

Development of a model for use in estimating exposure to ethylene oxide in a retrospective cohort mortality study

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One of the purposes of an occupational epidemiologic study is to examine the causal relationship between exposure to an agent and the development of a health outcome. The existence of causality is strengthened by the presence of a dose-response relationship, such that the greater the dose, the greater the response. Dose, however, is rarely known; therefore an estimate or surrogate for dose must be determined. A commonly used surrogate of dose is the airborne concentration of the agent. Such concentrations are generally determined from industrial hygiene measurements collected during field surveys. In the ideal study, such measurements exist for the entire duration of exposure. However, such extensive data are generally not available, particularly for past exposures. When this situation is encountered, an estimation of exposure must be made (1, 2, 4, 5, 10).

Methods

To facilitate the estimation of exposure values for years before which any industrial hygiene data were collected, as well as to fill any gaps in the existing data, a model has been developed for use in a current retrospective cohort mortality study of workers exposed to ethylene oxide in the medical supplies and spice industries (9). A weighted linear regression model will be used to estimate exposure to ethylene oxide by plant and year for each exposure category. An exposure category has been defined as a group of jobs and/or locations with a similar potential for exposure to ethylene oxide. Each exposure estimate is based on a small number of independent variables which have been shown to affect exposure (the dependent variable).

The data used to develop the exposure model were collected in the course of walkthrough surveys of 36 companies in the medical supplies and spice industries, and in-depth sampling surveys of two of these 36 companies (3, 9, 10).

The hygienic data consisted of 2 350 individual 8-h time-weighted average data points collected from workers' personal breathing zones by 21 of the 36 companies between 1976 and 1985. These individual data were grouped by plant, year, and type of sampling

media (charcoal tube versus passive monitor) for each job and location. Arithmetic means, in parts per million (ppm), of from 1 to 99 samples (average 8.5 samples per group) were available for each group, and these mean exposure values were then log-transformed.

The variance of the passive-monitor data was found to be substantially greater than the variance of the charcoal-tube data collected under similar conditions; therefore, the passive-monitor data were deleted (6, 7, 8). These charcoal-tube data were then divided into two groups, ie, data used to develop the model (230 mean exposure values from 14 plants) and data used for testing the model (50 mean exposure values from six other plants).

The weighting factor that was derived for use in the model was the inverse of the variance of the log of each arithmetic mean exposure to ethylene oxide. This use assured that observations based upon a larger number of samples and/or samples analyzed with greater precision (low coefficient of variation) were more influential in developing the model. For observations based upon one sample, or where no estimate of the standard deviation was available, an estimate of the weight was substituted by the average coefficient of variation among all other observations. Estimated coefficients of variation below 0.1 were fixed at 0.1, which was the estimated precision of the chemical analytical procedure.

Results

There were 23 independent variables examined for their potential association with the dependent variable, which was the logarithm of the average level of exposure to ethylene oxide (EtO) in parts per million. They were: year of operation, exposure category, type of product sterilized or treated with ethylene oxide, volume of sterilizer or treatment vessel in cubic feet, product age (day(s) since product was sterilized or treated), aeration procedure, rear exhaust valve in sterilizer or treatment vessel plant, pounds of ethylene oxide used annually, sterilant (gas or liquid solution), sterilant concentration (percentage of ethylene oxide in gas or liquid solution), multiple vessel vacuum cycles at end of ethylene oxide exposure (airwash), isolation of vessels, isolation of the vessel area, isolation of the vacuum pump, installation of a control room, local-

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ized exhaust over vessel door, localized exhaust over ethylene oxide gas cylinders, recycling of ethylene oxide gas vessel, charging (manual or automatic), gas purity assay, increase in general dilution ventilation in vessel area, and sealing of gap between vessel drain and sanitary sewer.

The regression analysis indicated that the first seven of these 24 variables had a significant influence (P value of <0.05) on the level of the average exposure value for ethylene oxide. Year (YR), volume of sterilizer or treatment vessel in cubic feet (CUF), and product age (AGE) were considered to be continuous; while exposure category (E), product type (P), facilitated product aeration (AER), and rear exhaust valve in the sterilizer or treatment vessel (EX) were considered to be categorical. In addition, two terms involving the interaction of exposure category with product type ($E \cdot P$) and also with year ($E \cdot Y$) were included in the final model. The model was of the form:

$$\ln(\text{EtO})_{ijklm} = \mu + \text{YR} + \text{YR}^2 + \text{CUF} + \text{CUF}^2 + \text{AGE}_i + \text{E}_j + \text{P}_k + \text{AER}_l + \text{EX}_m + (\text{E} \cdot \text{P})_{jk} + (\text{E} \cdot \text{YR})_{ij} + \varepsilon_{ijklm}$$

These terms explained a remarkable 90 % of the variation in the average levels of ethylene oxide, ie, $R^2 = 0.90$ for the 230 observations used to develop the model.

The model was first evaluated through the testing of its ability to estimate accurately exposure levels in a set of test data not used to build the model. The test data set consisted of 46 arithmetic mean exposure levels and the seven independent variables used in the model. The model demonstrated an average bias of -0.5 ppm and a standard deviation of 5.6 ppm. The model therefore underestimated the average exposure to ethylene oxide by 0.5 ppm.

Following this initial evaluation, a panel of industrial hygienists familiar with the medical supplies, spice, and hospital industries was requested to estimate the exposure levels for the same set of test data. The average bias for the panel of industrial hygienists was -2.9 ppm, which was significantly higher than that of the model (-0.5 ppm). The standard deviation for the estimates made by the panel was 5.2, which was not significantly different from that of the model.

These evaluations indicated that both the model and the panel underestimated the average exposure; however, the estimates of the model were more accurate than those made by the panel.

Discussion

The objective of this project was to derive a model that would provide an objective method for estimating aver-

age levels of exposure to ethylene oxide in the absence of industrial hygiene data. These values would then be used to examine the relationship between exposure to ethylene oxide and mortality as part of a retrospective cohort study. The model sufficiently explains a high proportion of the variability in the ethylene oxide exposure measurements ($R^2 = 0.90$), with as few terms as possible while retaining statistical validity. The performance of the model was ascertained in a comparison of its estimations of ethylene oxide exposure in a set of test data not used to build the model with estimates of exposure by a panel of knowledgeable industrial hygienists for the same set of test data. The model and the panel underestimated the average exposure; however, the model estimated the exposure values with greater accuracy than the panel. The estimation of exposure for all persons in the cohort through the use of a panel of industrial hygienists would be an enormous task. The use of the model to estimate exposure simplifies the procedure.

The development and use of such a model to estimate exposures to be used in a retrospective cohort mortality study represents a unique approach to this task. These methods may be useful for other investigators in future endeavors.

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