, \sigma_w^2)$, $\{\beta_i\}$ independent of $\{\varepsilon_{ij}\}$, and $Cov(\varepsilon_{ij}, \varepsilon_{ij'}) = \sigma_w^2 \rho_{jj'}$ for all $j \neq j'$. The variances σ_B^2 and σ_w^2 represent, respectively, the between- and within-person variance components.

The estimates of σ_B^2 and σ_w^2 (designated as $\hat{\sigma}_B^2$ and $\hat{\sigma}_w^2$), are compiled in Appendices C and D, for environmental and occupational settings, respectively (see *OEM* website: http://www.occenvmed.com/supplemental). Following Rappaport,[12] fold-ranges of variation between- and within-persons were also estimated, for illustration purposes, as the ratio of the 97.5^{th} centile to the 2.5^{th} centile of the appropriate lognormal distribution (X_{ij} for air measurements and P_{ij}, R_{ij}, $(RY)_{ij}$, or D_{ij} for biomarker measurements); that is, ${}_B\hat{R}_{0.95} = \exp(3.92\hat{\sigma}_B^2)$ and ${}_w\hat{R}_{0.95} = \exp(3.92\hat{\sigma}_w^2)$ denote the estimated between-person fold-range and the estimated within-person fold-range, respectively.

Covariance structures

Compound symmetry (CS) was adopted as the default covariance-matrix structure to estimate σ_B^2 and σ_w^2 under Model (1) using restricted maximum likelihood (REML). Under CS, it is assumed that the subjects are independent of one another and that the correlation between the jth and j'^{th} observations on the ith subject equals $\frac{\sigma_B^2}{(\sigma_B^2 + \sigma_w^2)}$ (the intraclass correlation). However, in some situations, it was anticipated that the correlation between measurements from the same person would decrease as the number of time intervals between observations increased. Such an autocorrelation structure would be appropriate when Δt is shorter than the residence time of the biomarker, as might be common for intermediate and long term biomarkers. To identify datasets containing significant autocorrelation, an exponential (EXP) covariance structure was also considered, based on the biomarker residence time, the intervals between measurements, and the average number of repeated observations per person ($n_i \geqslant 3$). For an EXP covariance structure, $\rho_{jj'} = \exp(-\phi|t_j - t_{j'}|)$ for all $j \neq j'$, where t_j and $t_{j'}$ are the times (the same for all subjects) at which the jth and j'^{th} measurements were taken. When measurements are taken at the same equally space times for all subjects, then EXP simplifies to the first-order autoregressive AR (1) covariance structure, where $\rho_{jj'} = \rho^{|j-j'|}$ with $\rho = e^{-\phi}$. Akaike's information criteria (AIC) and Schwarz's Bayesian information criterion (BIC) were used to compare CS and EXP under Model (1) to choose an appropriate covariance structure; CS was chosen unless both AIC and BIC were smaller for EXP than for CS. Appendices C and D list all situations in which EXP was used, rather than CS, to estimate variance components (see *OEM* website: http://www.occenvmed.com/supplemental).

Fixed time effects

Given a database consisting of studies ranging in duration from days to years, it was not uncommon to observe situations where average exposure levels changed systematically over time. We considered three types of time effects via $\gamma_{ij}(\underline{\delta})$ in Model (1), namely, seasonal effects (studies of at least 6 months), weekday effects (studies of less than 6 months), and linear trends (all studies). Time effects were identified graphically using scatter plots of the raw data, and were then confirmed statistically via likelihood ratio tests comparing Model (1) with and without the $\gamma_{ij}(\underline{\delta})$ component. If no significant time effects were found, variance components were estimated after removing $\gamma_{ij}(\underline{\delta})$ from Model (1). To avoid overfitting the model, only a single time effect was used.

If not explicitly specified in Model (1), a missing fixed time effect would tend to exert its biasing influence by increasing the estimate of σ_w^2 and reducing the estimate of σ_B^2.[19] To gauge the magnitude of such biases on estimation of variance components, whenever a significant time effect was observed, Model (1) was applied to the dataset with and without $\gamma_{ij}(\underline{\delta})$ and the estimates of σ_B^2 and σ_w^2 were compared.

Bias in estimating exposure-disease relationships

We designate the ratio of σ_w^2 to σ_B^2 as the variance ratio ($\lambda = \sigma_w^2/\sigma_B^2$). This variance ratio ($\lambda$) can be used to evaluate attenuation bias when estimating an exposure-disease relationship, given that either air or biomarker levels are used as surrogates for actual exposure levels.[6 20 21] Consider the simple situation where the underlying relationship between the logarithm of the true mean exposure for the ith person (based on air or biomarker levels) and the logarithm of the expected value of a continuous health outcome is a straight line with slope θ_{true} (see Appendix E, true regression model; *OEM* website: http://www.occenvmed.com/supplemental). Suppose a sample of persons is randomly selected from the population, each subject having n randomly collected measures of exposure. If the average of these n logged exposure measurements is used as a surrogate for the true logged mean exposure level for the ith person (see Appendix E, measurement error model), then the slope parameter actually being estimated (namely, θ^*) is related to θ_{true} via the following equation:

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$$\frac{\theta^*}{\theta_{true}} = \frac{1}{1 + \frac{\lambda}{n}[1 + (n-1)\Delta]}, \qquad (2)$$

where $\Delta = \frac{1}{n(n-1)} \sum_{all\, j \neq j'} \rho_{jj'}$. From Equation (2), we see that θ^* is less than θ_{true} (that is, there is attenuation), with the magnitude of the attenuation given by the expression on the right side. We have previously considered a simpler case[6 20] where $\rho_{jj'} = 0$ for all j and j' (under CS), giving $\Delta = 0$ and the well-known expression:[22]

$$\frac{\theta^*}{\theta_{true}} = \frac{1}{1 + \frac{\lambda}{n}}. \qquad (3)$$

In Appendix E, we consider the two special cases, $\rho_{jj'} = 0$ and $\rho_{jj'} = \rho^{|j-j'|}$, which correspond to the CS and AR(1) covariance structures, respectively. From Equations (2) and (3), we see that (for a fixed n) attenuation increases as the variance ratio λ increases, which suggests (at least for the simple straight-line model on the log scale being considered in Appendix E) that the exposure surrogate with the smallest λ should produce (on average) the least underestimation of θ_{true}. With this motivation, we use the estimated variance ratio $\hat{\lambda} = \hat{\sigma}_w^2/\hat{\sigma}_B^2$ to compare air measurements with biomarkers for a given study (smaller is better), consistent with our earlier work.[6] Here, we denote the estimated λs for air and biological monitoring as $\hat{\lambda}_{air}$ and $\hat{\lambda}_{bio}$ respectively. We also define $\hat{\lambda}_{bio}/\hat{\lambda}_{air}$ as the "lambda ratio"; when $\hat{\lambda}_{bio}/\hat{\lambda}_{air}$ is less than one, there is evidence that the biomarker would be a better surrogate for exposure than air measurements and vice versa.

Statistical methods

In addition to statistical analyses involving Model (1) described above, analysis of variance (ANOVA) or non-parametric Wilcoxon rank-sum tests (if the distributions were skewed) were used to compare variance components between air measurements and biomarkers. We used PROC MIXED for longitudinal analyses with the SAS statistical package version 8.02 (SAS Institute Inc., Cary, NC). The level of significance of all tests was 0.05.

RESULTS

Description of the database

A total of 12 181 repeated observations from 132 data sets were compiled from 22 studies covering a wide range of pollutants (notably metals, organic compounds, and pesticides) in both environmental and occupational settings (Appendices A and B). The data are summarised in table 1, which lists the numbers of air measurements, biomarker measurements, and subjects, as well as the category of each biomarker according to its type (kinetic compartment in fig 1) and residence time. The numbers of biomarkers in our database decreased from P (21), to M (12), to RY (7), to D (3), to R (2). The database was also reasonably populated with biomarkers in all three categories of residence time—that is, short term (21), intermediate term (15), and long term biomarkers (9). For some contaminants, more than one biomarker was measured. After excluding 104 pre-shift observations, the data used for analysis (12 077 observations) included 50 air-exposure data sets (4623 observations) and 77 biomarker data sets (7454 observations).

Effects of time on estimation of variance components

Significant effects of time were found in approximately one third (18 of 50) of air monitoring data sets and in approximately half (36 of 77) of biomarker data sets (Appendices C and D). One such effect is illustrated in fig 2A, which shows a seasonal effect in levels of free styrene glycol in blood (μg/ml) observed among reinforced plastics workers during three surveys conducted 3–4 months apart (unpublished data from a study described by Rappaport and colleagues[24]). When Model (1) was fitted to the data without a fixed seasonal effect, the residuals deviated from the horizontal line representing zero (fig 2B). In contrast, when Model (1) was fitted to the data with a fixed seasonal effect, the residuals varied randomly about zero (fig 2C). The estimated within- and between-person variance components were potentially biased due to fitting Model (1) to the data without a seasonal effect; that is, $\hat{\sigma}_w^2$ increased from 1.24 to 1.33 (+6.9%) and $\hat{\sigma}_B^2$ decreased from 0.595 to 0.562 (−5.5%).

Table 2 summarises the contributions of time effects to $\hat{\sigma}_w^2$ and $\hat{\sigma}_B^2$ in all datasets. If an important time effect was wrongly excluded from Model (1), then $\hat{\sigma}_w^2$ typically *increased* 18.2% (median value) for air measurements and 25.4% (median value) for biomarker measurements. Conversely, if an important time effect was excluded from Model (1), $\hat{\sigma}_B^2$ typically *decreased* by 11.3% (median value) for air measurements and 4.1% (median value) for biomarkers.

Alternative covariance structure

Of all the studies in our database, only two produced significantly better fits to Model (1) with an EXP (rather than a CS) covariance structure, namely, DDE and trans-nonachlor in blood,[30] both long term biomarkers, and inorganic lead and δ-aminolevulinate in urine,[26] both intermediate term biomarkers (see Appendices C and D). This suggests that CS is generally appropriate for applications of Model (1) to air and biomarker measurements.

Between- and within-person variance components

The cumulative distributions of the estimated between- and within-person variance components are shown in fig 3 in terms of the corresponding fold ranges (that is, ${}_B\hat{R}_{0.95}$ and ${}_w\hat{R}_{0.95}$, respectively) for air measurements and biomarkers. The difference between distributions of ${}_B\hat{R}_{0.95}$ for air measurements (median ${}_B\hat{R}_{0.95} = 7.4$) and for biomarkers (median ${}_B\hat{R}_{0.95} = 7.7$) was not significant (Wilcoxon rank sum test, $p = 0.54$) (see fig 3A). Within-person variation was much greater than between-person variation for both air measurements (median ${}_w\hat{R}_{0.95} = 48.9$) and biomarkers (median ${}_w\hat{R}_{0.95} = 17.4$) (fig 3B). Also, the distribution of values of ${}_w\hat{R}_{0.95}$ for biomarkers was significantly smaller than that for air measurements (Wilcoxon rank sum test, $p<0.01$). We attribute this to the smoothing of exposure variability in the human body, which increases with the residence time of the biomarker.[27 28] Indeed, median values of ${}_w\hat{R}_{0.95}$ for biomarkers decreased in the order: short term (median = 44.6) > intermediate term (median = 3.7) > long term (median = 3.3).

Environmental exposures varied much more within persons than occupational exposures for both air measurements (environmental: median ${}_w\hat{R}_{0.95} = 104$; occupational: median ${}_w\hat{R}_{0.95} = 13.7$) and biomarkers (environmental: median ${}_w\hat{R}_{0.95} = 36.6$; occupational: median ${}_w\hat{R}_{0.95} = 7.6$). For comparison, table 3 also shows the cumulative distributions of ${}_B\hat{R}_{0.95}$ and ${}_w\hat{R}_{0.95}$ estimated from occupational studies involving air measurements, reported by Kromhout and colleagues,[17] and biomarkers, reported by Symanski and Greeson.[18] Neither the ${}_B\hat{R}_{0.95}$ distribution nor the ${}_w\hat{R}_{0.95}$ distribution was found to significantly differ between our database and those earlier compilations (data not shown).

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Table 1 Descriptive characteristics of the database*

Air measurements	No. of obs.	No. of persons	Biomarkers	No. of obs.	No. of persons	Biomarker classification: Kinetic compartment†	Biomarker classification: Residence time‡
Metals							
Chromium	90	9	Urinary chromium	110	9	P	Intermediate
Mercury	592	16	Blood mercury	226	16	P	Intermediate
Nickel	35	9	Blood nickel	38	4	P	Intermediate
			Urinary nickel	82	12	P	Intermediate
Lead	287	51	Blood lead	387	79	P	Intermediate
			Urinary δ-aminolevulinate	181	6	M	Intermediate
			Urinary lead	181	6	P	Intermediate
Organic compounds							
Benzene	592	216	Breath benzene	570	208	P	Short
Chloroform	293	116	Breath chloroform	266	104	P	Short
Ethylbenzene	301	120	Breath ethylbenzene	276	110	P	Short
Ethylene oxide	47	13	Breath ethylene oxide	26	9	P	Short
			Blood ethylene oxide	24	9	P	Short
			Haemoglobin N-2-hydroxyethyl-valine	44	19	RY	Long
Methylchloroform	301	120	Breath methylchloroform	275	109	P	Short
Monoterpenes	39	10	Urinary verbenol	39	10	M	Short
o-Xylene	301	120	Breath *o*-xylenes	278	110	P	Short
Polycyclic aromatic hydrocarbons	40	10	Blood DNA adduct	40	10	RY	Intermediate
p-Dichlorobenzene	160	80	Breath *p*-dichlorobenzene	134	67	P	Short
Perchloroethylene	343	130	Breath perchloroethylene	311	120	P	Short
Styrene/Styrene oxide	611/17	189/7	Breath styrene	427	136	P	Short
			Blood free styrene glycol	104	42	M	Short
			Blood styrene	172	55	P	Short
			Blood SO-Albumin adduct (α)	108	42	RY	Intermediate
			Blood SO-Albumin adduct (β)	108	42	RY	Intermediate
			Blood SO-DNA adduct (1)	48	24	RY	Intermediate
			Blood SO-DNA adduct (2)	48	24	RY	Intermediate
			Blood haemoglobin adduct	117	44	RY	Long
			Blood HPRT mutation frequency	22	5	D	Long
			Blood sister chromatid exchange	68	34	D	Long
			Urinary mandelic acid	78	23	M	Short
Trichloroethylene	296	119	Breath trichloroethylene	268	106	P	Short
Pesticides							
Chlordane (cis and trans isomers)	32	9	Blood oxychlordane	89	32	R	Intermediate
Chlorpyrifos	57	16	Urinary 3,5,6-trichloro-2-pyridinol	312	69	M	Short
Dieldrin	11	3	Blood dieldrin	39	13	P	Long
Heptachlor	51	14	Blood heptachlor epoxide	20	5	R	Intermediate
			Biomarker data only§				
Organic compounds							
Environmental tobacco smoking			Urinary 1-hydroxypyrene	180	30	M	Short
			Urinary cotinine	48	21	M	Short
			Urinary NNAL-Gluc and NNAL	31	16	M	Intermediate
Mixed organic compounds			Blood sister chromatid exchange (HFC)	20	10	D	Long
Pesticides							
Atrazine			Urinary atrazine mercapturate	314	69	M	Short
Carbaryl			Urinary 1-naphthol¶	312	69	M	Short
DDE			Blood DDE	377	103	P	Long
Hexachlorobenzene			Blood hexachlorobenzene	314	72	P	Long
Malathion			Urinary malathion dicarboxylic acid	313	69	M	Short
Polychlorinated biphenyls			Blood polychlorinated biphenyls	60	30	P	Long
Trans-nonachlor			Blood trans-nonachlor	122	49	P	Long

DDE, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene; DNA, deoxyribonucleic acid; HFC, high frequency cell; HPRT, hypoxanthine guanine phosphoribosyl transferase; NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNAL-Gluc, [4-(methylnitrosamino)-1-(3-pyridyl) but-1-yl]-beta-O-D-glucosiduronic acid; SO, styrene oxide; SO-DNA(1), N^2-(2-hydroxy-1-phenylethyl)-2′-deoxyguanosine-3,5-biphosphate; SO-DNA (2), unidentified DNA adduct.[33]

*Five pre-shift datasets and three datasets containing unspecified categories of biomarkers were excluded from summary analysis. A total of 127 datasets and 12 077 observations were used for summary analysis.

†D, damaged cells; M, stable metabolite; P, parent compound (or procarcinogen); R, reactive intermediate; RY, reaction product between R and nucleophile Y (e.g. DNA base).

‡Residence time category: long, residence time >2 months; intermediate, 2 months ≥residence time >2 days; and short, residence time ≤2 days.

§Insufficient exposure data to estimate variance components.

¶Urinary 1-naphthol is a non-specific metabolite of the pesticide carbaryl.

Overall, the databases show that the median value of ${}_{W}\hat{R}_{0.95}$ was greater than that of ${}_{B}\hat{R}_{0.95}$ in a given setting for both air measurements and biomarkers.

Bias in estimating exposure-disease relationships.

Potential bias in the estimation of the slope (θ_{true}) of an assumed straight line log exposure-log disease relationship (see Appendix E) was evaluated by examining the estimated variance ratio, $\hat{\lambda} = \hat{\sigma}_W^2/\hat{\sigma}_B^2$ (smaller is better). In general, values of $\hat{\lambda}$ for biomarkers (median = 1.04) were significantly smaller than those for air measurements (median = 2.40) (Wilcoxon rank sum test, p = 0.02). From this result, we infer that using a biomarker as a surrogate exposure measure in a typical study would tend to provide a less biased estimate of the slope of a log exposure-log disease linear relationship than would the use of air measurements.

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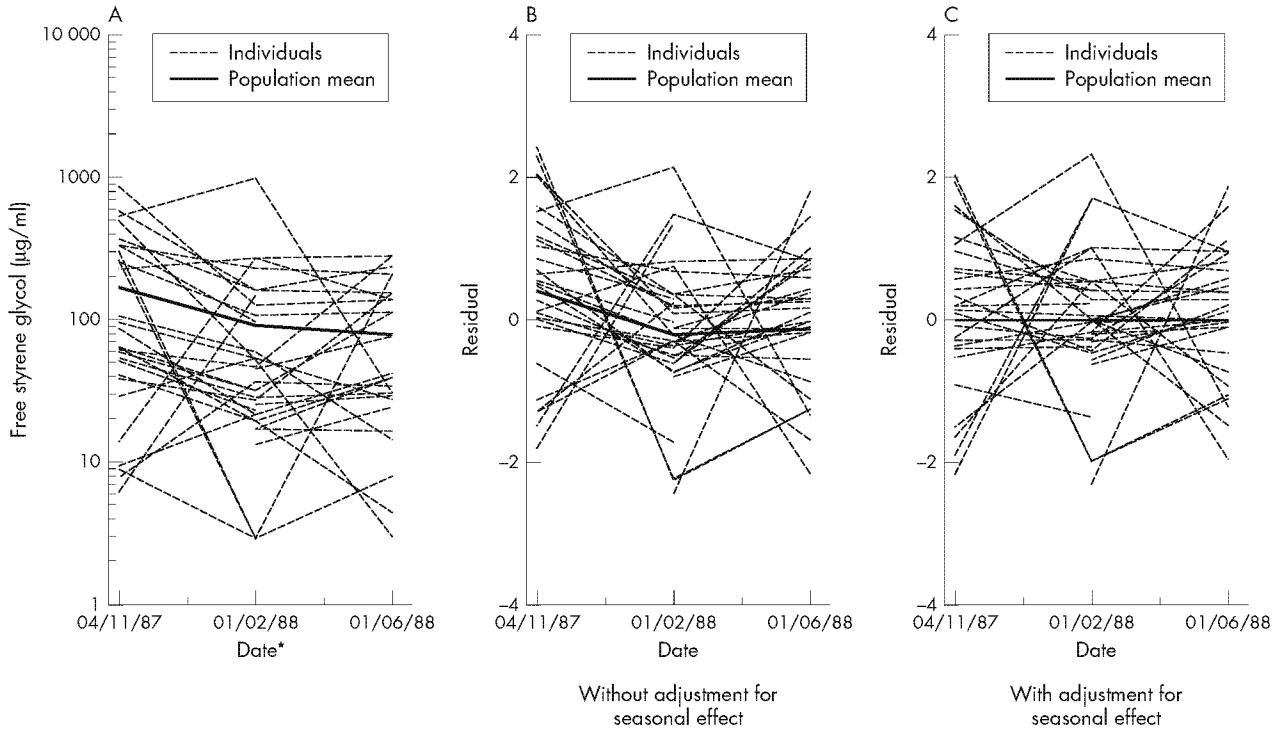

Figure 2 Characteristics of an example biomarker data set (free styrene glycol) (unpublished data, Rappaport and colleagues[24]). (A) Time profile of free styrene glycol in blood from workers exposed to styrene and styrene oxide. (B) Residuals (with adjustment for seasonal effect) under Model (1). (C) Residuals (without adjustment for seasonal effect) under Model (1). *European format.

Figure 4 shows the median and interquartile ranges of $\hat{\lambda}$ for both air measurements and biomarkers, stratified by exposure setting (fig 4A) and type of agent (fig 4B). Biomarkers produced significantly smaller values of $\hat{\lambda}$ than air measurements (Wilcoxon rank sum test) for environmental exposures ($p = 0.01$) (fig 4A) and for metal exposures ($p = 0.03$) (fig 4B). However, for pesticide exposures, air measurements produced significantly smaller $\hat{\lambda}$ values than did biomarker measurements ($p = 0.04$) (fig 4B). Estimates of $\hat{\lambda}$ are shown in fig 4C for measurements stratified by the residence time of the biomarker. Here, a decreasing trend for $\hat{\lambda}$ was observed for biomarkers in the order: short term > intermediate term > long term, consistent with reductions in $\hat{\sigma}^2_w$ noted previously.

The above comparisons were based on all studies in our database, whether or not parallel measurements of air levels *and* biomarkers were included in each investigation. To make direct comparisons between air and biomarker measurements in a given study, the estimated lambda ratio, $\hat{\lambda}_{bio}/\hat{\lambda}_{air}$, was investigated. Of the 54 data sets that provided parallel measurements, almost two thirds (62%) had estimated lambda ratios of less than one (median lambda ratio = 0.46), again providing evidence that biomarkers tend to provide less biasing measures of exposure than air measurements. The median and interquartile ranges of estimated lambda ratios were also stratified and compared by exposure setting, type of agent, and biomarker residence time as shown in fig 5. Results here are generally consistent with those from fig 4, with estimated lambda ratios less than one for environmental settings (fig 5A) and for metals, but not for pesticides (fig 5B). However, the estimated lambda ratios increased in the order: intermediate term biomarkers < short term biomarkers < long term biomarkers (fig 5C), which was unanticipated based on the earlier comparisons of $\hat{\lambda}$ (see fig 4C). This could reflect the relatively small numbers of studies with parallel air and biomarker measurements and the fact that the few long term biomarkers represented ($n = 6$) included several non-specific endpoints, such as HPRT mutations and SCEs, that could have been influenced by smoking, ionising radiation, and other types of exposures.[38]

DISCUSSION

Our findings support the notion that biomarkers can offer a desirable alternative to air sampling for assessing exposures to chemicals. In addition to providing the oft-mentioned theoretical advantages (accounting for all exposure routes and interindividual differences and residing closer to the disease process), biomarkers also tend to have smaller variance ratios ($\lambda = \frac{\sigma^2_w}{\sigma^2_B}$), and, therefore, to be potentially less biasing surrogate measures of exposure than air measurements for studies of health effects. This particular advantage of biomarkers has only been mentioned anecdotally heretofore.[6 20]

If values of λ are to be considered in designing a health effects study, it is important that σ^2_w and σ^2_B be estimated with minimal bias. For both air and biomarker measurements, we found that time effects and the choice of covariance structure could be important to the characterisation of these variance components. Excluding an important fixed time effect had a greater impact on $\hat{\sigma}^2_w$ than on $\hat{\sigma}^2_B$ as observed for other types of longitudinal data.[39] This would tend to increase values of $\hat{\lambda}$ for the candidate exposure measures, making them appear worse than they actually are. Regarding the choice of covariance structure, we found that CS was appropriate for characterising σ^2_w and σ^2_B in virtually all cases. However, CS assumes that repeated measurements collected from a given person have the same correlation no matter how far apart they are in time. Thus, investigators should be aware of potential problems arising from the timing of biomarker measurements relative to the residence

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Table 2 Contribution of time effects to the estimated variance components

	Time effect	Estimated within-person variance component ($\hat{\sigma}_w^2$) Without time effect	With time effect	% change*	Estimated between-person variance component ($\hat{\sigma}_B^2$) Without time effect	With time effect	% change*	Notes	Ref.
Air measurement									
Benzene	Season	0.707	0.626	12.9	0.263	0.262	0.4		29
	Season	0.687	0.543	26.5	0.048	0.094	−48.9	Los Angeles, CA	25
Chloroform	Season	2.302	2.014	14.3	0.000	0.101	−100.0	Los Angeles, CA	25
Chlorpyrifos	Season	0.261	0.220	18.6	1.920	1.972	−2.6		30
Ethylbenzene	Season	0.993	0.920	7.9	0.193	0.215	−10.2	Los Angeles, CA	25
Methylchloroform	Season	1.524	1.406	8.4	0.211	0.263	−19.8	Los Angeles, CA	25
Monoterpene	Season	0.677	0.577	17.3	0.325	0.216	50.5	Los Angeles, CA	25
o-Xylene	Season	1.647	1.398	17.8	0.000	0.059	−100.0	Los Angeles, CA	25
Lead	Season	0.279	0.207	34.8	0.022	0.024	−8.3		30
p-Dichlorobenzene	Season	2.240	1.647	36.0	0.422	0.725	−41.8	Bayonne, NJ	25
	Season	1.841	1.448	27.1	1.395	1.592	−12.4	Los Angeles, CA	25
Perchloroethylene	Season	1.730	1.455	18.9	0.046	0.136	−66.2	Los Angeles, CA	25
Styrene	Season	1.348	1.172	15.0	0.237	0.279	−15.1	Los Angeles, CA	25
Styrene oxide	Season	1.372	0.131	947.3	0.000	0.245	−100.0		24
Trichloroethylene	Season	3.619	3.508	3.2	1.073	1.078	−0.5	Los Angeles, CA	25
Mercury	Weekday	0.268	0.256	4.7	0.051	0.052	−1.9		31
Ethylene oxide	Linear trend	1.256	0.742	69.3	0.000	0.000	−†		32
Styrene	Linear trend	0.466	0.342	36.3	0.238	0.231	3.0		33
Biomarker									
Breath benzene	Season	0.779	0.655	18.9	0.310	0.370	−16.2		29
	Season	2.075	1.953	6.2	1.125	1.183	−4.9	Los Angeles, CA	25
Breath chloroform	Season	3.322	1.284	158.7	0.000	0.942	−100.0	Elizabeth, NJ	25
Breath ethylbenzene	Season	1.386	1.040	33.3	0.738	0.931	−20.7	Elizabeth, NJ	25
	Season	1.436	1.195	20.2	0.868	0.921	−5.8	Los Angeles, CA	25
Breath methylchloroform	Season	2.383	1.315	81.2	0.751	1.358	−44.7	Elizabeth, NJ	25
	Season	1.402	1.192	17.6	0.695	0.805	−13.7	Los Angeles, CA	25
Breath o-xylene	Season	1.129	0.846	33.5	0.296	0.387	−23.5	Los Angeles, CA	25
Breath p-dichlorobenzene	Season	0.973	0.645	50.9	0.467	0.620	−24.7	Elizabeth, NJ	25
	Season	1.098	0.938	17.1	2.642	2.721	−2.9	Los Angeles, CA	25
Breath perchloroethylene	Season	0.714	0.557	28.2	0.430	0.545	−21.1	Los Angeles, CA	25
Breath styrene	Season	0.617	0.426	44.8	0.310	0.419	−26.0	Bayonne, NJ	25
	Season	1.363	0.898	51.8	0.000	0.246	−100.0	Elizabeth, NJ	25
Breath trichloroethylene	Season	1.011	0.621	62.8	0.053	0.272	−80.5	Bayonne, NJ	25
	Season	1.919	1.670	14.9	0.715	0.784	−8.8	Los Angeles, CA	25
Blood SO-albumin adduct (α)	Season	1.041	0.796	30.8	0.000	0.000	–		24
Blood SO-albumin adduct (β)	Season	0.444	0.388	14.4	0.007	0.027	−74.1		24
Blood DDE	Season	0.076	0.062	22.6	0.345	0.348	−0.9		30
Blood SO-DNA adduct (1)	Season	4.219	3.533	19.4	0.000	0.000	–		24
Blood SO-DNA adduct (2)	Season	3.004	2.513	19.5	0.000	0.102	−100.0		24
Blood free styrene glycol	Season	1.328	1.242	6.9	0.562	0.595	−5.5		24
Blood haemoglobin adduct	Season	0.317	0.269	17.8	0.000	0.000	–		24
Blood hexachlorobenzene	Season	0.145	0.101	43.6	0.029	0.030	−3.3		30
Blood lead	Season	0.113	0.109	3.7	0.278	0.278	0.0		30
Blood styrene	Season	1.666	1.484	12.3	1.708	1.692	0.9		24
Urinary 3,5,6-trichloro-2-pyridinol	Season	0.406	0.361	12.5	0.149	0.147	1.4		30
Urinary atrazine mercapturate	Season	0.164	0.160	2.5	0.154	0.153	0.7		30
Urinary malathion dicarboxylic acid	Season	0.524	0.511	2.5	0.114	0.107	6.5		30
Blood mercury	Weekday	0.029	0.028	3.6	0.119	0.119	0.0		31
Urinary 1-hydroxyprene	Weekday	0.271	0.192	41.1	0.321	0.324	−0.9		34
Urinary chromium	Weekday	0.088	0.035	151.4	0.566	0.576	−1.7		35
	Weekday	0.107	0.040	167.5	0.617	0.630	−2.1		36
Urinary nickel	Weekday	0.428	0.243	76.1	0.180	0.242	−25.6		37
	Weekday	0.053	0.018	194.4	0.171	0.162	5.6		36
Breath ethylene oxide	Linear trend	1.165	0.618	88.5	0.000	0.000	–		32
Blood ethylene oxide	Linear trend	1.127	0.783	43.9	0.000	0.000	–		32

DDE, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene; DNA, deoxyribonucleic acid; SO, styrene oxide.
*{Variance component$_{\text{without time effect}}$ − Variance component$_{\text{with time effect}}$} × 100/Variance component$_{\text{with time effect}}$
†Undefined because denominator is zero; assigned a provisional value of zero when estimating the median of the distribution.

time, particularly for intermediate and long term biomarkers, or should use an EXP covariance structure.

We found that values of $\hat{\sigma}_w^2$ tended to be larger for environmental exposures than for occupational exposures regarding both air and biomarker measurements (fig 2B). This indicates that members of the general public experience greater ranges of pollutant levels in their everyday lives than do workers in a given factory and job (as noted in Rappaport and Kupper[21]), and may explain why biomarkers had consistently smaller lambda ratios in environmental studies than in occupational studies (fig 5A). Thus, biomonitoring may be more advantageous in environmental settings than in occupational settings.

Among biomarkers, we noticed a decreasing trend for $\hat{\lambda}$ in the order: short term > intermediate term > long term due to the likely smoothing of exposure variability related to slow elimination of the biomarker (fig 4C). This suggests that biomarkers with longer residence times would be preferred to those with shorter residence times. That is, smaller numbers of biomarker measurements per subject would be needed to

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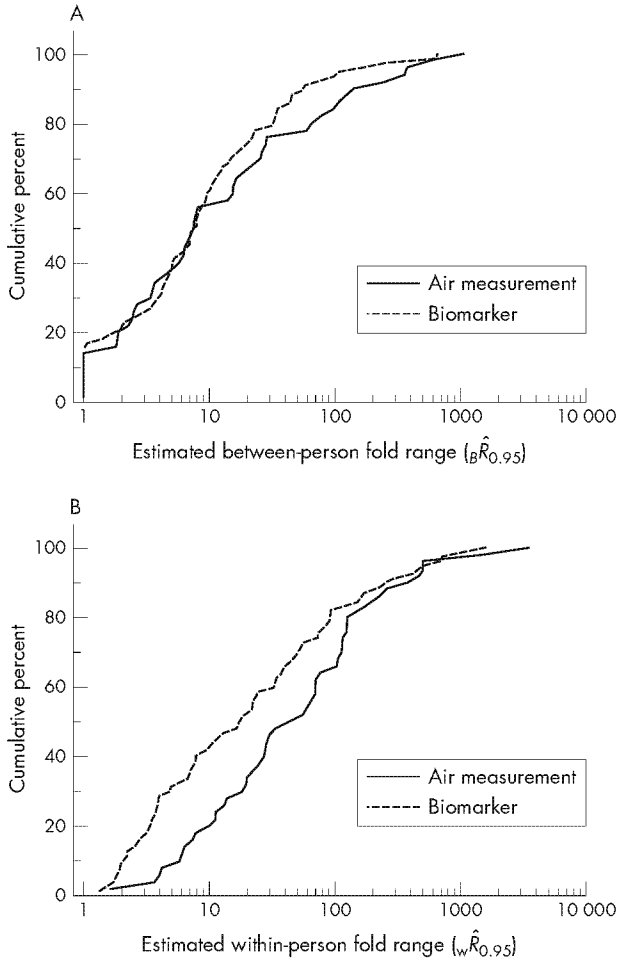

Figure 3 Cumulative distributions of fold ranges of variability for exposure and biomarker measurements. (A) Estimated fold range ($_B\hat{R}_{0.95}$) containing 95% of average exposure (and biomarker) encountered by the population. (B) Estimated fold range ($_w\hat{R}_{0.95}$) containing 95% of average exposure (and biomarker) encountered by a given person.

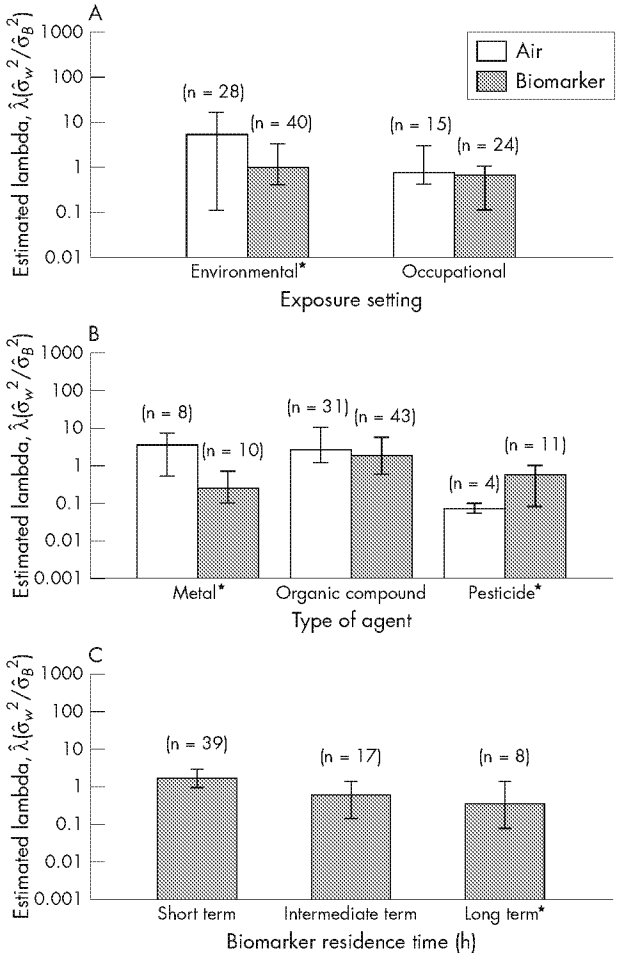

Figure 4 Median $\hat{\lambda}$ values and interquartile ranges of $\hat{\lambda}$ values for: (A) exposure setting; (B) exposure agent; and (C) biomarker residence time. Error bars represent interquartile ranges. *p<0.05, Wilcoxon rank sum test for median values.

help control for attenuation bias in an exposure-response relationship (see Appendix E). For example, to estimate the slope of the linear relationship between logged inorganic lead exposure and some logged continuous health outcome, with a bias no larger than 0.10, we use the data of Cope and colleagues[26] to estimate n. From equation (2), the number of measurements per subject required for a given bias $b = \left(1 - \frac{\theta^*}{\theta_{true}}\right)$ can be determined as the smallest positive integer n satisfying the inequality:

$$n \geq \frac{(1-\Delta)}{\frac{b}{(1-b)\lambda} - \Delta}, 0 \leq \Delta < \frac{b}{(1-b)\lambda} \leq 1, \quad (4)$$

Table 3 Comparison of between- and within-person estimated fold ranges across studies and exposure settings

	No. of datasets	No. of obs	No. of persons	$_B\hat{R}_{0.95}$ Median	$_B\hat{R}_{0.95}$ Interquartile range	$_w\hat{R}_{0.95}$ Median	$_w\hat{R}_{0.95}$ Interquartile range	Ref.
Environmental setting								
Air (current study)	33	2901	1146	7.7	2.3–43.4	104.4	48.9–207	
Biomarker (current study)	46	5286	1681	9.3	4.4–33.2	36.6	4.8–90.6	
Occupational setting								
Air (current study)	17	1722	237	7.0	3.6–49.2	13.7	8.8–27.3	
Air (Kromhout *et al*)	165	13945	1569	4.0	2.0–13.0	15.2	5.9–70.3	17
Biomarker (current study)	31	2168	563	4.8	1.6–10.8	7.6	2.5–32.1	
Biomarker (Symanksi and Greeson)†	91	3234	942	8.1	2.1–30.2	5.0	2.5–10.4	18

$_B\hat{R}_{0.95}$, estimated between-person fold range; $_w\hat{R}_{0.95}$, estimated within-person fold range.
†Pre-shift and mid-shift observations (persons) were excluded from 122 original data sets that included 4367 observations from 1155 persons.

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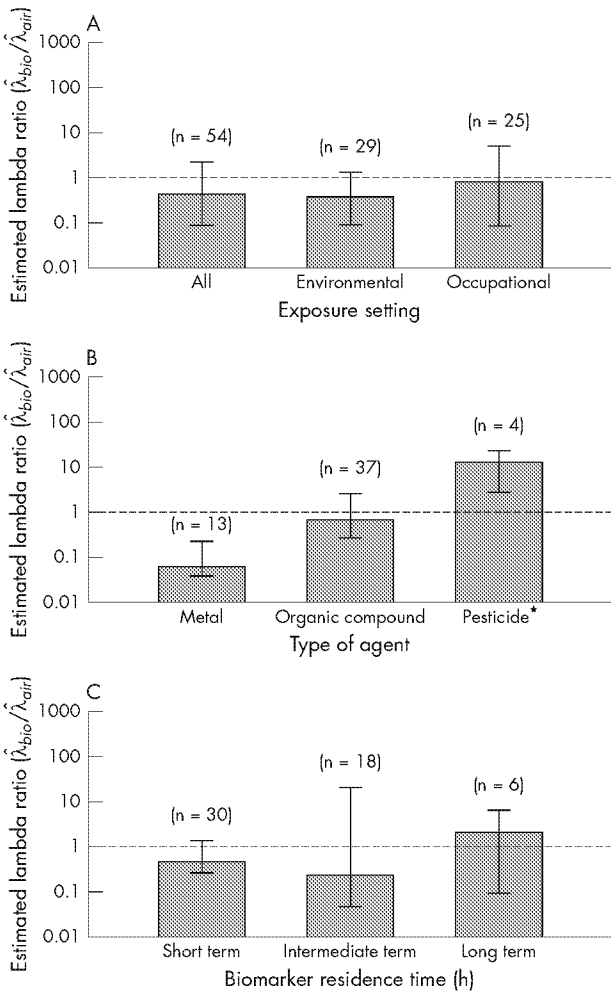

Figure 5 Median estimated lambda ratios and interquartile ranges of estimated lambda ratios for: (A) exposure setting; (B) exposure agent; and (C) biomarker residence time. Error bars represent interquartile ranges, and the dashed line represents a lambda ratio of one. * $p<0.05$, Wilcoxon rank sum test for median values.

where $\Delta = \frac{1}{n(n-1)} \sum_{all\ j \neq j'} \rho_{jj'}$. The minimum sample size was estimated by substituting $b = 0.10$ into equation (4), along with the estimates of λ (16.6 for inorganic lead exposure, and 0.654 for urinary lead, Appendix D) and ρ (zero for air lead and 0.25 for urinary lead under AR(1)) for the corresponding true parameters. This leads to estimated sample sizes of $n = 10$ measurements per subject for lead in urine and $n = 150$ measurements per subject for lead in air. There should be little doubt in this case that the biomarker would provide a better surrogate measure of exposure than air measurements for investigating health effects in this population, as has previously been argued in the context of hazard control.[40]

The advantage noted above for intermediate and long term biomarkers (relative to air measurements) will not generally be realised for short term biomarkers, which reflect exposure during the current or preceding day. In the study by Rappaport and colleagues,[26] for example, styrene in exhaled air (a short term biomarker) was measured along with styrene in air. Using data from that investigation, $\hat{\lambda}$ was 0.28 for air styrene and 0.99 for styrene in exhaled air (Appendix D), and Δ was 0 in both cases. To achieve the desired goal of $b \leqslant 0.1$, from equation (4) we require $n = 3$ measurements per person for air styrene and $n = 9$ measurements of styrene in exhaled air. In this case, there is evidence that styrene in air would be a better surrogate measure of exposure than styrene in exhaled air.

Although the above calculations indicate that biomarkers with longer residence times would generally be preferred to those with shorter residence times, the specificity of candidate biomarkers and the precision of assays can also be important. Consider for example, the eight biomarkers listed in Appendix D for styrene and styrene oxide. Values of $\hat{\lambda}$ for these biomarkers increased in the following order: blood styrene (0.770, two studies) < breath styrene (0.989) < urinary mandelic acid (1.44, two studies) < lymphocyte SCEs (1.58) < lymphocyte HPRT mutation frequency (1.77) < blood styrene glycol (2.09) < blood SO-albumin adduct (14.3) < SO-DNA adduct (24.7). The two smallest values of $\hat{\lambda}$ were observed for short term biomarkers (styrene in blood and breath) while the two largest values of $\hat{\lambda}$ were for intermediate term biomarkers (albumin and DNA adducts of SO). This can partially be explained by the imprecision of the adduct assays; indeed, the coefficient of variation of the post-labelling assay for the DNA adduct was about 200%.[23]

Our analyses did not permit inferences to be made about the effects on variance ratios of important metabolising and repair genes. However, it is reasonable to expect that functional SNPs of these gene alleles would increase σ_B^2 of relevant biomarkers while having little affect on σ_W^2. Since air levels should be independent of SNP status, the practical effect of functional SNPs would be to preferentially decrease variance ratios for biomarkers relative to air levels. This would also reduce the biasing effect of such biomarkers as surrogates for exposure.

Aside from the biasing potential of using air and biomarker measurements as surrogates for true exposure levels, other constraints could loom large, such as the difficulty of repeatedly collecting blood specimens rather than air samples from a population or the increased costs of biological measurements compared to air measurements. Also, our analyses implicitly assume that air represents the dominant route of exposure to the toxic chemical. This will not always be the case. For example, we found that air measurements of pesticides produced significantly smaller $\hat{\lambda}$ values than did biomarker measurements (fig 4B), suggesting that ingestion and/or dermal contact were reflected by biomarkers in those studies. Taking all factors into account, the optimal measure of exposure for an epidemiology study depends not only on variance ratios of the air and biomarker measurements (smaller is better), but also on projected sample sizes (larger is better), based on practical considerations and costs, and on knowledge of the dominant route of exposure (if multiple routes, biomarkers are better).

Finally, it is worth mentioning that studies that collect *both* air measurements and biomarkers are particularly valuable because they provide information with which to estimate the rates of human uptake, elimination, and metabolism of toxic chemicals. Given the paucity of human toxicokinetic data for most contaminants, the quantification of such rates with primary data from observational studies would be valuable. When collected in longitudinal sampling designs, where repeated exposure and air measurements are obtained from representative persons, these data can also allow interindividual differences in uptake, etc to be estimated and ultimately related to genetic, physiological, and lifestyle factors (for example, see Rappaport and colleagues[41]).

Limitations of the study

Our analyses were limited in several important ways. First, we were constrained by the relatively few studies that provided longitudinal data of *both* air measurements and

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Main messages

- There is considerable within- and between-person variability in both air and biomarker levels that affect valid and precise characterisation of exposure-disease relationships.
- Although air measurements and biomarkers each have distinct advantages and disadvantages as surrogate measures of exposure, biomarkers appear to provide less biased estimates of true exposure levels for epidemiological studies.

Policy implications

- Epidemiologists should consider using biomarkers instead of, or in addition to, air measurements for assessing levels of chemical exposure.

biomarkers from a given population and by the limited numbers of measurements per subject in most investigations. Small sample sizes particularly limited our ability to draw clear conclusions in stratified comparisons (for example, for biomarkers of pesticides and long term biomarkers). Second, since most of our database was derived from secondary data, it was only possible to examine the effects of a relatively small number of covariates, such as occupational or environmental sources of exposure, etc. Third, we focused entirely on exposures to airborne contaminants, recognising that other routes (dermal contact or ingestion) could have produced significant contributions to biomarker levels in some cases. Fourth, we considered biasing measurement error effects only in the context of individual based studies where air measurements or biomarkers were obtained from each person in a sample and the logged continuous health outcome was related to the logged individual mean measure of exposure. The statistical issues in such an individual based study are somewhat different from those in a group based study, where the mean health outcome for each group is compared with the corresponding group mean of the exposure measure.[42] And finally, we recognise that our database was confined largely to published investigations of biological monitoring. These studies could well have been biased in favour of biomarkers that had previously been shown to be useful, such as metals in blood and urine. If this were the case, then we somewhat overstate the generally less biasing advantage of biomarkers that we observed.

Conclusions

We identified consistently great variability in air levels and biomarkers both between and within persons in a large number of longitudinal studies of chemical exposure. We argue that the air or biological measure with the smallest (within- to between-person) variance ratio should be the optimal—that is, least biasing surrogate for exposure in a study of health effects. We present evidence that biomarkers tend to have smaller variance ratios than air measurements. Epidemiologists should consider the magnitudes of variance ratios of air measurements and biomarkers as one criterion for selecting the optimal surrogate for exposure in their studies.

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APPENDICES

Appendix A. Descriptive characteristics of environmental settings

Exposure agent	Exposure monitoring characteristics: Conc. range (median)	N* (*k*)	Sampling interval	Biomarker	Biological monitoring characteristics: Conc. range (median)	N (*k*)	Sampling interval	Notes	Ref.
Metals									
Airborne lead†	0.36-4.7 ng/m^3 (0.93)	106 (45)	2 months	Blood lead	0.6-9.8 µg/dl (2.4)	351 (73)	2 months		[30]
Organic compounds									
Airborne benzene	0.012-36.1 mg/m^3 (1.20)	122 (30)	1-7 months	Breath benzene	0.002-1.40 mg/m^3 (0.052)	122 (30)	1-7 months	During self-service refuel	[43]
Airborne benzene	0.105-63.0 µg/m^3 (13.0)	42 (21)	14-17 months	Breath benzene	0.050-72.0 µg/m^3 (6.08)	34 (17)	14-17 months	Bayonne, NJ	[25]
	0.030-150 µg/m^3 (17.0)	52 (26)	14-17 months		0.030-150 µg/m^3 (12.0)	42 (21)	14-17 months	Elizabeth, NJ	[25]
	1.30-163 µg/m^3 (11.0)	192 (70)	3-40 months		0.030-116 µg/m^3 (3.40)	189 (70)	3-40 months	Los Angeles, CA	[25]
Airborne chloroform	0.070-25.5 µg/m^3 (1.88)	42 (21)	14-17 months	Breath chloroform	0.049-4.40 µg/m^3 (0.665)	34 (17)	14-17 months	Bayonne, NJ	[25]
	0.075-73.0 µg/m^3 (2.38)	52 (26)	14-17 months		0.050-28.0 µg/m^3 (0.466)	42 (21)	14-17 months	Elizabeth, NJ	[25]
	0.022-92.0 µg/m^3 (0.720)	199 (69)	3-40 months		0.030-18.0 µg/m^3 (0.170)	190 (66)	3-40 months	Los Angeles, CA	[25]
Airborne ethylbenzene	0.225-47.5 µg/m^3 (7.55)	42 (21)	14-17 months	Breath ethylbenzene	0.025-11.0 µg/m^3 (1.45)	34 (17)	14-17 months	Bayonne, NJ	[25]
	0.950-1100 µg/m^3 (11.0)	52 (26)	14-17 months		0.250-290 µg/m^3 (2.10)	42 (21)	14-17 months	Elizabeth, NJ	[25]
	0.131-198 µg/m^3 (5.92)	207 (73)	3-40 months		0.010-22.0 µg/m^3 (0.653)	200 (72)	3-40 months	Los Angeles, CA	[25]

Airborne methylchloroform	0.85-580 μg/m^3 (18.0)	42 (21)	14-17 months	Breath methylchloroform	0.060-15.5 μg/m^3 (2.35)	34 (17)	14-17 months	Bayonne, NJ	[25]
	0.085-8400 μg/m^3 (16.1)	52 (26)	14-17 months		0.210-360 μg/m^3 (5.35)	40 (20)	14-17 months	Elizabeth, NJ	[25]
	1.04-3994 μg/m^3 (15.0)	207 (73)	3-40 months		0.043-1294 μg/m^3 (4.76)	201 (72)	3-40 months	Los Angeles, CA	[25]
Airborne *p*-dichlorobenzene	0.338-270 μg/m^3 (4.98)	42 (21)	14-17 months	Breath *p*-dichlorobenzene	0.131-43.0 μg/m^3 (1.06)	32 (16)	14-17 months	Bayonne, NJ	[25]
	0.269-770 μg/m^3 (3.35)	52 (26)	14-17 months		0.150-31.0 μg/m^3 (1.15)	40 (20)	14-17 months	Elizabeth, NJ	[25]
	0.060-232 μg/m^3 (2.09)	66 (33)	3-40 months		0.050-76.0 μg/m^3 (0.501)	62 (31)	3-40 months	Los Angeles, CA	[25]
Airborne perchloroethylene	0.170-230 μg/m^3 (9.80)	42 (21)	14-17 months	Breath perchloroethylene	1.10-33.0 μg/m^3 (5.45)	34 (17)	14-17 months	Bayonne, NJ	[25]
	0.750-1800 μg/m^3 (8.45)	52 (26)	14-17 months		1.63-170 μg/m^3 (4.50)	42 (21)	14-17 months	Elizabeth, NJ	[25]
	0.026-520 μg/m^3 (5.40)	191 (70)	3-40 months		0.119-487 μg/m^3 (4.58)	178 (69)	3-40 months	Los Angeles, CA	[25]
Airborne styrene	0.080-23.0 μg/m^3 (1.65)	42 (21)	14-17 months	Breath styrene	0.070-3.00 μg/m^3 (0.333)	30 (15)	14-17 months	Bayonne, NJ	[25]
	0.095-130 μg/m^3 (2.58)	52 (26)	14-17 months		0.060-14.0 μg/m^3 (0.660)	42 (21)	14-17 months	Elizabeth, NJ	[25]
	0.022-29.5 μg/m^3 (1.90)	205 (73)	3-40 months		0.030-13.0 μg/m^3 (0.174)	199 (71)	3-40 months	Los Angeles, CA	[25]
Airborne trichloroethylene	0.135-29.0 μg/m^3 (2.40)	42 (21)	14-17 months	Breath trichloroethylene	0.075-1.70 μg/m^3 (0.438)	34 (17)	14-17 months	Bayonne, NJ	[25]
	0.140-53.0 μg/m^3 (4.00)	52 (26)	14-17 months		0.075-5.80 μg/m^3 (0.699)	40 (20)	14-17 months	Elizabeth, NJ	[25]
	0.022-350 μg/m^3 (0.785)	202 (72)	3-40 months		0.030-180 μg/m^3 (0.169)	194 (69)	3-40 months	Los Angeles, CA	[25]
Airborne *o*-xylenes	0.265-42.0 μg/m^3 (6.70)	42 (21)	14-17 months	Breath *o*-xylenes	0.150-11.0 μg/m^3 (1.10)	34 (17)	14-17 months	Bayonne, NJ	[25]
	0.550-770 μg/m^3 (9.55)	52 (26)	14-17 months		0.050-220 μg/m^3 (1.75)	42 (21)	14-17 months	Elizabeth, NJ	[25]

	0.026-160 μg/m^3 (8.00)	207 (73)	3-40 months		0.034-10.6 μg/m^3 (0.738)	202 (72)	3-40 months	Los Angeles, CA	[25]
Pesticides									
Airborne chlordane†	0.71-71.3 ng/m^3 (9.15)	32 (9)	2 months	Blood oxychlordane	21-156 ng/g lipid (45)	89 (32)	2 months		[30]
Airborne chlorpyrifos†	0.84-283 ng/m^3 (11.4)	57 (16)	2 months	Urinary TCPY	0.197-25 μg/g creatinine (4.65)	312 (69)	2 months		[30]
Airborne dieldrin†	1.95-57.9 ng/m^3 (12.8)	11 (3)	2 months	Blood dieldrin	21-202 ng/g lipid (59)	39 (13)	2 months		[30]
Airborne heptachlor†	1.04-389 ng/m^3 (7.7)	51 (14)	2 months	Blood heptachlor epoxide	26-130 ng/g lipid (81)	20 (5)	2 months		[30]
				Biomarker data only					
Organic compounds									
Mixed exposure to toluene, benzene, and other organic compounds with concentration ranging from non-detectable to 11.4 μg/ m^3.				Blood lymphocytes HFC	20-78 per subject (53)	20 (10)	2 years	Excluding 1993 data.	[44]
Children exposed to polycyclic aromatic hydrocarbons (PAH).				Urinary 1-hydroxypyrene	0.07-3.6 μmol/mol creatinine (0.41)	180 (30)	Daily		[34]
Children exposed to environmental tobacco smoking (ETS).				Urinary cotinine	10.1-91.7 ng/ml (24.8)	28 (14)	3 months		[45]
				Urinary NNAL+NNAL-Gluc	0.013-0.51 pmol/ml (0.13)	31 (16)	3 months		[45]
Pesticides									
Women exposed to chlorinated hydrocarbons.				Blood DDE	0.0005-4 μg/g lipid (0.93)	62 (31)	2 months		[46]
				Blood PCB	0.15-1.49 μg/g lipid (0.53)	60 (30)	2 months		[46]
				Blood trans-nonachlor	0.01-0.11 μg/g lipid (0.04)	60 (30)	2 months		[46]
U.S. EPA National Human Exposure Assessment Survey (NHEXAS) Maryland study.				Blood DDE	77-4445 ng/g lipid (518)	315 (72)	2 months		[30]
				Blood hexachlorobenzene	13-112 ng/g lipid (47)	314 (72)	2 months		[30]

	Blood trans-nonachlor	36-165 ng/g lipid (57)	62 (19)	2 months	[30]
	Urinary atrazine mercapturate	0.13-1.64 μg/g creatinine (0.40)	314 (69)	2 months	[30]
	Urinary malathion dicarboxylic acid	0.13-51 μg/g creatinine (0.43)	313 (69)	2 months	[30]
	Urinary 1-naphthol	0.2-4600 μg/g creatinine (3.4)	307 (69)	2 months	[30]

Abbreviations:
DDE, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene; HFC, high frequency cell analysis; NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNAL-Gluc, [4-(methylnitrosamino)-1-(3-pyridyl) but-1-yl]-beta-O-D-glucosiduronic acid; PCB, polychlorinated biphenyls; TCPY, 3,5,6-trichloro-2-pyridinol.
*N, total number of observations; *k,* number of persons.
†Indoor air samples.

Appendix B. Descriptive characteristics of occupational settings

Exposure agent	Exposure monitoring characteristics: Conc. range (median)	N* (*k*)	Sampling interval	Biomarker	Biological monitoring characteristics: Conc. range (median)	N (*k*)	Sampling interval	Notes	Ref.
Metals									
Airborne chromium	0.01-0.51 mg/m^3 (0.08)	25 (5)	Daily†	Urinary chromium	13-153 µg/g creatinine (52)	25 (5)	Daily	Post-shift.	[35]
					11-88 µg/g creatinine (29)	25 (5)	Daily	Pre-shift‡.	[35]
Airborne chromium	0.01-0.59 mg/m^3 (0.16)	20 (4)	Daily†	Urinary chromium	11.7-152 µg/g creatinine (69.1)	20 (4)	Daily	Post-shift.	[36]
					10.9-86.7 µg/g creatinine (39.1)	20 (4)	Daily	Pre-shift‡.	[36]
Airborne nickel	0.5-21.2 µg/m^3 (9.1)	15 (5)	2 days	Urinary nickel	5-139 µg/l (33)	21 (8)	2 days	Post-shift.	[37]
					7-142 µg/l (23)	23 (8)	2 days	Pre-shift‡.	[37]
Airborne nickel	0.03-0.16 mg/m^3 (0.09)	20 (4)	Daily†	Blood nickel	2.4-14.1 µg/l (9.3)	18 (4)	Daily	Post-shift.	[36]
					1.2-8.8 µg/l (3.4)	20 (4)	Daily	Pre-shift‡.	[36]
				Urinary nickel	24-109 µg/l (76)	18 (4)	Daily	Post-shift.	[36]
					12-73 µg/l (41)	20 (4)	Daily	Pre-shift‡.	[36]
Airborne alkyl lead	1.3-1249 µg/m^3 (23.4)	176 (6)	Daily	Blood lead	24-52 µg/100 g (41)	36 (6)	4-7 days		[26]
Airborne inorganic lead	1.3-62.6 µg/m^3 (15.7)	176 (6)	Daily	Urinary δ-aminolevulinate	30-840 mg/100ml (320)	181 (6)	Daily		[26]
				Urinary lead	10-165 µg/l (71)	181 (6)	Daily		[26]

Airborne mercury	2.23-155 μg/m^3 (18.7)	592 (16)	Daily	Blood mercury	20-280 nmol/l (90)	226 (16)	3-11 days		[31]
Organic chemicals									
Airborne benzene	1.30-1140 μg/m^3 (59.9)	184 (69)	1-7 months	Breath benzene	2.10-2026 μg/m^3 (23.2)	183 (70)	1-7 months		[29]
Airborne carcinogenic PAH	5.3-76 ng/m^3 (15.7)	40 (10)	1-11 months	Blood cell DNA adducts/10^8 nucleotides	2.71-11.1 (4.90)	40 (10)	1-11 months		[47]
Airborne ethylene oxide	0.4-22.5 mg/m^3 (5.5)	27 (9)	Daily	Breath ethylene oxide	0.2-7 mg/m^3 (1.5)	26 (9)	Daily	Only post-shift data is used. The mid-shift data is excluded.	[32]
				Blood ethylene oxide	4-103.7 μg/l (36.7)	24 (9)	Daily		[32]
Airborne ethylene oxide†	0.65-12.1 mg/m^3 (2.95)	20 (4)	Daily	Blood *N*-2-hydroxyethyl-valine	53.1-115 pmol/g globin (69.4)	12 (4)	Daily		[48]
Airborne monoterpenes	6-228 mg/m^3 (66)	39 (10)	2-120 days	Urinary verbenol	2.0-75 μmol/mol creatinine (16)	39 (10)	2-120 days		[20]
Airborne styrene	1-102 mg/m^3 (23.5)	36 (12)	2-6 months	Urinary mandelic acid	13.5-353 mg/g creatinine (99.8)	36 (12)	2-6 months		[20]
Airborne styrene	15-268 mg/m^3 (70)	27 (9)	7-11 months	Blood styrene	0.1-2.3 mg/l (0.6)	26 (9)	2-5 months		[33]
				T-lymphocytes HPRT mutation frequency x10^6	7.1-86.8 (16.6)	22 (5)	1-13 months		[33]
				Urinary mandelic acid	51-1310 mmol/mol creatinine (164)	42 (11)	2-11 months		[33]
Airborne styrene	0.34-391 mg/m^3 (19.9)	249 (48)	2-3 months	Breath styrene	0.01-12.2 mg/m^3 (2.1)	156 (29)	3-4 months		[24]
Airborne styrene oxide	10.4-444 μg/m^3 (139)	17 (7)	1-8 months	Blood styrene	0.0007-3.58 μg/ml (0.09)	146 (46)	3-4 months		[24]
				Blood free styrene glycol	2.95-979 μg/ml (39.8)	104 (42)	3-4 months		[24]
				Blood SO-albumin adduct(α)	0.01-3.4 nmol/g albumin (0.16)	108 (42)	3-4 months	Attack of SO on the α carbon.	[24]
				Blood SO-albumin adduct(β)	0.25-6.0 nmol/g albumin (1.4)	108 (42)	3-4 months	Attack of SO on the β carbon.	[24]

				Blood (lymphocyte) SO-DNA(1)	0.06-195 μg/m^3 (5.9)	48 (24)	3 months		[24]
				Blood (lymphocyte) SO-DNA(2)	0.07-131 μg/m^3 (9.0)	48 (24)	3 months		[24]
				Blood hemoglobin adduct	0.01-0.27 nmol/g hemoglobin (0.05)	117 (44)	3-4 months		[24]
				Blood (lymphocyte) sister chromatid exchange	3.7-9.6 per cell (6.4)	68 (34)	4 months		[24]
Airborne perchloroethylene	0-58.2 ppm (4.05)	58 (13)	Daily	Breath perchloroethylene	0.140-12.4 ppm (1.58)	57 (13)	Daily		[49]
				Quantitative Biomarker only					
Organic compounds									
Workers exposed to ethylene oxide. Individual exposure data is not available.				Blood *N*-2-hydroxyethyl-valine	0-295 pmol/g globin (72)	20 (9)	3-12 months	Only used data from routine operation.	[50]
Workers exposed to ethylene oxide ranging from 0.2 to 8.5 ppm. Individual exposure data is not available.				Blood *N*-2-hydroxyethyl-valine	5219-32738 pmol/g globin (12746)	12 (6)	4 months		[51]
Workers exposed to toluene with a mean exposure of 46 ppm. Individual exposure data is not available.				Urinary microalbumin	0.04-8.8 mg/mmol creatinine (N/A)	292 (142)	2-24 months	This study is not included in the summary statistics.	[52]
				Urinary NAG	0.09-1.14 IU/mmol creatinine (N/A)	292 (142)	2-24 months		[52]
				Urinary AAP	0.16-2.48 IU/mmol creatinine (N/A)	292 (142)	2-24 months		[52]

Abbreviations:
AAP, alanine aminopeptidase; DNA, deoxyribonucleic acid; HPRT, hypoxanthine guanine phosphoribosyl transferase; N/A, Not available; NAG, N-acetyl-beta-D-glucosaminidase NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNAL-Gluc, [4-(methylnitrosamino)-1-(3-pyridyl) but-1-yl]-beta-O-D-glucosiduronic acid; PAH, polycyclic aromatic hydrocarbons; SO, Styrene oxide; SO-DNA(1), N^2-(2-hydroxy-1-phenylethyl)-2′-deoxyguanosine-3,5-biphosphate; SO-DNA (2), unidentified DNA adduct [23].
*N, total number of observations; *k*, number of persons.
†Daily average.
‡Excluded from the summary analysis (illustrative purposes only).

Appendix C. Estimated variance components for air and biomarker measurements in environmental settings*

Exposure agent	Air measurements			Biomarker	Biomarker measurements			Notes	Ref.
	$\hat{\sigma}_B^2$ †	$\hat{\sigma}_W^2$ †	$\hat{\lambda}$ †		$\hat{\sigma}_B^2$	$\hat{\sigma}_W^2$	$\hat{\lambda}$		
Metals									
Lead	0.024‡	0.207‡	8.60‡	Blood lead	0.278‡	0.109‡	0.394‡		[30]
Organic compounds									
Benzene	0.049	2.51	50.9	Breath benzene	0.462	1.90	4.10		[44]
Benzene	0.000	1.51	N/A	Breath benzene	0.501	1.65	3.29	Bayonne, NJ	[25]
	0.482	2.47	5.12		0.796	2.81	3.53	Elizabeth, NJ	[25]
	0.094‡	0.543‡	5.80‡		1.18‡	1.95‡	1.65‡	Los Angeles, CA	[25]
Chloroform	0.000	1.51	N/A	Breath chloroform	0.000	2.33	N/A	Bayonne, NJ	[25]
	0.022	1.79	80.8		0.942‡	1.28‡	1.36‡	Elizabeth, NJ	[25]
	0.101‡	2.01‡	19.9‡		0.167	2.78	16.6	Los Angeles, CA	[25]
Ethylbenzene	0.000	1.12	N/A	Breath ethylbenzene	0.465	1.33	2.85	Bayonne, NJ	[25]
	1.41	1.04	0.741		0.931‡	1.04‡	1.12‡	Elizabeth, NJ	[25]
	0.215‡	0.920‡	4.28‡		0.921‡	1.20‡	1.30‡	Los Angeles, CA	[25]
Methylchloroform	0.678	1.22	1.80	Breath methylchloroform	0.000	2.43	N/A	Bayonne, NJ	[25]

	0.270	4.33	16.0		1.36‡	1.32‡	0.97‡	Elizabeth, NJ	[25]
	0.263‡	1.41‡	5.35‡		0.805‡	1.19‡	1.48‡	Los Angeles, CA	[25]
p-Dichlorobenzene	0.725‡	1.65‡	2.27‡	Breath *p*-dichlorobenzene	1.05	1.05	0.998	Bayonne, NJ	[25]
	0.716	2.52	3.52		0.620‡	0.645‡	1.04‡	Elizabeth, NJ	[25]
	1.59‡	1.45‡	0.909‡		2.72‡	0.938‡	0.345‡	Los Angeles, CA	[25]
Perchloroethylene	0.000	1.91	N/A	Breath perchloroethylene	0.129	0.531	4.12	Bayonne, NJ	[25]
	0.041	2.29	55.3		0.322	0.974	3.02	Elizabeth, NJ	[25]
	0.136‡	1.46‡	10.7‡		0.545‡	0.557‡	1.02‡	Los Angeles, CA	[25]
Styrene	0.449	0.672	1.50	Breath styrene	0.419‡	0.426‡	1.02‡	Bayonne, NJ	[25]
	0.557	1.17	2.10		0.246‡	0.898‡	3.65‡	Elizabeth, NJ	[25]
	0.279‡	1.17‡	4.20‡		1.05	2.07	1.98	Los Angeles, CA	[25]
Trichloroethylene	0.107	1.17	10.9	Breath trichloroethylene	0.272‡	0.621‡	2.28‡	Bayonne, NJ	[25]
	0.694	1.52	2.18		0.000	1.72	N/A	Elizabeth, NJ	[25]
	1.08‡	3.51‡	3.25‡		0.784‡	1.67‡	2.13‡	Los Angeles, CA	[25]
o-Xylenes	0.000	1.09	N/A	Breath *o*-xylenes	0.007	0.841	126	Bayonne, NJ	[25]
	1.13	1.46	1.29		0.756	1.319	1.75	Elizabeth, NJ	[25]
	0.059‡	1.40‡	23.8‡		0.387‡	0.846‡	2.19‡	Los Angeles, CA	[25]

Pesticides									
Chlordane	2.25	0.123	0.055	Blood oxychlordane	0.076	0.072	0.946		[30]
Chlorpyrifos	1.97‡	0.220‡	0.112‡	Urinary TCPY	0.147‡	0.361‡	2.45‡		[30]
Dieldrin	1.35	0.107	0.079	Blood dieldrin	0.170	0.097	0.573		[30]
Heptachlor	3.15	0.196	0.062	Blood heptachlor epoxide	0.295	0.027	0.091		[30]
				Biomarker data only					
Organic compounds									
Mixed exposure to toluene, benzene, and other organic compounds.				Blood lymphocytes HFC	0.000	0.084	N/A	Excluding 1993 data.	[44]
Children exposed to polycyclic aromatic hydrocarbons (PAH).				Urinary 1-hydroxypyrene	0.324‡	0.192‡	0.593‡		[34]
Children exposed to environmental tobacco smoking (ETS).				Urinary cotinine	0.000	0.272	N/A		[45]
				Urinary NNAL + NNAL-Gluc	0.240	0.517	2.15		[45]
Pesticides									
Women exposed to chlorinated hydrocarbons.				Blood DDE	2.72	0.040	0.015		[46]
				Blood PCB	0.273	0.022	0.082		[46]
				Blood trans-nonachlor	0.208	0.122	0.585	Including one outlier.	[46]
				Blood trans-nonachlor	0.265	0.027	0.102	Excluding one outlier§.	[46]
Persons in the Maryland area exposed to environmental pesticides.				Blood DDE	0.348‡	0.062‡	0.179‡	AR (1). AIC=190.1; BIC= 196.9	[30]
				Blood DDE	0.356‡	0.049‡	0.140‡	Compound symmetry§. AIC= 209.4; BIC= 214.0	[30]

Blood hexachlorobenzene	0.030‡	0.101‡	3.30‡		[30]
Blood trans-nonachlor	0.000	0.161	N/A	AR (1). AIC= 35.8; BIC= 37.7	[30]
Blood trans-nonachlor	0.107	0.062	0.580	Compound symmetry§. AIC= 44.5; BIC= 46.3	[30]
Urinary atrazine mercapturate	0.153‡	0.160‡	1.05‡		[30]
Urinary malathion dicarboxylic acid	0.107‡	0.511‡	4.77‡		[30]
Urinary 1-naphthol	1.41	1.00	0.709		[30]

Abbreviations:
DDE, 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene; HFC, high frequency cell analysis; NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNAL-Gluc, [4-(methylnitrosamino)-1-(3-pyridyl) but-1-yl]-beta-O-D-glucosiduronic acid; PCB, polychlorinated biphenyls; TCPY, 3,5,6-trichloro-2-pyridinol.
*Parameters estimated using logged response data with compound symmetry as the default variance-covariance matrix. When the first-order autoregressive, AR (1), model provides a better model fit based upon Akaike Information Criteria (AIC) and Bayesian Information Criterion (BIC), results for both are reported, but only results for the AR (1) model will be included in the summary analysis.
† $\hat{\sigma}^2_B$, estimated between-person variance component; $\hat{\sigma}^2_W$, estimated within-person variance component; $\hat{\rho}$, estimated correlation between measurements; $\hat{\lambda}$, the estimated ratio of within-person to between-person variance components.
‡Adjusted for a time effect.
§Excluded from the summary analysis (illustrative purposes only).

Appendix D. Estimated variance components for air and biomarker measurements in occupational settings*

Exposure agent	Air measurements			Biomarker	Biomarker measurements			Notes	Ref.
	$\hat{\sigma}_B^2$ †	$\hat{\sigma}_W^2$ †	$\hat{\lambda}$ †		$\hat{\sigma}_B^2$	$\hat{\sigma}_W^2$	$\hat{\lambda}$		
Metals									
Chromium	1.49	0.797	0.536	Urinary chromium	0.576‡	0.035‡	0.061‡	Post-shift.	[35]
				Urinary Chromium	0.300‡	0.054‡	0.179‡	Pre-shift§.	[35]
Chromium	1.22	0.705	0.576	Urinary chromium	0.630‡	0.040‡	0.064‡	Post-shift.	[36]
				Urinary chromium	0.394‡	0.061‡	0.160‡	Pre-shift§.	[36]
Nickel	0.195	0.572	2.93	Urinary nickel	0.242‡	0.243‡	1.00‡	Post-shift.	[37]
				Urinary nickel	0.285	0.337	1.18	Pre-shift§.	[37]
Nickel	0.482	0.015	0.030	Blood nickel	0.317	0.055	0.173	Post-shift.	[36]
				Blood nickel	0.266‡	0.106‡	0.400‡	Pre-shift§.	[36]
				Urinary nickel	0.162‡	0.018‡	0.113‡	Post-shift.	[36]
				Urinary nickel	0.323‡	0.016‡	0.050‡	Pre-shift§.	[36]
Alkyl lead	0.161	0.719	4.47	Blood lead	0.038	0.010	0.276		[26]

Inorganic lead	0.023	0.377	16.6	Urinary δ-aminolevulinate	0.242	0.249	1.03	AR (1). AIC=268.1; BIC= 267.5	[26]
				Urinary δ-aminolevulinate	0.241	0.244	1.01	Compound symmetry§. AIC= 282.7; BIC= 282.3	[26]
				Urinary lead	0.139	0.091	0.654	AR (1). AIC=97.8; BIC= 97.1	[26]
				Urinary lead	0.143	0.089	0.630	Compound symmetry§. AIC= 104.7; BIC= 104.3	[26]
Mercury	0.052‡	0.256‡	4.87‡	Blood mercury	0.119‡	0.028‡	0.237‡		[31]
Organic compounds									
Benzene	0.262‡	0.626‡	2.40‡	Breath benzene	0.370‡	0.655‡	1.77‡		[29]
Carcinogenic PAH	0.000	0.446	N/A	Blood cell DNA adducts/10^8 nucleotides	0.000	0.112	N/A		[47]
Ethylene oxide	0.000‡	0.742‡	N/A‡	Breath ethylene oxide	0.000‡	0.618‡	N/A‡	Only post-shift data used. Mid-shift data excluded.	[32]
				Blood ethylene oxide	0.000‡	0.783‡	N/A‡		[32]
Ethylene oxide	0.502	0.374	0.746	Blood *N*-2-hydroxyethyl-valine	0.058	0.005	0.080		[48]
Monoterpenes	0.216‡	0.577‡	2.67‡	Urinary verbenol	0.282	0.616	2.19		[20]
Styrene	0.621	0.269	0.434	Urinary mandelic acid	0.349	0.317	0.908		[20]
Styrene	0.231‡	0.342‡	1.48‡	Blood styrene	0.406	0.269	0.663		[33]
				Lymphocyte HPRT mutation frequency x10^6	0.130	0.231	1.77		[33]
				Urinary mandelic acid	0.177	0.350	1.98		[33]
Styrene	2.61	0.725	0.278	Breath styrene	0.816	0.806	0.989		[24]

Styrene oxide	0.245‡	0.131‡	0.537‡	Blood styrene	1.69‡	1.48‡	0.877‡		[24]
				Blood free styrene glycol	0.595‡	1.24‡	2.09‡		[24]
				Blood SO-albumin adduct (α)	0.000‡	0.796‡	N/A‡		[24]
				Blood SO-albumin adduct (β)	0.027‡	0.388‡	14.3‡		[24]
				Blood (lymphocyte) SO-DNA (1)	0.000‡	3.53‡	N/A‡		[24]
				Blood (lymphocyte) SO-DNA (2)	0.102‡	2.51‡	24.7‡		[24]
				Blood hemoglobin adduct	0.000‡	0.269‡	N/A‡		[24]
				Blood (lymphocyte) sister chromatid exchange	0.014	0.022	1.58		[24]
Perchloroethylene	2.28	0.427	0.187	Breath perchloroethylene	2.00	0.117	0.058		[49]
				Biomarker data only					
Occupational exposure to ethylene oxide				Blood *N*-2-hydroxyethyl-valine	0.000	3.10	N/A	Data from routine Operation used.	[50]
Occupational exposure to ethylene oxide				Blood *N*-2-hydroxyethyl-valine	0.225	0.118	0.524		[51]
Occupational exposure to toluene				Urinary microalbumin	0.231	0.207	0.900	This study is not included in the summary statistics§.	[52]
				Urinary NAG	0.117	0.088	0.750		[52]
				Urinary AAP	0.071	0.055	0.770		[52]

Abbreviations:
AAP, alanine aminopeptidase; DNA, deoxyribonucleic acid; HPRT, hypoxanthine guanine phosphoribosyl transferase; N/A, Not available; NAG, N-acetyl-beta-D-glucosaminidase; NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNAL-Gluc, [4-(methylnitrosamino)-1-(3-pyridyl) but-1-yl]-beta-O-D-glucosiduronic acid; PAH, polycyclic aromatic hydrocarbons; SO, Styrene oxide; SO-DNA(1), N^2-(2-hydroxy-1-phenylethyl)-2′-deoxyguanosine-3,5-biphosphate; SO-DNA (2), unidentified DNA adduct [23].
*Parameters estimated using logged response data with compound symmetry as the default variance-covariance matrix. When the first-order autoregressive, AR (1), model provides a better model fit based upon Akaike Information Criteria (AIC) and Bayesian Information Criterion (BIC), results for both are reported, but only results for the AR (1) model will be included in the summary analysis.
† $\hat{\sigma}^2_B$, the estimated between-person variance component; $\hat{\sigma}^2_W$, the estimated within-person variance component; $\hat{\rho}$, the estimated correlation between measurements; $\hat{\lambda}$, the estimated ratio of within-person to between-person variance components.
‡Adjusted for time effect.
§Excluded from the summary analysis (illustrative purposes only).

Appendix E. Measurement error involving the variance ratio $\left(\lambda = \sigma_{\mathrm{W}}^2 / \sigma_{\mathrm{B}}^2\right)$ under different covariance structures, n measurements per subject.

True regression model:

$\ln \mathrm{E}(R_i \mid \mu_i) = \theta_0 + \theta_{true} \ln \mu_i$, where R_i is the (continuous) health outcome for the i-th person, μ_i is the true but unobservable air (or biomarker) measurement for the i-th person, and θ_{true} is the parameter quantifying the strength of the true underlying (log-log) exposure-disease relationship. Note that, on the original unlogged scale, $\mathrm{E}(R_i \mid \mu_i) = e^{\theta_0} \mu_i^{\theta_{true}}$; so the relationship between $\mathrm{E}(R_i \mid \mu_i)$ and μ_i is concave upwards if $\theta_{true} > 1$, is concave downwards if $\theta_{true} < 1$, and is linear if $\theta_{true} = 1$.

Measurement error model:

$Y_{ij} = \ln(X_{ij}) = \gamma_0 + \gamma_{ij}\left(\delta_{0/0}\right) + \beta_i + \varepsilon_{ij}$, where β_i : $\mathrm{N}(0, \sigma_{\mathrm{B}}^2)$, ε_{ij} : $\mathrm{N}(0, \sigma_{\mathrm{W}}^2)$, $\{\beta_i\}$ independent of $\{\varepsilon_{ij}\}$ and $\mathrm{Cov}(\varepsilon_{ij}, \varepsilon_{ij'}) = \sigma_{\mathrm{W}}^2 \rho_{jj'}$, $\forall j \neq j'$.

Some possible choices for $\rho_{jj'}$ are:

(1) $\rho_{jj'} = \rho$ [compound symmetry, $\rho \geq 0$; when $\rho = 0$, $\mathrm{cov}(Y_{ij}, Y_{ij'}) = \sigma_{\mathrm{B}}^2/(\sigma_{\mathrm{B}}^2 + \sigma_{\mathrm{W}}^2)$];

(2) $\rho_{jj'} = \rho^{|j-j'|}$, (first-order autoregressive, $\rho > 0$);

(3) $\rho_{jj'} = \exp(-\phi |t_j - t_{j'}|)$, ϕ is a decay constant, (exponential correlation, $\phi > 0$).

Let $\bar{Y}_i \left(= \frac{1}{n} \sum_{j=1}^{n} Y_{ij}\right)$ be the surrogate measure for $\ln \mu_i$; then, $\bar{Y}_i = \frac{1}{n} \sum_{j=1}^{n} \left(\gamma_0 + \gamma_{ij}\left(\delta_{0/0}\right) + \beta_i + \varepsilon_{ij}\right)$

$= \gamma_0 + \bar{\gamma}_i\left(\delta_{0/0}\right) + \beta_i + \bar{\varepsilon}_i = \ln \mu_i + \bar{\varepsilon}_i$, where $\bar{\gamma}_i\left(\delta_{0/0}\right) = \frac{1}{n} \sum_{j=1}^{n} \gamma_{ij}\left(\delta_{0/0}\right)$, $\ln \mu_i = \gamma_0 + \bar{\gamma}_i\left(\delta_{0/0}\right) + \beta_i$, and $\bar{\varepsilon}_i = \frac{1}{n} \sum_{j=1}^{n} \varepsilon_{ij}$.

So, $\bar{Y}_i$ is normally distributed with $\mathrm{E}(\bar{Y}_i) = \gamma_0 + \bar{\gamma}_i\left(\delta_{0/0}\right)$, and with

$$\mathrm{Var}\,(\overline{Y}_i) = \sigma_{\mathrm{B}}^2 + \mathrm{Var}\,(\overline{\varepsilon}_i) = \sigma_{\mathrm{B}}^2 + \frac{1}{n^2}\mathrm{Var}\,(\sum_{j=1}^{n}\varepsilon_{ij}) = \sigma_{\mathrm{B}}^2 + \frac{1}{n^2}\left[n\,\sigma_{\mathrm{W}}^2 + \sum_{\text{all } j\neq j'}\sigma_{\mathrm{W}}^2\,\rho_{jj'}\right] = \sigma_{\mathrm{B}}^2 + \frac{\sigma_{\mathrm{W}}^2}{n}\left[1+(n-1)\,\mathrm{V}\right],$$

where $\mathrm{V} = \dfrac{1}{n\,(n-1)}\sum_{\text{all } j\neq j'}\rho_{jj'}$.

To evaluate the bias when using $\overline{Y}_i$ as a surrogate for $\ln\mu_i = \gamma_0 + \overline{\gamma}_i\left(\underset{0/0}{\delta}\right) + \beta_i$, we need to evaluate $\ln \mathrm{E}(R_i \mid \overline{Y}_i) = \theta_0 + \theta_{true}\,\mathrm{E}(\ln\mu_i \mid \overline{Y}_i)$. Because $\ln\mu_i$ and $\overline{Y}_i$ jointly follow a bivariate normal distribution, it follows that $\mathrm{E}(\ln\mu_i \mid \overline{Y}_i) = \mathrm{E}(\ln\mu_i) + \dfrac{\mathrm{Cov}\,(\ln\mu_i, \overline{Y}_i)}{\mathrm{Var}\,(\overline{Y}_i)}\left[\overline{Y}_i - \mathrm{E}\left(\overline{Y}_i\right)\right]$. Clearly, $\mathrm{E}(\ln\mu_i) = \gamma_0 + \overline{\gamma}_i\left(\underset{0/0}{\delta}\right)$, and $\mathrm{Cov}\,(\ln\mu_i, \overline{Y}_i) = \mathrm{Var}\,(\beta_i) = \sigma_{\mathrm{B}}^2$. Hence,

$$\mathrm{E}(\ln\mu_i \mid \overline{Y}_i) = \gamma_0 + \overline{\gamma}_i\left(\underset{0/0}{\delta}\right) + \frac{\sigma_{\mathrm{B}}^2}{\sigma_{\mathrm{B}}^2 + \dfrac{\sigma_{\mathrm{W}}^2}{n}\left[1+(n-1)\,\mathrm{V}\right]}\left[\overline{Y}_i - \gamma_0 - \overline{\gamma}_i\left(\underset{0/0}{\delta}\right)\right]$$

$$= \gamma_0 + \overline{\gamma}_i\left(\underset{0/0}{\delta}\right) + \frac{1}{1 + \dfrac{\lambda}{n}\left[1+(n-1)\,\mathrm{V}\right]}\left[\overline{Y}_i - \gamma_0 - \overline{\gamma}_i\left(\underset{0/0}{\delta}\right)\right], \text{ where } \lambda = \frac{\sigma_{\mathrm{W}}^2}{\sigma_{\mathrm{B}}^2}.$$

Thus, $\mathrm{E}(R_i \mid \overline{Y}_i) = \theta_0 + \theta_{true}\left\{\gamma_0 + \overline{\gamma}_i\left(\underset{0/0}{\delta}\right) + \dfrac{1}{1 + \dfrac{\lambda}{n}\left[1+(n-1)\,\mathrm{V}\right]}\left[\overline{Y}_i - \gamma_0 - \overline{\gamma}_i\left(\underset{0/0}{\delta}\right)\right]\right\} = \theta_{0i}^* + \theta^*\,\overline{Y}_i$

where $\theta_{0i}^* = \theta_0 + \theta_{true}\left[\gamma_0 + \overline{\gamma}_i\left(\underset{0/0}{\delta}\right)\right]\left\{1 - \dfrac{1}{1 + \dfrac{\lambda}{n}\left[1+(n-1)\,\mathrm{V}\right]}\right\}$ and $\theta^* = \dfrac{\theta_{true}}{1 + \dfrac{\lambda}{n}\left[1+(n-1)\,\mathrm{V}\right]}$,

where $\lambda = \dfrac{\sigma_{\mathrm{W}}^2}{\sigma_{\mathrm{B}}^2}$ and $\mathrm{V} = \dfrac{1}{n\,(n-1)}\sum_{\text{all } j\neq j'}\rho_{jj'}$.

Two special cases are of interest:

(1) $\rho_{jj'} = 0$ (compound symmetry):

Then, V = 0, so that $\theta^* = \dfrac{\theta_{true}}{1 + \dfrac{\lambda}{n}}$, and $\lim_{n \to \infty} \theta^* = \theta_{true}$.

(2) $\rho_{jj'} = \rho^{|j-j'|}$ (first-order autoregressive), $\rho > 0$:

$$\text{Then, } V = \frac{1}{n\,(n-1)} \sum_{\text{all } j \neq j'} \rho^{|j-j'|} = \frac{2}{n\,(n-1)} \sum_{j=1}^{n-1} \sum_{j'=j+1}^{n} \rho^{(j'-j)} = \frac{2}{n\,(n-1)} \sum_{j=1}^{n-1} \left\{ \rho \left[\frac{1-\rho^{n-j}}{1-\rho} \right] \right\}$$

$$= \frac{2}{n\,(n-1)} \left(\frac{\rho}{1-\rho} \right) \sum_{j=1}^{n-1} \left(1-\rho^{n-j} \right) = \frac{2}{n\,(n-1)} \left(\frac{\rho}{1-\rho} \right) \left[(n-1) - \sum_{j=1}^{n-1} \rho^{n-j} \right]$$

$$= \frac{2}{n\,(n-1)} \left(\frac{\rho}{1-\rho} \right) \left[(n-1) - \rho \left(\frac{1-\rho^{n-1}}{1-\rho} \right) \right] = \frac{2}{n} \left(\frac{\rho}{1-\rho} \right) - \frac{2}{n\,(n-1)} \left(\frac{\rho}{1-\rho} \right)^2 \left(1-\rho^{n-1} \right).$$

$$\text{Thus, } \theta^* = \frac{\theta_{true}}{1 + \dfrac{\lambda}{n} \left\{ 1 + 2 \left(\dfrac{n-1}{n} \right) \left(\dfrac{\rho}{1-\rho} \right) - \dfrac{2}{n} \left(\dfrac{\rho}{1-\rho} \right)^2 \left(1-\rho^{n-1} \right) \right\}}, \text{ and } \lim_{n \to \infty} \theta^* = \theta_{true}.$$