

## Comprehensive evaluation of long term trends in occupational exposure: part 2. Predictive models for declining exposures

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### Abstract

**Objectives**—To explore the effects of various factors related to the industry, the contaminant, and the period and type of sampling on long term declining trends in occupational exposure.

**Methods**—Linear regression analyses were used to assess the relation between reductions in exposure and geographical location, industrial sector, type of contaminant, type of monitoring, carcinogenic classification, calendar period, duration of sampling, and number of reductions in the threshold limit value during the sampling period. Both univariable and multivariable models were applied.

**Results**—Based on univariable analyses, the findings suggest that exposures declined more rapidly in manufacturing than in mining, more rapidly for aerosol contaminants than for vapours, and more rapidly when biological, rather than airborne, monitoring was conducted. Exposures collected more recently (first year of sampling in 1972 or later) fell more rapidly than exposures first evaluated during earlier periods. Irrespective of when the data were collected, the results also suggest that the longer the duration of sampling the slower the rate of decline. Taken together, we found that characteristics related to the contaminant, the industry, the sampling period, and the type of sampling explained a substantial proportion of the variability for exposures evaluated before 1972 ( $R^2=0.78$ ) and for sites evaluated both before and after 1972 ( $R^2=0.91$ ), but explained essentially no variation for data gathered exclusively after 1972 ( $R^2=0.04$ ).

**Conclusions**—By identifying factors that have affected the rates of reduction in a consistent fashion, the results should guide investigators in estimating historical levels when studies assessing exposure-response relations are carried out.

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Keywords: occupational exposure; retrospective assessment; long term trends

Occupational epidemiological studies based on retrospective exposure assessments are fraught with problems. As cumulative exposure is often the primary exposure measure, historical data

documenting systematic changes in concentrations of airborne contaminants are needed to obtain reliable estimates of past exposures. If different patterns of exposure give rise to different risks, models relating exposure to disease must weigh exposures according to when they occurred.<sup>1,2</sup> Such models require investigators to construct meaningful exposure histories, which in turn depend on the availability of information about the temporal patterns of exposure.

When extensive monitoring data are available, retrospective assessments can use statistical models which predict exposures based on such data as well as factors related to the contaminant, the process, and engineering controls.<sup>3,4</sup> More often, however, monitoring data are either unavailable, sporadic, or only exist for recent periods. In such instances, investigators either must assume that exposures have not changed<sup>5</sup> or must extrapolate from later periods backwards in time. Such extrapolations often use subjective judgments about the effects of important changes to the working environment,<sup>6,8</sup> or take advantage of exposure data from other workplaces thought to represent similar conditions.<sup>9,10</sup> In many cases, however, the historical record may be judged inadequate for any kind of quantitative estimation; then only semiquantitative<sup>11-13</sup> or qualitative<sup>14</sup> measures of exposure can be constructed. In any case, retrospective assessment methods raise questions related to the precision and validity of the estimated exposures and can obscure or distort exposure-response relations when errors are large.<sup>15,16</sup>

Given the paucity of information about the long term behaviour of occupational exposures, the primary objective of this investigation was to evaluate historical trends in exposure for a wide range of contaminants among a broad cross section of industries. In a companion paper<sup>17</sup> we describe a database of long term exposures and used those data to identify declining trends in about 78% of the data sets. In this paper, we explore the effects on these decreasing trends from various factors related to the industry, the type, and source of the contaminant, and the period and type of sampling.

### Methods

#### COMPILATION OF THE DATABASE AND ANALYSIS OF TEMPORAL TRENDS

We reviewed the literature to identify studies that reported occupational exposures over time. In total, 696 data sets were compiled

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from 119 published studies and several unpublished sources. As well as information on exposure levels, details about the source and type of the contaminant, and the type of sampling were recorded. A complete description of the database appears in the accompanying paper.<sup>17</sup>

As described in the accompanying paper,<sup>17</sup> a simple linear regression of the natural logarithm of the average level of exposure versus time was applied to characterise any linear trend for each data set. The unweighted least squares slope estimate ( $\hat{\beta}_i$ ) that was obtained from the regression of the logged exposures on time for the *i*-th data set was used to compute the estimated median percentage change in exposure per year—that is,  $100(\hat{\theta}_i)$ , where  $\hat{\theta}_i = (e^{\hat{\beta}_i} - 1)$ .<sup>17</sup>

#### EVALUATION OF FACTORS INFLUENCING LONG TERM TRENDS

Potential covariates related to the type and source of the contaminant, the sampling regimen, and the sampling period were identified. Contaminants were designated as vapours, non-metallic aerosols, or metals (including metalloids). The type of sampling was categorised as biological, personal (including data evaluated with both area and personal monitoring), or area monitoring. With the International Agency for Research on Cancer (IARC) system of classification,<sup>18–30</sup> a dichotomous variable was created to identify contaminants which had been designated as carcinogens (class 1, 2A, or 2B) by the end of the sampling period. With the international standard industrial classification (ISIC) of all economic activities,<sup>31</sup> type of industry was categorised as mining and quarrying, manufacturing, and all other types of activities. Data were collapsed into five broad geographical regions world wide (western Europe, eastern Europe, North America (Canada and the United States), Japan, and all other countries). The number of reductions in the threshold limit value (TLV)<sup>32–33</sup> which occurred for the contaminant during the period sampled were classified into three categories (0, 1, and >1). To evaluate time dependent effects, data were stratified into three periods based on the period of sampling—that is, up to and including 1972 (before 1972), both before and after 1972, or from 1972 onwards (after 1972). The duration of the sampling period (years) was calculated and used to categorise duration of sampling (< 5 y, 6–10 y, 11–15 y, 16–20 y, and  $\geq$  21 y). For variables with three or more levels, nominal (dummy) variables were created so that no ordinal structure was imposed between categories (if the categorical variable had *j* possible values, then *j*–1 nominal variables were constructed).

As factors that cause exposures to decrease—for example, engineering controls or improved hygiene practices—are likely to be different from those that cause exposures to increase—for example, start up operations or increases in production rates—these two sets of data were evaluated separately. Here, we report on the analysis of declining trends (*n*=543 data sets). Linear regression analysis was used to

assess the relation between changes in exposure and the factors, applying both univariable and multivariable models.

The figure shows the distribution of the slope estimates ( $\hat{\beta}_i$ s) for declining trends, and of the corresponding annual rates of reduction in exposure ( $\hat{\theta}_i$ s). As both distributions were highly skewed, we used a logarithmic transformation of the negative value of the estimated beta coefficient [ $\ln(-\hat{\beta}_i)$ ] as the dependent variable in our regression analyses. The bottom of the figure shows that this log transformed variable was roughly normally distributed.

The general form of the multivariable model for *K* covariates is given by:

$$Y_i = \gamma_0 + \gamma_1 C_{1i} + \gamma_2 C_{2i} + \gamma_3 C_{3i} + \dots + \gamma_K C_{Ki} + \varepsilon_i \quad (1)$$

where the dependent variable,  $Y_i$ , represents the natural logarithm of the negative value of the *i*-th estimated beta coefficient [ $\ln(-\hat{\beta}_i)$ ] for *i*=1, 2, ..., *n* data sets,  $C_{1i}$ ,  $C_{2i}$ , ...,  $C_{Ki}$  represent the values of *K* covariates specific to the *i*-th data set,  $\gamma_0$  is the intercept term,  $\gamma_1$ ,  $\gamma_2$ , ...,  $\gamma_K$  are the regression coefficients associated with the *K* covariates, and  $\varepsilon_i$  is the error term. It is assumed under the model that the  $\varepsilon_i$ s are mutually independent, each normally distributed with zero mean. As the variance of  $Y_i$  varies with *i*, weighted least squares was applied, where the weight  $w_i$  associated with  $Y_i$  was proportional to the reciprocal of the estimated variance of  $Y_i$ .<sup>34</sup> In our application, the estimated variance of  $Y_i$  for *i*=1, 2, . . . , *n* is

$$\text{given by } \hat{V}(Y_i) \approx \frac{[\text{SE}(\hat{\beta}_i)]^2}{\hat{\beta}_i^2}, \text{ where } \text{SE}(\hat{\beta}_i) \text{ is the}$$

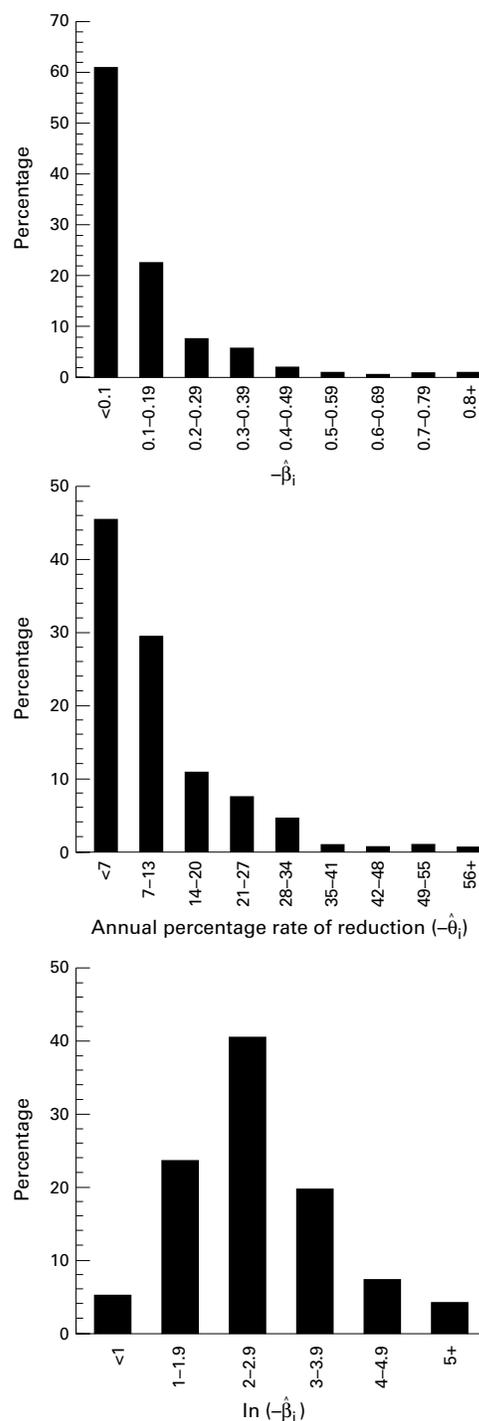
estimated standard error of  $\hat{\beta}_i$  (see appendix for a derivation of this approximate variance of  $Y_i$ ).

Multivariable (weighted) linear regression models were constructed to simultaneously evaluate effects of the predictive factors together. Stepwise selection techniques were used to identify the most influential factors with a significance level of 0.10 for adding and dropping covariates from the model. Standard regression diagnostics were used to assess the adequacy of the final model.<sup>35</sup> All statistical analyses were carried out with the statistical analysis system (SAS Institute, Cary, NC).

## Results

### IDENTIFICATION OF FACTORS EXPLAINING CHANGES IN EXPOSURE: UNIVARIABLE REGRESSION ANALYSES

Table 1 shows the results from the (weighted) regression analyses of the separate associations among categories of relevant factors and decreasing exposures. Factor categories associated with negative coefficients indicate smaller rates of reduction in exposure (relative to the reference category) whereas those with positive values indicate faster rates of reduction. The last column of table 1 shows the annual percentage changes in exposure level predicted by the model comparing categories of each factor to the reference category. (To provide an example of this computation, for the factor “region”, the predicted annual percentage rate of reduction for



Frequency distributions of the negative value of the slope estimates ( $-\hat{\beta}_i$ ), the annual rates of reduction in exposure ( $-\hat{\theta}_i$ ), and the logarithmic transformations of the negative value of the estimated beta coefficients ( $-\hat{\beta}_i$ ) for the set of decreasing exposures ( $n=543$ ).

exposures arising in workplaces in western Europe would be calculated as  $100(\exp(-\exp(-1.71-0.12))-1)=-15\%$ .)

Compared with North America, our results indicate a similar decline in exposures arising in workplaces in western Europe but steeper declines in Japan and eastern Europe. Our findings also suggest that exposures in mining have fallen considerably more slowly than those in manufacturing. A similar, although

not significant, effect was found for other (non-manufacturing) industries. It seems that exposures to vapours decreased less rapidly than either group of aerosols (metallic and non-metallic aerosols), and that exposures have decreased slightly more rapidly when biological, rather than airborne, monitoring was conducted. Reductions for carcinogens did not differ from those for non-carcinogens. Exposures collected more recently (after 1972) seem to have fallen more rapidly than exposures before 1972. Our results also suggest that the longer the duration of sampling the slower the rate of decline. (Note that much of the variation was explained by both the calendar period during which sampling was conducted ( $R^2=0.47$ ) and the duration of the sampling period ( $R^2=0.61$ .) Consistent with our earlier finding, the rates of reduction were smaller if the TLVs had been lowered during the period of investigation.

#### IDENTIFICATION OF FACTORS EXPLAINING CHANGES IN EXPOSURE: MULTIVARIABLE REGRESSION ANALYSES

Because the influence of the predictor variables on changes in exposure may vary across calendar time, stratified analyses were conducted to investigate such interactions based on when the data had been collected (before 1972, both before and after 1972, and after 1972). Although our choice of 1972 was somewhat arbitrary as a cut off point for evaluating temporal differences, similar results were obtained after stratifying the data at other calendar years (1973, 1974, and 1975). Given that longer sampling periods often extend to earlier periods within each stratum (compared with data collected over shorter intervals), the number of years over which sampling had been conducted was included in all models.

Before conducting the multivariable analyses, the bivariate distributions of all variables were examined to detect problems with small cell sizes. To minimise the number of small cells, only data from western Europe and North America were evaluated ( $n=427$  data sets); the number of reductions in the TLV was collapsed into two categories (0 and  $\geq 1$ ); and categorical variables based on industry and type of contaminant were created (aerosol exposures arising in mining, aerosol exposures arising in manufacturing, and vapour exposures arising in manufacturing). Among exposures evaluated before 1972, effects related to classification as a carcinogen could not be evaluated and models were run with and without the few biological monitoring data sets ( $n=4$ ) that were available. Finally, as relatively few exposures had been assessed with area monitoring in the group of exposures evaluated after 1972, potential differences between biological and airborne monitoring were evaluated within this stratum.

Table 2 shows the results from the multivariable analysis of declining exposures. Controlling for other variables in the model, factors associated with negative estimated coefficients indicate a slower rate of reduction in exposure (compared with the reference group), whereas

Table 1 Individual associations between each factor and the reduction in exposure levels per year\* (n=543)

Factor	Estimated coefficient (SE)†	p Value	Predicted reduction in exposure/year (%)
Region (R <sup>2</sup> = 0.13):			
North America‡	-1.71 (0.07)	0.0001	-17
Western Europe	-0.12 (0.08)	0.1433	-15
Eastern Europe	+1.62 (0.24)	0.0001	-60
Japan	+1.25 (0.37)	0.0008	-47
Other countries	-1.20 (0.31)	0.0001	-5
Industrial classification (R <sup>2</sup> = 0.05):			
Manufacturing‡	-1.69 (0.04)	0.0001	-17
Mining	-0.89 (0.17)	0.0001	-7
Other industries	-1.01 (1.57)	0.5205	-6
Type of contaminant (R <sup>2</sup> = 0.15):			
Vapour‡	-2.58 (0.09)	0.0001	-7
Non-metallic aerosol	+0.99 (0.13)	0.0001	-19
Metal	+1.01 (0.10)	0.0001	-19
Carcinogenicity§ (R <sup>2</sup> = 0.02):			
Non-carcinogen‡	-1.83 (0.05)	0.0001	-15
Carcinogen	+0.30 (0.09)	0.0007	-19
Type of monitoring (R <sup>2</sup> = 0.28):			
Area monitoring‡	-1.74 (0.10)	0.0001	-16
Biological monitoring	+0.25 (0.11)	0.0224	-20
Personal monitoring	-1.14 (0.13)	0.0001	-5
Personal and area monitoring	-0.55 (0.38)	0.1417	-10
Calendar period (R <sup>2</sup> = 0.47):			
Before 1972‡	-2.92 (0.17)	0.0001	-5
Before and after 1972	+0.10 (0.18)	0.5758	-6
After 1972	+1.56 (0.18)	0.0001	-23
Duration of sampling (y) (R <sup>2</sup> = 0.61):			
≤ 5‡	-1.28 (0.04)	0.0001	-24
6-10	-0.23 (0.06)	0.0001	-20
11-15	-0.79 (0.26)	0.0022	-12
16-20	-1.20 (0.28)	0.0001	-8
≥21	-1.94 (0.07)	0.0001	-4
TLV **reductions (R <sup>2</sup> = 0.16):			
Zero reductions‡	-1.40 (0.05)	0.0001	-22
One reduction	-0.69 (0.08)	0.0001	-12
Two or three reductions	-1.32 (0.24)	0.0001	-6

\*Dependent variable in regression analyses:  $\ln(-\hat{\beta}_i)$  where  $\hat{\beta}_i$  is the estimated beta coefficient for the i-th data set obtained from the linear regression analysis of the logged exposure levels versus time.

†SE=standard error.

‡Reference category.

§Designated by IARC as a class 1, 2A, or 2B carcinogen by the end of the sampling period.

\*\*TLV= threshold limit value of the American Conference of Governmental Industrial Hygienists (ACGIH).

those with positive values indicate a more rapid decline. Among exposures evaluated before 1972, the rates of reduction seem to have been slower for exposures arising in mining than in manufacturing. (No significant effect was found between vapours and aerosols in manufacturing.) Compared with exposures assessed by area monitoring, the rates of decline have been faster when personal monitoring was conducted, but slower when biological monitoring was used. This observation contrasts with what we found when the univariable analysis was conducted. Independent of the effects of sampling duration, which showed a slowing of the rates of reduction over longer periods of time, the lowering of TLVs seems to have been associated with slower rates of reduction in exposure. Taken together, industrial sector, type of monitoring, TLV reductions, and the duration of the sampling period explained a substantial proportion of the variation (R<sup>2</sup>=0.78). (Although not shown, nearly identical results were obtained after excluding the biological monitoring data.)

As table 2 shows for the group of exposures evaluated before and after 1972, a remarkable 91% of the variability in 153 data sets was explained by the model. Steeper rates of decline were found for exposures to aerosols rather than vapours, with aerosols in mining coming down faster than aerosols in manufac-

turing. The rates of decline were higher for exposures that were known carcinogens at the time of sampling. Although exposures assessed by personal sampling have fallen at slightly lower rates than those evaluated by area monitoring, those evaluated by biological monitoring declined at considerably slower rates. As with exposures evaluated before 1972, there seems to have been a slowing of the rates of reduction with the duration of the sampling period. However, no effect related to the lowering of TLVs was detected.

In the multivariable analysis of exposures evaluated after 1972, the only two factors that remained significantly associated with declining rates in exposure levels were sampling duration and classification of the contaminant as a carcinogen (table 2). Very little of the total variation, however, was explained by these two variables (R<sup>2</sup>=0.04). Although duration of the sampling period had a stronger association with slower rates of reduction in exposure than in the two earlier sets of data, classification as a carcinogen had less influence on declining exposure levels than data collected before and after 1972.

#### EXAMPLE: EXTRAPOLATION OF HISTORICAL EXPOSURE LEVELS

To provide an example of how our results might be applied to predict exposure levels in the past, the database was accessed to identify a data set with historical exposures that spanned a period of at least 20 years so that a comparison between extrapolated and actual levels could be made. A data set comprising average styrene concentrations from 1960 to 1988 for Danish laminators in the reinforced plastics industry<sup>10</sup> was selected for the comparison.

For exposures evaluated before and after 1972, the full model is represented as follows (table 2):

$$\hat{Y} = -2.02 + 0.42X_1 + 0.72X_2 + 0.84X_3 - 1.00X_4 - 0.32X_5 - 0.03X_6$$

where:

X<sub>1</sub>=1 if aerosol exposure arises in manufacturing, 0 otherwise;

X<sub>2</sub>=1 if aerosol exposure arises in mining, 0 otherwise;

X<sub>3</sub>=1 if air contaminant is classified as a carcinogen, 0 otherwise;

X<sub>4</sub>=1 if exposure is assessed by biological monitoring, 0 otherwise;

X<sub>5</sub>=1 if exposure is assessed by personal monitoring, 0 otherwise; and

X<sub>6</sub>=duration of exposure (years).

For the exposure scenario described above, we obtain:

$$\hat{Y} = -2.02 + 0.42(0) + 0.72(0) + 0.84(1) - 1.0(0) - 0.32(1) - 0.03(28) = -2.34$$

The predicted value  $\hat{Y}$  would then be used to obtain the predicted annual rate of reduction of 9.18% (100(exp(-2.34))-1)=-9.18%; thus, the predicted level in any given calendar year would be 1-0.0918=0.9082 of that from the preceding year. Given that the estimated exposure level in 1988 was 15 mg/m<sup>3</sup>, the predicted level in 1965 (extrapolating back 23 years in

Table 2 Final multiple linear regression models of declining exposure levels\* on selected predictors stratified by period

	Predictor	Coefficient (SE) <sup>†</sup>
Before 1972 (n=66)	Intercept	-1.09 (0.17)
	Industrial sector:	
	Manufacturing exposures‡	
	Mining exposures	-0.29 (0.09)
	Type of sampling:	
	Area monitoring‡	
	Biological monitoring	-2.05 (0.19)
	Personal monitoring	0.84 (0.11)
	Number of TLV§ reductions:	
	0‡	
≥1	-0.78 (0.17)	
Total model R <sup>2</sup> =0.78	Sampling duration (y)	-0.04 (0.007)
Before and after 1972 (n=153)	Intercept	-2.02 (0.14)
	Contaminant and industrial sector:	
	Vapours in manufacturing‡	
	Aerosols in manufacturing	0.42 (0.11)
	Aerosols in mining	0.72 (0.10)
	Carcinogenicity:	
	Non-carcinogen‡	
	Carcinogen	0.84 (0.10)
	Type of sampling:	
	Area monitoring‡	
Biological monitoring	-1.00 (0.08)	
Personal monitoring	-0.32 (0.09)	
Total model R <sup>2</sup> =0.91	Sampling duration (y)	-0.03 (0.004)
After 1972 (n=208)	Intercept	-1.14 (0.10)
	Carcinogenicity:	
	Non-carcinogen‡	
	Carcinogen	0.27 (0.14)
Total model R <sup>2</sup> =0.04	Sampling duration (y)	-0.08 (0.03)

\*Dependent variable in regression analyses:  $\ln(-\hat{\beta}_i)$  where  $\hat{\beta}_i$  is the estimated beta coefficient for the *i*-th data set obtained from the simple linear regression of the logged exposure levels versus time.

<sup>†</sup>SE=standard error.

<sup>‡</sup>Reference category.

<sup>§</sup>TLV= threshold limit value of the American Conference of Governmental Industrial Hygienists (ACGIH).

time) would have been 137 mg/m<sup>3</sup> (15/0.9082<sup>23</sup>). This value is somewhat lower than the actual measured level of 205 mg/m<sup>3</sup>. However, it is not possible without much further validation to make general statements about the degree of error in such extrapolated values.

### Discussion

Exposure assessment in retrospective studies can be conducted with various methods, depending on the information that is available.<sup>36,37</sup> When historical data are sparse, as is usually the case, estimating exposures is made much more difficult and often involves a large degree of judgment. In this instance, investigators are forced to rely on crude surrogates for exposure level, such as job title, or to develop statistical or deterministic models. Although such methods often assume that exposure levels were higher in the past, the degree to which exposure levels have changed has remained problematic.

Our investigation of long term occupational exposures showed that most exposures have tended to go downwards at rates ranging from -4% to -14% per year.<sup>17</sup> Here we report that the rates of reduction in exposure were higher for exposures arising in Japanese and eastern European workplaces than in other regions of the world, for exposures related to manufacturing compared with mining, for exposures assessed with biological (rather than airborne) monitoring, and for contaminants measured after but not before 1972.

The rate of decline in exposures in North America and western Europe differed signifi-

cantly by the calendar period of sampling (before 1972, both before and after 1972, and after 1972, table 2). Although a substantial proportion of the variation in the rates of reduction for data collected before 1972 or both before and after 1972 was explained by the physical characteristics of the contaminant and by the type of sampling, the same variables explained very little of the variation for data collected after 1972. Thus, it is clear that other factors, which were not evaluated in our study, were responsible for or associated with changes in exposure that have occurred more recently. It may well be that these factors are related to social, political, or economic forces that affected the main industrial sectors, perhaps differentially, causing exposures to decline at different rates. A similar conclusion was reached by Hornung *et al*<sup>1</sup> who found that calendar year of operation remained a significant determinant of exposure to ethylene oxide, one which was independent of engineering controls instituted in the late 1970s.

Comparing the results between the two sets of earlier exposures suggests greater differences in the decline in exposures between type of industry (mining or manufacturing) for exposures evaluated before 1972, whereas type of contaminant (aerosol or vapour) seemed to be a more relevant predictor for data collected both before and after 1972. Although exposures in mining may have been more difficult to control than those in manufacturing earlier on, the higher rates of reduction that were found for aerosols in the later data may be related to control technologies that effectively reduced exposures in both industrial sectors.

Steeper declines were found for exposures evaluated before 1972 by personal (or by a combination of personal and area) monitoring, compared with purely area monitoring. In contrast, exposures declined less rapidly when personal sampling rather than area monitoring was conducted over periods both before and after 1972. Here, the results may not be directly comparable because the breakdown by type of personal monitoring varied between the two groups. Whereas all of the personal sampling results before 1972 consisted of short term breathing zone samples, only 40% of the data before and after 1972 included short term measurements. As short term measurements could arguably have been collected to evaluate the need for or effectiveness of controls,<sup>38</sup> such data would tend to overestimate the rates at which average exposures declined. When biological, rather than airborne (area or personal) monitoring had been conducted, we found consistently lower rates of reduction. We suspect that this result relates, at least in part, to the relatively slow rates of clearance of some metals—for example, lead and cadmium—which were well represented in our database.

For exposures evaluated before 1972, we found that revisions in the TLVs were associated with slower rates of reduction, even when the duration of sampling was included in the model. No effect related to the lowering of

TLVs was found in the other two sets of data. Although it is possible that reductions in the TLV may be a surrogate for an uncontrolled confounder, our results suggest that the lowering of the TLVs has not operated to accelerate reductions in exposure. Conversely, the IARC classification of a contaminant as a carcinogen was associated with steeper declines in exposure, particularly for data collected both before and after 1972.

It is also important to note that about 40% of the exposures in the database had been aggregated over job groups at a particular workplace or across workplaces for a particular industry and do not allow generalisations to be made for particular occupational groups. Thus, although our findings support the notion that long term trends in exposure have taken place for many contaminants among a broad cross section of industries, these results will not necessarily provide accurate predictions for all groups of workers. Notwithstanding this limitation, our results provide information which may be of use in estimating historical exposures. Given the limited options which are sometimes available, the rates of reduction predicted by our models, with reference to the earliest period of good data collection (see example), may yield historical levels that are as "good" as those obtained from more subjective or costlier methods. However, questions about the validity of these models remain unanswered. Thus, we encourage investigators who have access to historical data to make comparisons with the rates of reduction predicted by our models and determine how useful such models may be in predicting earlier exposures when data are sparse.

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#### Appendix: Derivation of the variance of a natural log transformed variable

Consider a random variable  $X$  with mean  $\mu_x$  and variance  $\sigma_x^2$ . Let  $Y$  represent a function of  $X$  where  $Y=g(X)$ .

In our application,  $Y = \ln(-\hat{\beta})$  and  $X = -\hat{\beta}$ .

The variance of  $Y$  can be approximated as follows:

$$V(Y) \approx \left[ \frac{dg(X)}{dX} \right]_{\mu_x}^2 (\sigma_x^2). \text{ So, when } Y = \ln(X),$$

$$V(Y) \approx \left( \frac{1}{X} \right)_{\mu_x}^2 \sigma_x^2 = \frac{\sigma_x^2}{\mu_x^2}.$$

Thus, the variance of  $Y$  can be estimated as:

$$\hat{V}(Y) \approx \frac{[SE(\hat{\beta})]^2}{\hat{\beta}^2} \text{ where } SE(\hat{\beta}) \text{ represents the estimated standard error of } \hat{\beta}.$$

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minimum. Letters are accepted on the understanding that they be subject to editorial revision and shortening.

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