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Case-Cohort Study of Styrene Exposure and Ischemic Heart Disease

Genevieve M Matanoski and Xuguang Tao

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HEI STATEMENT
Synopsis of Research Report 108

Case-Cohort Study of Styrene Exposure and Ischemic Heart Disease

INTRODUCTION

In this report, Drs Matanoski and Tao present results of a study designed to follow up several occupational studies that had indicated a possible relation between styrene exposure and death from ischemic heart disease. For example, in a previous study Matanoski and coworkers reported that while mortality of styrene-exposed workers from atherosclerotic heart disease was less than mortality of the overall US population, it was significantly higher among a subgroup of black workers than would be expected based on general population rates. Although results have not been consistent, other investigators have also found evidence of an association between styrene exposure and heart disease. This study was undertaken to investigate that association further.

APPROACH

In the current study, Drs Matanoski and Tao examined workers exposed to styrene while working in styrene-butadiene polymer manufacturing plants between 1943 and 1982. Workers who had died from ischemic heart disease were compared to a subgroup of all men employed in two styrene-butadiene polymer manufacturing plants during that time. Individual exposure histories were determined from job records. When exposure data were missing, a statistical method was used to estimate exposure. This method is based on the assumption that exposure concentrations in all jobs in a plant are normally distributed and that processing methods throughout the rubber industry did not change appreciably during the time under consideration.

RESULTS AND INTERPRETATION

Drs Matanoski and Tao found that the incidence of death from ischemic heart disease was lower in subjects in their study than in the US general population. This discrepancy is often found in such studies because workers tend to be healthier than the general population (the healthy worker effect). However, they also found that a subgroup of nonwhite men had elevated rates of death from chronic ischemic heart disease when compared with the overall US population. Workers who were still employed at the time of death and had worked for more than 5 years had increased risk for death from acute ischemic heart disease. Further analysis suggested that intensity of exposure was a more important risk factor for death from ischemic heart disease than total exposure. Dr Matanoski estimated an increased risk of 4% to 8% for each additional part per million of styrene exposure over 1 year. The investigators discuss the study's implications for the general population.

Drs Matanoski and Tao successfully carried out a difficult occupational cohort study with an appropriate and well-designed approach. The study found associations between styrene exposure and death from acute ischemic heart disease. The lack of correlation between styrene and butadiene exposures rules out the possibility that the findings are related to coexposure to butadiene. However, limitations of the data make it difficult to assess the roles of factors such as diet, smoking, physical activity, blood pressure or type of job within the industry. Although the results are statistically significant, uncertainties regarding the causes of the associations will need to be addressed before extrapolating results to the general population (whose average exposures are several orders of magnitude lower than occupational exposures).

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr Genevieve M Matanoski of Johns Hopkins University, Baltimore MD. The following Research Report contains both the detailed Investigators' Report and a Critique on the study prepared by the Institute's Health Review Committee.

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HEI

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Research Report 108

HEALTH EFFECTS INSTITUTE

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HEI STATEMENT

This Statement is a nontechnical summary of the Investigators' Report and the Health Review Committee's Critique.

INVESTIGATORS' REPORT

When an HEI-funded study is completed, the investigators submit a final report. The Investigators' Report is first examined by three outside technical reviewers and a biostatistician. The Report and the reviewers' comments are then evaluated by members of the HEI Health Review Committee, who had no role in selecting or managing the project. During the review process, the investigators have an opportunity to exchange comments with the Review Committee and, if necessary, revise the report.

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INVESTIGATORS' REPORT

Case-Cohort Study of Styrene Exposure and Ischemic Heart Disease

Genevieve M Matanoski and Xuguang Tao

ABSTRACT

Recent epidemiologic studies have consistently reported increased daily mortalities and hospital admissions associated with exposure to particulate air pollution. Ischemic heart disease (IHD*, *International Classification of Diseases, Eighth Revision* [*ICD-8*], codes 410–414) is among those diseases that contribute in large measure to this excess mortality. Some occupational studies have suggested elevated risk of IHD among workers exposed for short periods to styrene, which can be emitted from fossil fuel combustion, aircraft exhausts, and motor vehicle exhausts. Styrene is found in ambient air at average concentrations of a few micrograms per cubic meter or less but may reach very high concentrations at particular locations and times. Unmeasured aerosols of styrene may also increase population exposures.

This case-cohort study explored a possible association and dose-response relation between styrene exposure and risk of acute IHD in an occupational setting. The population under study was 6587 male workers employed between 1943 and 1982 in two US plants manufacturing styrene-butadiene polymers used in synthetic rubber. The study assessed all 498 subjects who died from IHD along with a subcohort of twice that size, 997 subjects, selected as a 15% random sample of the full target cohort. IHD deaths during the study led to some overlap between cases and the subcohort, leaving 1424 unique subjects. Job histories were collected for all subjects. Industrial hygienists and engineers from the industry estimated relative exposures for all jobs. Exposure data were collected for many of the jobs from different sources. For any job with no available exposure measurements, *z* scores were used to estimate job exposure in each plant from the relative exposure level for that job in similar plants and the measurement distribution parameters of the study plant.

Standardized mortality ratio (SMR) analyses were used to examine the overall risk of dying from IHD among study subjects compared with the US general population. A significantly elevated SMR of 1.47 with a 95% confidence interval (95% CI) of 1.17 to 1.77 for chronic IHD was found among black workers who had left the plants. A modification of the Cox proportional hazard regression model was used to control for confounders and examine dose-response relations between styrene exposure and the risk of IHD. Employment time-weighted average (TWA) styrene concentration intensity for the most recent 2 years was found significantly associated with death from acute IHD among active workers with a relative hazard of 3.26 to 6.60, depending on duration of employment. In this analysis, the highest relative hazard of 6.60 (95% CI, 1.78–24.54) was among active workers who had been employed for at least 5 years.

The results suggest that the exposure intensity was more important than duration of exposure. On the basis of the dose-response relation established in this study, we estimate that for each 10 $\mu g/m^3$ increase in ambient styrene, acute IHD mortality might increase 0.4%. At normal ambient styrene levels, the relative risk would be increased, at most, 0.1% compared with no exposure. At certain locations and times, however, ambient styrene could reach levels that would result in a relative hazard for acute IHD mortality as high as 3.386-fold the risk at no exposure.

* A list of abbreviations and other terms appears at the end of the Investigators' Report.

This Investigators' Report is one part of Health Effects Institute Research Report 108, which also includes a Critique by the Health Review Committee and an HEI Statement about the research project. Correspondence concerning the Investigators' Report may be addressed to Dr Genevieve M Matanoski, Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, 111 Market Place, Suite 850, Baltimore MD 21202.

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INTRODUCTION

Recent epidemiologic studies have consistently reported increased daily mortality associated with exposure to particulate air pollution. IHD is among those diseases that contribute in large measure to this excess mortality (Dockery et al 1993; Samet 1993; Schwartz 1993; Schwartz et al 1996). After controlling for seasonal and other long-term temporal trends, Schwartz and Morris (1995) found that particulate matter with an aerodynamic diameter of 10 μm or less (PM_{10}) was associated with daily hospital admissions for IHD. Despite these observations of immediate increases in IHD and death associated with exposure to particulate matter, however, it is difficult to see biologically how dust could cause such immediate effects. One possibility is that substances appearing with the particulate matter, or a chemical that can adhere to it, might result in an immediate disease outcome or death.

Several epidemiologic studies have found that occupational exposure to styrene is probably associated with increased risk of IHD, especially among workers with short-term exposure to styrene (Matanoski et al 1990; Bond et al 1992), suggesting that styrene may have acute adverse effects on the human cardiovascular system. The biological mechanism behind these observations has never been investigated.

Styrene (cinnamene, cinnamol, ethenylbenzene, phenethylene, phenylethene, phenylethylene, styrol, styrole, styrolene, vinylbenzene, and vinylbenzol) is an important chemical used in production of a wide variety of polymers, copolymers, and glass-reinforced plastics. Although the highest levels of exposure to styrene occur in occupational settings, styrene is widespread in ambient air in most industrialized countries at average concentrations of a few micrograms per cubic meter or less. Styrene may be discharged to the environment during use, manufacture, and processing via waste air, waste water, and waste disposal by various industries and services. Styrene is also present in the exhaust gases of carburetor-type engines, diesel engines (Schofield 1974; Hampton et al 1982, 1983), and aircraft engines (Beratergremium für Umweltrelevante Altstoffe [BUA] 1990). This chemical is also formed when fossil fuels are burned (in industrial power plants and in domestic boilers) and has been detected in cigarette smoke (BUA 1990).

In the Total Exposure Assessment Methodology (TEAM) study conducted for the United States Environmental Protection Agency, mean ambient air concentrations of styrene at various locations and times differed by 10-fold, ranging from 0.4 to 3.8 $\mu g/m^3$ (equivalent to 0.094 to 0.893 ppb) (Wallace 1986; Wallace et al 1987; Miller et al 1994). Given the large variation in mean concentrations, the ranges of instantaneous styrene concentrations could vary widely by time and location with possible extreme peak values. Under special circumstances styrene concentrations have reached as high as 2934 $\mu g/m^3$ in ambient air of communities near some industrial sources (Mckay et al 1982). However, these measured mean concentrations of ambient styrene could understate exposure because air samples for styrene are usually obtained by charcoal tube collection or passive dosimeter air samplers, which only measure vapor. Exposure to styrene is thus attributed to vapors alone; styrene in aerosol form or adhered to suspended particles is not considered.

One experimental study (Malek et al 1986) showed that aerosol constituted 26% to 33% of the total air concentration of styrene during resin spraying operations in industry and that 96% of the total aerosols generated during the operations comprised particles equal to or smaller than 1 μm (within respirable size range). It was also found that styrene aerosols could undergo physical and chemical changes such as vaporization and polymerization. These processes could reasonably be assumed to be continuous once the aerosols are generated. Their impact on estimation of inhalation exposure depends on how quickly the aerosol reaches the respiratory system. For instance, if vaporization occurs after inhalation, it would result in a more concentrated vapor dose to the respiratory system than if it occurred before inhalation. Styrene could also adhere to other existing suspended particles in the ambient air. Little information is available regarding the extent to which styrene in air occurs in this form.

Styrene is an aromatic and highly volatile hydrocarbon. It is a colorless liquid that has a sweet and pleasant odor. Styrene is rapidly transformed in the atmosphere by a reaction with hydroxyl radicals, which are formed photochemically and preferentially attack the aliphatic moiety. The half-life of styrene in the atmosphere is 7.3 hours. The half-life of styrene degradation by ozone is of the same order of magnitude. Thus styrene is not expected to undergo extensive transport (BUA 1990). This suggests that styrene concentrations measured at scattered air monitoring stations might not reflect possible high concentrations in limited areas near the source.

Styrene can be inhaled as vapor or as an aerosol adherent to particulate matter. Information on the amount of styrene adhered to particulate matter is not available. The amount could be much larger than that in vapor form, especially when the air has high levels of particulate matter, because styrene is highly lipophilic (BUA 1990). Inhaled styrene is almost completely absorbed and rapidly

dispersed throughout the body The substance is mainly degraded by oxidation of the side chain to soluble metabolites and then excreted. The metabolism of styrene is shown in Figure 1 (Boyd et al 1990). The half-life in human blood is 2 hours 40 minutes (Wigaeus et al 1983; BUA 1990). When the concentration of styrene during exposure exceeds the body's capacity to metabolize it, however, the styrene is stored preferentially and reversibly in the fatty tissue (BUA 1990).

Our hypothesis is that styrene could have both acute and chronic health effects that influence the risk of IHD, although the mechanisms behind this hypothesis have never been investigated. Since styrene can be distributed in the fatty tissue, it is probably also distributed to atherosclerotic plaques, the clinically significant lesions of coronary arteriosclerosis. These plaques are composed of fibrous tissue, lipid-laden foam cells, and extracellular lipid deposits. Their proximity to the heart muscle and blood vessels may allow styrene or its metabolites to directly or indirectly modify atherosclerotic plaque. Such an influence would lead to narrowing of blood vessels, reversibly or temporarily, especially in individuals with blood flow previously compromised by arteriosclerosis.

Styrene and its metabolites may also have a long-term effect on human lipid metabolism and increase the risk of formation of atherosclerotic plaques. In a study of 53 subjects occupationally exposed to styrene for 1 to 29 years in the Czech Republic, pathologically higher levels of high-density lipoprotein (HDL) cholesterol were found, indicating an alteration in cholesterol metabolism. The authors suggested that styrene can affect lipid metabolism, possibly through induction of the microsomal liver enzymatic system (Buresova et al 1991).

Previous studies have suggested that deaths from IHD are elevated among people exposed to styrene in occupational settings. It is biologically possible that styrene inhaled as vapor or adhered to particulate matter can be well absorbed and distributed in the human body with possible acute and chronic effects, which could lead to myocardial ischemia or death from IHD. To test this possibility, an occupational cohort for which complete job histories and measured levels of styrene exposure are available would be an excellent resource to determine whether the known exposures to styrene are related to IHD death. This would be the first step in establishing a clear association between styrene and IHD, which may lead to a better understanding of the association between air pollution and IHD mortality.

SPECIFIC AIMS

In the current study, the full target cohort was composed of 6587 male workers who were employed in two styrene-butadiene polymer manufacturing plants at some time from 1943 to 1982. A case-cohort design was used to study all 498 cases of workers who died from IHD and a reference subcohort of twice that size, 997 workers, selected as a 15% random sample of the total target cohort. The general objective of the study was to explore the possible association and dose-response relation between exposure to styrene and death from IHD using complete job histories of workers and measured styrene exposures within the industry. The association was controlled for possible confounding factors such as exposure to butadiene, a major coexisting chemical in the rubber manufacturing industry.

The specific aims of this study were as follows:

- to conduct a case-cohort study within a cohort of male workers in two synthetic styrene-butadiene rubber plants whose workers had been followed for 40 years from 1943 to 1982;
- to establish complete concentration matrices for styrene and butadiene, a coexisting chemical in the industry, by job, by plant, and by different periods of time for the two plants, based on measurement data and other available exposure-related information;
- to establish time-dependent methods to record personal exposures to styrene and butadiene based on an individual's detailed job history and the corresponding exposure data connected to the jobs for specific periods of time;
- to explore possible associations between styrene exposure and IHD using multivariate proportional hazard models controlling for possible confounders such as butadiene exposure and demographic characteristics; and
- to develop methods to estimate the risk of IHD for those exposed to styrene at reported ambient environmental levels, using the association between styrene exposure and IHD established in this study.

METHODS

SUBJECTS AND STUDY DESIGN

Target Cohort Population

The criteria for the selection of plants for this study were availability of styrene measurements, completeness

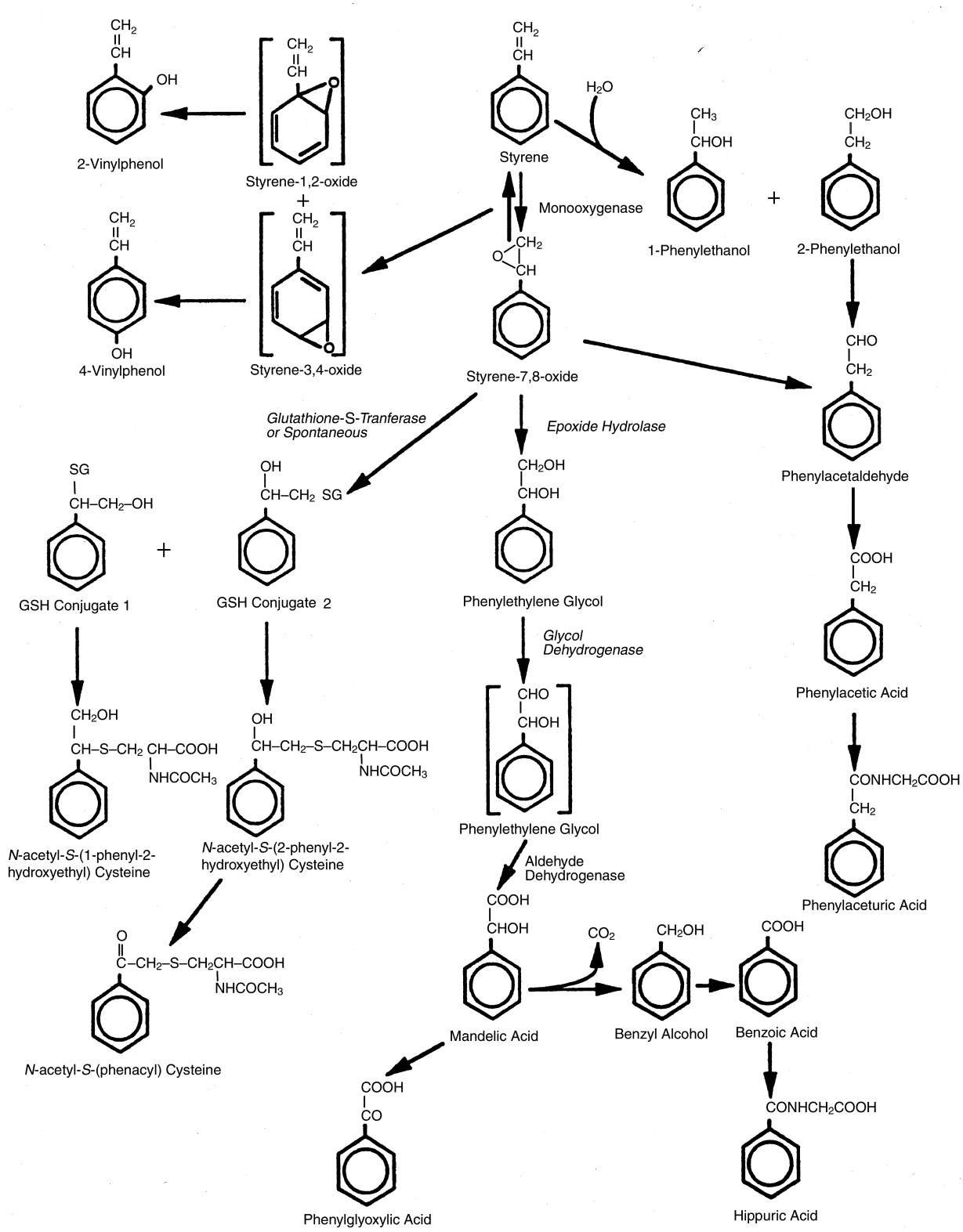

Figure 1. Metabolism of styrene (adapted from Boyd et al 1990).

of job histories, length of operation, and size of the plants. Of the eight plants studied previously by Matanoski and associates (Matanoski and Schwartz 1987; Matanoski et al 1990, 1997), only five had styrene measurement data. One of them was a Canadian plant that had different features from the US plants, so we excluded it. Two of the US plants were excluded because they had opened late, in 1964 and 1970, and had relatively small population sizes. The two plants we used, plant 6 and plant 7, had relatively large populations, opened at the inception of the industry in 1943, and had complete job histories on all employees since then. The current study used the populations from the two plants. Job histories completed between 1943 to 1982 for workers in these two plants were available on microfilm. All 6587 male workers (2793 in plant 6 and 3794 in plant 7) employed between 1943 and 1982 were the target population. This cohort therefore included all male workers in both plants from the early years of the industry with a follow-up as long as 40 years. The protocol excluded female workers (840 [11.27%] of total 7453 workers) and an additional 26 workers for whom critical variables, such as sex, birth date or hire date, were missing (0.35%).

Case Definition

The vital status of each male worker from 1943 to 1982 was determined for the two plants through the death notification system and vital status records of the Social Security Administration and the National Death Index, as well as through follow-up by local plant beneficiary records and motor vehicle administration records. The vital status information for individuals who were not working in 1982 was traced through all these sources. Sometimes we were able to conclude from Social Security records that a subject was alive (receiving benefits or paying into the system) or was deceased (a death benefit issued or system was otherwise informed of death). If these criteria were not met, his vital status was considered unknown. Direct follow-up was conducted on those individuals for whom vital status was unknown.

For these subjects, all deaths recorded during the follow-up period had been coded according to *ICD-8* by a senior nosologist in a previous study. Deaths from IHD were defined as those deaths with codes from 410 to 414 in *ICD-8*, including acute myocardial infarction (code 410), other acute and subacute forms of IHD (code 411), chronic IHD (code 412), angina pectoris (code 413), and asymptomatic IHD (code 414). In the target population, no subjects were recorded as having died from angina pectoris (code 413) or asymptomatic IHD (code 414) during the follow-up period. We classified codes 410 and 411 as acute IHD and code 412 as chronic IHD in the analysis for this study.

Case-Cohort Design

Full-cohort studies can be expensive, especially when the number of subjects is large and the amount of information to be collected is extensive. For instance, although detailed job histories for each of the 6587 male workers in the two plants were available, the records had not been abstracted, coded, and computerized, except those for selected workers chosen as subjects in previous cancer case-control studies. The case-cohort approach permits direct estimation of the risk ratio from a cohort without the need to make any rare-disease assumption or investigate the full cohort (Kupper et al 1975; Miettinen 1982; Prentice 1986). In the case-cohort design, all cases from the full cohort are collected as study cases, while only a random sample of the full cohort is the source of the comparison group.

This study to explore the relation between styrene exposure and IHD included 498 male case subjects who had died from IHD between 1943 and 1982 and 997 male workers in a subcohort representing a random sample of approximately 15% of all men ever employed between 1943 and 1982 in the two plants. When sampling for the subcohort, eligible subjects in the two plants were pooled. Subcohort subjects were not matched with cases on any characteristics to ensure the representativeness of the subcohort. In this case-cohort study, the cases represented all cases from the full target population of 6587 male workers, except for one instance of missing critical information, and the reference group was a random sample of the same target population. Because the reference subcohort was a random sample of the target population, one could do analyses of different case groups, such as subjects with acute or chronic IHD, using the same reference subcohort.

Of the 498 case subjects, 71 were originally subcohort members. These 71 subjects were included in the reference subcohort until their deaths, at which time they became cases. Because of this overlap, the reference subcohort was reduced by 71, from 997 to 926, so with the 498 cases, the total number of unique subjects in the study was 1424. The general case-cohort sampling information is shown in Table 1. Each individual was followed from when they were first hired until their death or until the end of the study on December 31, 1982. Workers who left their jobs during the study were still followed until death or the end of the study.

Table 1. Distribution of IHD Cases and Subcohort Subjects by Plant

Plant	Cases in Subcohort	Cases Not in Subcohort	Noncases in Subcohort	Total
Plant 6	30	196	371	597
Plant 7	41	231	555	827
Total[a]	71	427	926	1424

[a] Total cases, 71 + 427 = 498; total subcohort members, 71 + 926 = 997.

EXPOSURE ASSESSMENT

Job Dictionary

A job dictionary containing 579 unique jobs had been developed for this industry in previous studies (Matanoski and Schwartz 1987; Matanoski et al 1990, 1997; Appendix B). Each of these 579 jobs was assigned a unique job code, which was a combination of the codes for the subdivision, the work area, the subarea, and the particular job title. The current study used the same system to code the jobs in the job history for each subject. Although this job dictionary includes all possible jobs in the industry for the years covered by the study, the two plants did not have all of the jobs represented in the dictionary, and the subjects in this study did not work in all of the jobs existing in the two plants. Of the 579 jobs in the industry, the actual number of unique jobs in the job histories of the subjects in this study was only 166.

Job Histories

Detailed job histories for all of the study subjects were available from employment history forms on microfilm. The specific job information included a cumulative record of jobs and department transfers to form a complete job history for each individual in the current study.

According to detailed instructions for job history abstraction, the personal job histories taken from the employment records for each study subject were coded and entered into a database. In the initial step the total personal record was abstracted onto a job history form. The form included personal identification information, department name, job description, and the start and end dates for each job the individual ever had during the period, in addition to the information on file location and abstractor. These items provided the information that allowed each job to be coded as one of the 579 unique jobs in the job dictionary.

The job history information was the key link to the individual styrene and butadiene exposure information because the styrene and butadiene concentrations were measured or ranked by job.

Industrial Hygienists' Ranks of Job Exposures

For previous studies (Matanoski and Schwartz 1987; Matanoski et al 1990, 1997), all jobs had been reviewed by a group of expert industrial hygienists (IH) and engineers, both from industry and from academia, to determine the accuracy of job classification. These experts then were asked to rank each of the jobs on the job code list from 0 to 10 for both styrene exposure and butadiene exposure (henceforth referred to as *IH rank*). The IH ranks were based on the personal experience of these engineers, most of whom had worked in the industry from its inception. Any factors that they thought might influence the rank, such as plant characteristics or activities or calendar time, were included as modifications of the rank. The assumptions behind the IH rank were that the exposures by job were similar across the industry because tasks associated with those jobs were similar. The IH rank may be a good relative exposure indicator although it may not be a good indicator of actual exposure. Industrial hygienists' ranks for styrene and butadiene were assigned to 579 jobs in the job dictionary.

Measurement Data

Measurement data were collected for many of the jobs from different sources such as the National Institute for Occupational Safety and Health (NIOSH), the International Institute of Synthetic Rubber Producers, and the participating plants. Of the eight plants studied previously (Matanoski and Schwartz 1987; Matanoski et al 1990, 1997), only five plants provided styrene measurements. One of the five was a Canadian plant and the remaining four were US plants. In order to have the benefit of all available measurement information, all measurements from the five plants were used to determine the relative styrene exposure for each job. For butadiene, available measurement data from six US plants and one Canadian plant were used to estimate job exposures.

As in many other occupational studies, there were two problems with the measurement data. First, not all jobs were measured, so we had to develop a method to estimate the missing values for those unmeasured jobs. Second, measurements were not taken during the full 40 years of the follow-up period. The majority of measurements were from 1976 forward when all sources of measurements for styrene and butadiene were combined. Styrene and butadiene measurements were available from 1978 to 1982 for plant 6 and from 1977 to 1985 for plant 7. The following two sections describe the method for calculating z scores (Tao et al 1996; Matanoski et al 1997) used to estimate unmeasured jobs (developed in a previous study of butadiene) and a method for estimating concentration change

over time developed in the current study. Geometric means of styrene and butadiene for each job measured in each plant were used as concentration indicators.

Exposure Estimation for Unmeasured Jobs Using *z* Score Method

Because we did not know in advance which jobs would be involved in the case-cohort analysis, we estimated styrene and butadiene concentrations for all unmeasured jobs among the 579 jobs in the dictionary. For any job for which there were no measurements, the *z* score was calculated to estimate exposures by plant. This method of estimation assumed that the relative exposures of a job were similar across the industry because tasks associated with the job were similar but that individual plants might have had overall differences in the actual levels of chemical exposure. The *z* score method used the actual measurement values from the other six US plants, NIOSH, and the International Institute of Synthetic Rubber Producers, as well as IH ranks, to estimate the relative exposure by job. The available measurements for other jobs in the specific plant were used to determine the measurement distribution parameters. The exposures for unmeasured jobs in a specific plant could then be estimated from the relative exposure values for the job and the measurement distribution parameters of the chemical concentrations in the plant. The following three steps were used to estimate exposures for unmeasured jobs using the *z* score method (Appendix A).

Step 1 was to determine the relative exposure for each job by converting all available exposure measurements (geometric means) and the IH ranks of jobs into standardized *z* scores. The *z* score is a proportion calculated as the difference between observed values and their mean divided by the standard deviation. The *z* score method allowed transformation of data from different sources with different magnitudes, ranges, and units into a unitless standard distribution with constant mean of 0 ± 1 SD. The exposure *z* score of a job showed the relative exposure level of that job among all jobs in a plant, and these values were highly comparable among plants. Theoretically, *z* scores for the same job from different data sources should be consistent (given the assumption that the relative exposures by job were similar across the industry), but the real exposure levels might vary. The average *z* score calculated for the same job using different sources was weighted according to the number of measurements per source involved in its calculation.

Step 2 was to determine the exposure distribution for each plant from random samples of jobs within the plant. The measured jobs in a plant were assumed to be a random sample of all jobs in that plant. The geometric mean of multiple measurements for a job was used as the average concentration for that job. The mean of the geometric means of all measured jobs represented the average styrene and butadiene exposures within the plant.

Step 3 was to estimate exposure concentrations for unmeasured jobs based on the relative exposure value for the job, a *z* score for the job, and the actual distribution of measured values in the plant. This procedure was a reverse form of *z* score transformation. The average *z* score for a job multiplied by standard deviation of all measurements in the plant plus the mean of geometric means of measurements for all jobs in the plant produced the estimated exposure measurement for a specific job in a specific plant.

In the analysis, a combination of observed and estimated styrene concentrations was used. Whenever measurement data were available, they overrode the estimated values. An exposure matrix established for all 579 possible jobs for both plants provided styrene and butadiene concentrations for each job in each plant, allowing investigators to estimate individual exposure by linking job history to the calculated chemical exposure.

Estimation of Exposure Change over Time

Styrene and butadiene measurements were available only from 1978 to 1982 for plant 6 and from 1977 to 1985 for plant 7. The information was not sufficient to estimate the concentration of styrene and butadiene in the 1940s, 1950s, or 1960s. The overall concentrations of styrene and butadiene had reportedly decreased over time, however, according to a large cohort study that included these two plants (Macaluso et al 1996). Exposure estimation in the study by Macaluso and colleagues, as described by the authors, consisted of three major steps.

First, an analysis described individual manufacturing processes at each plant, the work areas in which each process was carried out, and specific operations performed in each area. This step also identified job titles of workers assigned to carry out operations with exposure potential as well as historical changes that may have affected exposure.

Next, a job analysis specified the tasks associated with exposure (equipment used, duration and frequency of the task, work practices, presence of exposure-reduction mechanisms) and the historical changes in exposure determinants. These analyses provided profiles of each job that identified all sources of exposure.

Third, exposures were characterized by specifying exposure models, estimating exposure intensities for specific tasks in different time periods, computing job-specific and time period–specific summary indices, estimating exposure intensities for each generic work area group (eg, "production workers") in different time periods

in order to compile job-exposure matrices for butadiene, styrene and benzene. Linking the job-exposure matrices with each subject's work history allowed calculation of cumulative exposure indices for individual workers.

Although the estimation in the study was not based on measurements and thus the absolute concentration estimation could be questionable, the information about relative changes of styrene and butadiene concentrations over time based on these models should be valid. Macaluso and colleagues presented the concentration changes by decade from the 1940s to the 1990s. In the present study, concentration measurements covered the period from 1976 to 1985, the mid period of the 1970s and 1980s, and were considered the average concentrations for those two decades. On the basis of information from Macaluso and colleagues (1996), ratios were calculated for styrene and butadiene concentrations for other periods compared with the average concentrations for the 1970s and 1980s (Figure 2). Figure 2 indicates the ratio of the levels of the two chemicals for three earlier decades relative to the actual measurements in 1970 to 1989. These ratios of change in styrene and butadiene concentrations were used to adjust for concentration changes over time and by job by the following method.

We assumed that for any time period during the follow-up, the relative exposure for jobs in a plant was consistent although the absolute exposures were probably different. We also assumed that the ratios of change were similar for different jobs (Figure 2) and that concentrations for different jobs regressed toward recent levels over time. Following these assumptions, the decreasing slope of concentration (ppm/year) for each specific job was proportional to the average decreasing slope. This proportion could be determined by the ratio of a known concentration for that job in a year over the average concentration in the same year. All estimates of styrene and butadiene were adjusted for time using this method. Appendix A provides an expanded description of these calculations.

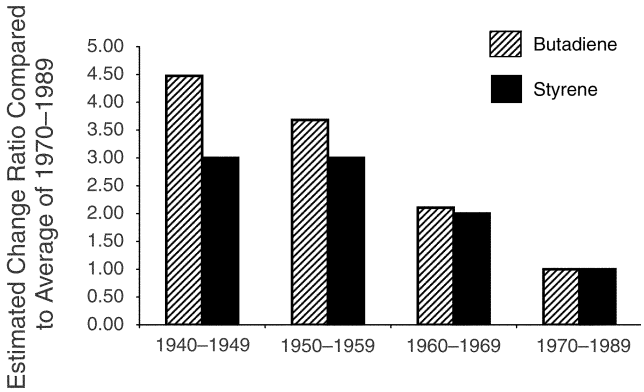

Figure 2. Estimated changes in ratios of styrene and butadiene exposure concentrations relative to 1970–1989 levels (based on Macaluso et al 1996).

Merge of Job History and Chemical Exposure Data

All jobs in each subject's job history were coded according to the 579 job classifications in the exposure matrix. The database of time-adjusted styrene and butadiene concentrations was merged with the job history database by job code and calendar period. From this step, individual exposures were obtained by linking personal job histories with the measurement-based exposure matrix by job code and time.

DATA ANALYSIS

Standardized Mortality Ratio Analysis

Causes of death were examined for the full cohort. Standardized mortality ratio analysis was performed on the full cohort to evaluate the risk of death from acute IHD and from chronic IHD in this cohort compared with the same risks in the US general population by race. A previous study that included this population demonstrated an increased SMR for IHD among black men. Expected case numbers were based on US white male and black male IHD mortality rates and 106,424 observed person-years for white men and 25,477 for black men among workers with known race. The total 131,901 person-years for these workers is 81.07% of the total 162,696 person-years for the full cohort of workers in the two plants. The remaining person-years belong to workers for whom race was unknown. Because of this, the expected numbers calculated for white male and black male workers would be underestimated and would lead to overestimated SMRs. Thus expected case numbers for the white male and black male population were adjusted up by adding more observed person-years, assuming the race ratio was the same in those without race information as in the population with known race information. Only 45 (0.68%) of 6587 workers were classified as "other race," and they were assumed to have the average mortality rates of combined white and black male workers. The SMR values and 95% confidence intervals were calculated using published methods (Monson 1974; Beaumont and Breslow 1981; Berry 1983).

Determination of Basic Cox Proportional Hazard Model

In keeping with the case-cohort design of this study, the Cox proportional hazard model was used in risk analyses, and the variance correction was based on published reports using SAS PHREG (Kupper et al 1975; Miettinen

1982; Prentice 1986; Sato 1992; Schouten et al 1993; Barlow 1994; Therneau and Li 1999).

Major Time Measure Age was used as the time measure in the Cox proportional hazard model. This ensured that age was carefully controlled in the analysis because age generally has a major influence on health outcomes. Having age as the time measure in the analysis meant the program used age as a matching variable when creating risk sets for comparison and the analysis was automatically stratified by age.

Control for Birth Year Controlling for birth year was necessary to reduce the influence from changes over calendar years. Birth year as a continuous variable that is not time-dependent was used in every regression model.

Control for Race Among confounding factors, race was an important variable. In a previous study (Matanoski et al 1990), a significant excess SMR for IHD (SMR, 1.48; 95% CI, 1.23–1.76) was found for black men. Only one subject had missing race information in plant 6. However, race information was missing for 171 subjects in Plant 7 (Table 2). Bias can occur because subjects with missing race are always noncases. A random race assignment was used for subjects with missing race information. Since 14.6% of subcohort members with known race in Plant 7 were black, the same proportion was used to assign race to the 171 subjects with missing race in Plant 7, yielding an expected number of additional black workers of 25. Computer-generated binomial random numbers, 0 (no) or 1 (yes), randomly assigned a race status to the 171 subjects based on the rate of 14.59%. Multiple computations were done in final risk analysis to test the effects of different random race assignments. Races other than white and black were rare in the population.

Odds ratios (ORs) and 95% confidence intervals (95% CIs) for death from acute and chronic IHD among black men compared with white men were calculated by plant to examine the effect of race in the analyses.

Stratification by Plant The two plants under study had several different characteristics. Among these were the completeness of race information, styrene exposure levels, and employment time of workers. Plant 7 had much higher styrene and butadiene levels than plant 6 and workers in plant 7 had much shorter employment times than workers in plant 6 on average. There may have been other plant differences, which we could not evaluate, such as differences in their exposure sampling methods. Potential biases could be introduced if we pooled the data from the two plants without stratification. Thus all the risk analyses were stratified by plant. We believed that if styrene were associated with IHD, then the association would not disappear as a result of stratification by plant.

Selection of Appropriate Outcome Time Windows

Many of the workers, especially workers whose employment time was less than 1 year, had terminated their jobs in the plant long before they died from IHD. It was unlikely that a death from acute IHD in later years could be attributed to a job of 6 months' duration, held 30 years earlier, especially when individual exposures after the rubber industry employment were unknown. In order to take into account the length of time between the job termination and death in evaluating the risk of a disease that may occur acutely or chronically in relation to exposure, we proposed a method to specify outcome time windows after the last date of employment. For instance, to look at the immediate effect of styrene, we used only active workers, and only IHD case subjects who died while employed were counted as cases in the analysis. To look for chronic effects we used two different outcome time windows. One

Table 2. Distribution of Study Population by IHD Case Status and Race

	Plant 6			Plant 7			Total		
Race	Acute IHD	Chronic IHD	Noncases	Acute IHD	Chronic IHD	Noncases	Acute IHD	Chronic IHD	Noncases
White	104	53.	277	156	77	330	260	130	607
Nonwhite	28	41.	93	16	23	48	44	64	141
Other	0	0.	0	0	0.	6	0	0	6
Unknown	0	0.	1	0	0.	171	0	0	172
Total	132	94.	371	172	100	555	304	194	926

included only cases who died after, but within 10 years of, leaving the plant; and the other time window included only cases who died more than 10 years after they had left the plant.

Time Dependence of Exposure Variables

Sources of exposure variables used in the analysis were measurement-based and time-corrected styrene and butadiene concentration estimations, along with IH ranks of styrene and butadiene concentrations. More attention was directed to the analysis of measurement-based estimated concentration data, which would demonstrate a dose-response relation between styrene and the disease if an association existed. The IH ranks were used in the estimation of styrene and butadiene concentrations but not directly in the analysis. All exposure variables used in risk analysis were time dependent, which meant the exposure variables were changing over time and were calculated at each time point when a death from IHD took place.

For instance, using age as the time scale, if a case subject died of IHD at age 40, then all subjects in the subcohort who ever reached age 40 would be used as references for this case to form a risk set. The individual exposures would be calculated only to age 40 although some of the subjects might live beyond 40. If another case subject died at age 44, then all subjects in the subcohort who ever reached age 44 would be used as references for this case to form another risk set, and individual exposures would be calculated in this example only to age 44. In other words, a subcohort member who reached age 85 at the end of study could have served as a reference for almost every risk set, and his time-dependent exposures would have been calculated many times and with changing values at each time point. There were two types of time-dependent exposure variables used in the study: time-weighted averages and time-dependent cumulative exposures.

Time-Weighted Averages These were continuous variables calculating average exposure intensity in parts per million weighted by exposure time up to time of event (death from IHD) for each risk set. The TWA intensity for styrene in ppm can be calculated at each desired time point using the following formula, where *ppm* and *duration* represent styrene concentration and exposure duration for each job *i*, respectively:

$$\text{Time-Weighted Average} = \frac{\Sigma(\text{ppm}_i \cdot \text{Duration}_i)}{\Sigma(\text{Duration}_i)}$$

In this study the TWA was also defined by specified time windows, such as TWA for the most recent 2 years. It should be noted that time-dependent TWAs were not fixed for each individual. They changed with the time scale because the definition of the most recent 2 years was based on different time points.

The other important feature of TWA is that it is an intensity indicator that is independent of the exposure duration. For instance, if two workers had the same job with styrene exposure at 2 ppm during the follow-up for the most recent 2 years, but one of the workers had worked for only 1 month while the other one had worked for 2 years, the TWAs for the two workers during the recent 2 years would be equal—that is, 2 ppm (please refer to the previous formula). Usually in analyses involving TWAs, we controlled for duration by including it as a variable in the model. This independence of TWA from duration has important implications in the current study. If a styrene TWA of 2 ppm had been found significantly associated with IHD at a 2-fold risk after controlling for exposure duration, then the 2-fold risk could be solely attributed to styrene intensity rather than duration. If the exposure duration mattered, the risk association with duration would show up independently. The results could suggest that the styrene intensity at 2 ppm would always have the same 2-fold risk no matter how long the exposure duration. Actual ambient air pollution episodes might only last a couple of days; using TWA as an exposure variable would resolve the problem of risk assessment for such short periods.

Time-Dependent Cumulative Exposures These continuous variables represent the accumulating product of exposure levels, in parts per million × exposure duration in years (ppm-years) from a defined start time to the time of event:

$$\text{Cumulative ppm-years} = \Sigma(\text{ppm}_i \cdot \text{Duration}_i)$$

Values of time-dependent cumulative exposure variables change with the time scale or risk set time. Time-dependent cumulative exposure variables were created for analysis of chronic or cumulative effects.

Selection of Exposure Time Windows

In choosing appropriate exposure time windows to assess acute effects, we needed to address two concerns: (1) The study analyzed only cases of death from IHD, rather than incident cases, so the IHD onset might have occurred 1 year or more before death. (2) Workers could change their jobs to cleaner areas after adverse symptoms associated with IHD were noticed. We believed that using exposures in the last job or exposure within the recent 1-year period might miss the actual exposures related to IHD death. The TWAs in

time windows of the most recent 2 years and most recent 3 to 5 years for active workers were used as exposure variables in the analysis for acute effects.

To assess risk of long-term accumulative exposure, time-dependent cumulative exposure variables (ppm-years) from first hire up to the time of death were used in the analyses for styrene and butadiene.

Data Preparation for Proportional Hazard Model Analysis

Change of Disease Status Over Time One of the important features of this case-cohort study was that all cases of a target population were compared with a random sample of the population. Using the case-cohort design, data were prepared such that (*a*) cases occurring within the subcohort were coded as 1, and these cases were considered as noncases and remained in the reference group until the last day, when they became cases; (*b*) cases occurring outside the subcohort were coded as 2, and these cases never served as references but only as cases on the day they died; and (*c*) noncase subcohort members were coded as 0, and they were always in the reference group.

As described above, an outcome time window determined those IHD cases that died within a specified time period and were counted as cases. Deaths that occurred outside the time window would be counted as noncases if the subjects were part of the subcohort. If subjects were not part of the subcohort, they would not be considered as noncases and would not be part of the comparison group.

Time-Dependent Variables There are usually two strategies in data preparation for analysis involving time-dependent variables. One is to do the calculations during the course of Cox model fitting. The data preparation for this strategy is easy, but there are some disadvantages: it becomes time-consuming when running the model fitting, since time-dependent calculations need to be done whenever a case occurs during the 40-year follow-up; and because of the nature of the time dependence, it is impossible to obtain distribution information for those time-dependent variables.

The second strategy is to do the time-dependent accumulation before running the model fitting. This involves intensive work in data preparation, since each time-dependent variable at each time point or for each risk set must be calculated. An advantage is that the program runs much faster than with the first method when fitting the models. Further, because all time-dependent variables are precalculated and become fixed variables, distribution information about them can be obtained as simply as for other variables. In this study, this second strategy was used.

Risk Sets At the first step of risk set preparation, data for each subject were obtained as multiple records. Each of the records represented a job, and there were job codes and start and end times for each job. Variables for all exposure factors such as styrene and butadiene concentrations were then merged to each job record by job code, by plant, and by time period. At the second step, the data were transferred from a multirecord format into a single-record format. Different exposure intervals were recorded as separate time segments. Each of the segments had one set of variables recording start and end times, and values for all exposure factors. This format was helpful in calculating time-dependent exposures at any given time. At the third step, ages at death for all IHD cases were identified, since age was used as a time measure in the analysis. A risk set was created for each age stratum of the cases. This set included as cases all subjects who died in the time stratum and included as references all eligible noncases; the reference group would contain some subjects who later became cases when they died from IHD. To be eligible, subjects should have attained or exceeded the age of cases in the risk set. All time-dependent variables were calculated for each subject in each risk set.

Estimation of IHD Risk from Exposure to Styrene at Ambient Levels

On the basis of dose-response relations established by proportional hazard models, relative hazards were estimated for exposures at different ambient levels of styrene and for various periods of time. The study focused on risks from most recent exposures for active workers because of the possible relevance of such data to the association between air pollution and cardiovascular mortality. Risks of acute and chronic IHD were examined separately. Because the concentrations of styrene in occupational settings were much higher than ambient levels, an interpolation method was used to estimate risks at ambient levels, assuming log linear nonthreshold models. The TWA exposure intensity of styrene calculated based on jobs in the most recent 2 years was used to estimate the acute effect of styrene on the risk of IHD mortality. Ambient measurements were adopted from published reports (Mckay et al 1982; Hartwell et al 1987) to estimate the risk of IHD from exposure to styrene at usual daily pollution levels and at some extreme air pollution levels that may exist in special situations and, in particular, may have occurred during pollution episodes in the past.

QUALITY CONTROL

In a previous study on the same population, direct follow-up by telephone was conducted for those individuals whose vital status was unknown. The purpose of this follow-up was to determine the accuracy of passive methods used to define what proportion of the population not currently employed in the plants was truly still alive. Approximately 900 people who were either current or former employees at the rubber-producing companies were randomly selected for follow-up by direct telephone contact. Telephone directories were searched, and approximately 811 people were contacted as a result of this information. The vital status of the contacted person was determined at the time of the telephone conversation. A questionnaire was mailed to the above group, and 424 questionnaires were returned. Among them 73 subjects were from plant 6 and 59 were from plant 7. Information gathered from these two plants was analyzed to estimate variation in smoking histories by job.

Two experienced abstractors were responsible for job history abstraction. A random sample of 10% of the total records abstracted was checked by a supervisor who had worked with the data in previous job history abstractions. To evaluate the validity of the exposure estimation models, model-predicted values were compared with actual measurements. Real distributions were examined using available measurements to verify the assumptions made in estimating missing values.

The available data from the study cohort did not allow us to do any morbidity analysis, but IHD deaths are clearly related to incident cases of IHD. The use of existing mortality data should be an appropriate approach to study the acute effects of a chemical on the risk of heart attack. The mortality data were especially useful in our attempts to draw parallels to deaths from exposure to air pollution.

RESULTS

EXPOSURE ASSESSMENT

Estimation of Styrene Concentration for Each Job in Two Plants

Of eight plants studied previously, only five plants provided styrene measurements as part of the study. One of the five was a Canadian plant and the remaining four were US plants. In order to use all available information, all 3553 measurements of styrene for 134 jobs from five plants were used. After *z* score transformation, styrene measurements were estimated for all unmeasured jobs in all five plants, using the procedures described in the Methods section and in Appendix A. Because the estimated styrene concentrations were plant specific and each plant potentially had 579 unique jobs, the total number of jobs estimated for five plants was 2895.

Figure 3 shows the distribution of measured styrene concentrations for 134 jobs and the distribution of estimated styrene concentrations for 2895 jobs in the five plants. The distribution pattern for estimated concentrations was similar to the distribution pattern for actual styrene measurements for the same five plants (Figure 3). The majority of both measured and estimated concentrations were below 0.2 ppm. Figure 4 shows the correlation between measured styrene concentrations and the estimated concentrations based on available data from 134 measured jobs. The squared correlation coefficient (R^2) was 0.77 ($P < 0.001$).

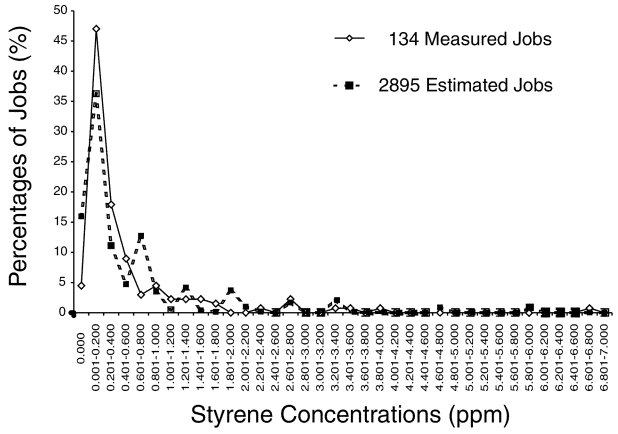

Figure 3. Distribution of measured and estimated styrene geometric mean concentrations in five plants with measurements (1976–1985).

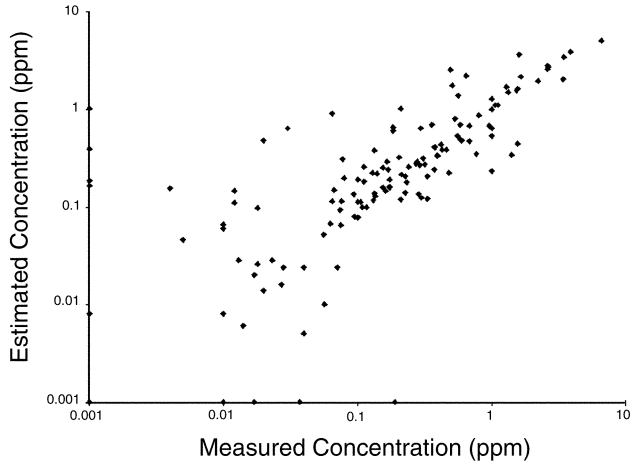

Figure 4. Correlation between measured and estimated styrene concentrations for 134 jobs with 3553 measurements in five plants. $R^2 = 0.7666$, $P < 0.001$, 0 ppm is treated as 0.001 in log scale of the graph.

The distribution of estimated styrene concentrations by IH ranks is shown for all four US plants in Table 3. (The Canadian plant used a different ranking system so its data are not shown.) The estimated data clearly reflected the changing rank score, with a 10-fold increase in measured score for ranks 1 to 10. Estimated styrene concentrations increased with each IH rank score. Table 3 gives estimated concentrations calculated for all jobs at each rank. In accordance with the previously defined assumptions and concentration estimation methods used in this study, concentrations for jobs without any measurements were basically determined by IH rank as relative order and by the concentration distribution parameters in the specified plant for absolute magnitudes of exposure level.

A combination of observed and estimated styrene concentrations was actually used in the data analysis. Whenever measurements were available, they overrode the estimated data. The measured (observed), estimated, and combined styrene concentrations for all 579 jobs for Plants 6 and 7 are listed in Appendix C. Butadiene concentrations for unmeasured jobs were also estimated using the same method described above and in Appendix A, resulting in complete concentration data for the other major confounding chemical exposure.

To further examine the distributions of measured and estimated styrene concentrations in the two study plants, major distribution parameters are shown in Table 4 for both plants. Figures 5 and 6 show the graphic distribution patterns for measured and estimated concentrations by plant. Plant 7, on average, had higher styrene levels and a wider range of concentrations than plant 6. In both plants estimated concentrations were distributed in the same pattern as measured concentrations.

Table 3. Estimated Styrene Concentrations in Four US Plants

IH Rank	Mean of GM[a] (ppm)	Standard Deviation	Number of Jobs
0	0.020	0.069	932
1	0.157	0.152	300
2	0.281	0.211	468
3	0.455	0.387	276
4	0.616	0.441	100
6	0.780	0.647	136
8	1.230	0.925	88
10	1.207	1.084	16
Total	0.267	0.444	2316

[a] Geometric mean.

Correlations Between Styrene and Butadiene

Butadiene was the major coexisting chemical with styrene in the industry. The relation between styrene and

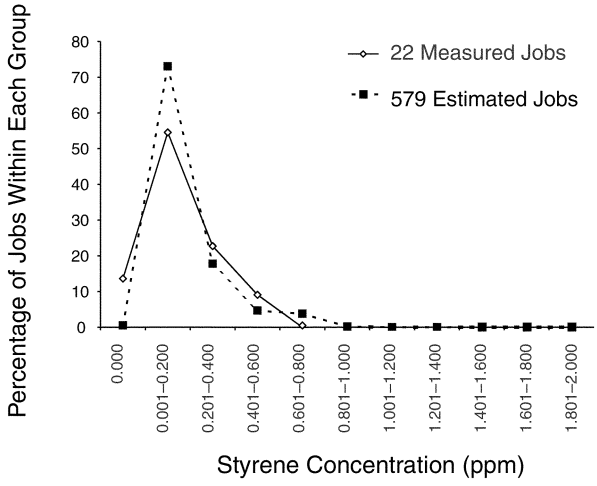

Figure 5. Distributions of measured and estimated styrene concentrations for jobs in plant 6 (1976–1985).

Table 4. Distribution Parameters of Measured and Estimated Styrene Concentrations in Two Study Plants (1976–1985)

Exposure Parameter	Plant 6 (ppm)		Plant 7 (ppm)	
	22 Measured Jobs	579 Estimated Jobs	44 Measured Jobs	579 Estimated Jobs
Median	0.122	0.100	0.170	0.165
75th Percentile	0.209	0.240	0.361	0.472
25th Percentile	0.023	0.025	0.079	0.016
Mean	0.153	0.148	0.290	0.273
Standard error	0.034	0.006	0.051	0.014
Minimum	0.000	0.000	0.010	0.000
Maximum	0.580	0.834	1.573	1.667

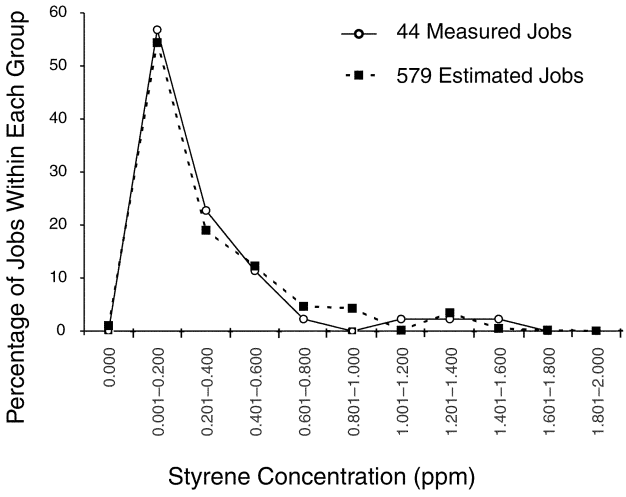

Figure 6. Distributions of measured and estimated styrene concentrations for jobs in plant 7 (1976–1985).

butadiene was reviewed to determine the degree of collinearity between them.

Styrene and Butadiene IH Ranks Table 5 shows the distribution of all 579 jobs in the industry by IH ranks for styrene and butadiene exposure. Although the ranks for the two chemicals were correlated, many jobs with high styrene ranks had low butadiene ranks, and vice versa. For instance, 21 jobs had exposure to styrene at rank 8 but to butadiene at rank 1, while 33 jobs had exposure to styrene at rank 0 but to butadiene at rank 5. These patterns allowed us to put the two chemicals into one model and control for each.

Styrene and Butadiene Concentrations The correlation between styrene and butadiene concentrations is shown in Figure 7. The low correlation (R^2 = 0.16) is significant because of the large sample size (579 + 579 = 1158). Figure 7 shows that some jobs had reversed styrene and butadiene concentrations, with butadiene concentrations much higher than styrene concentrations.

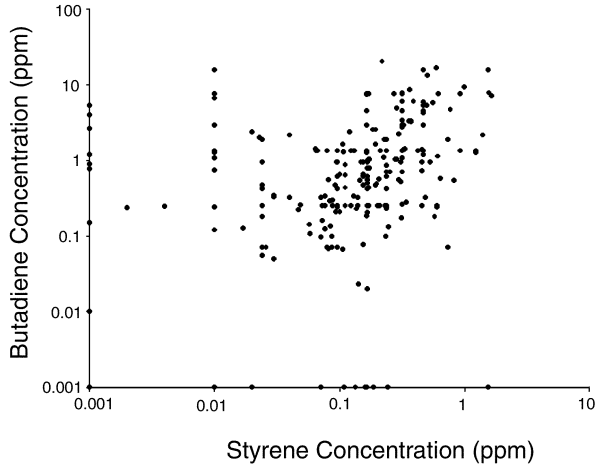

Figure 7. Correlation between styrene and butadiene concentrations for 579 jobs in two study plants. R^2 = 0.1602, $P < 0.05$, 0 ppm is treated as 0.001 in the log scale of this graph.

Table 5. Number of Jobs Distributed by IH Rank of Styrene and Butadiene Exposures for 579 Jobs

Styrene IH Rank	Butadiene IH Rank											Total
	0	1	2	3	4	5	6	7	8	9	10	
0	184	9	4	0	0	33	0	0	0	0	3	233
1	27	40	5	1	0	2	0	0	0	0	0	75
2	0	48	29	13	6	21	0	0	0	0	0	117
3	0	22	21	1	0	0	0	0	0	0	25	69
4	0	0	0	0	0	25	0	0	0	0	0	25
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	6	2	0	0	26	0	0	0	0	0	34
7	0	0	0	0	0	0	0	0	0	0	0	0
8	1	21	0	0	0	0	0	0	0	0	0	22
9	0	0	0	0	0	0	0	0	0	0	0	0
10	1	0	0	0	0	0	0	0	0	0	3	4
Total	213	146	61	15	6	107	0	0	0	0	31	579

Job History Abstraction

Detailed job histories of all 1424 case-cohort subjects were abstracted. The total number of job changes was 6865. However, the total number of unique jobs in the histories of case-cohort subjects was only 166 of the total 579 unique jobs in the industry.

GENERAL INFORMATION ON FULL COHORT

Distribution of All Causes of Death

In total, 162,696 person-years were observed for the 40 years of follow-up from 1943 to 1982 for the full target population. The distributions of all causes of death are shown in Figure 8 for plant 6 and in Figure 9 for plant 7. The causes of death that occurred with high frequency were IHD, other circulatory diseases (*ICD-8,* codes 390–450 excluding codes 410–414), and injuries (*ICD-8,* codes 800–999). Of all plant 7 deaths, 30% were due to IHD and 14% to injury; of all plant 6 deaths, 36% were due to IHD and 9% to injury.

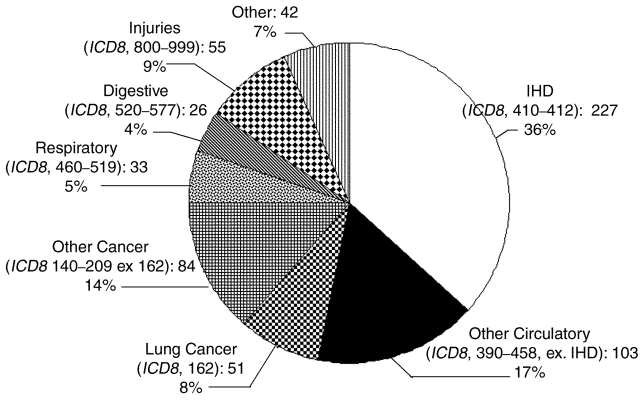

Figure 8. Causes of 621 deaths among plant 6 workers (1943–1982).

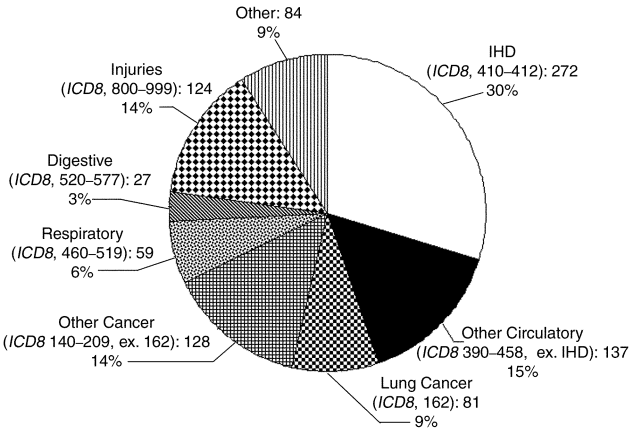

Figure 9. Causes of 912 deaths among plant 7 workers (1943–1982).

Standardized Mortality Ratio Analysis

During the 40 years of follow-up from 1943 to 1982, in the full target population 304 cases of death from acute IHD and 194 cases of death from chronic IHD were observed. Case subjects dying of acute IHD were 5 years younger on average than those who died of chronic IHD, which might be expected. The SMR results for white men, nonwhite men, and men of all races are shown in Table 6. (See Tables D.1 to D.10 in Appendix D for detailed information related to calculation of race-specific SMRs.) Table 6 shows that in terms of IHD risk compared with the US general population, the full cohort demonstrated the "healthy worker effect" (that is, occupational populations tend to be healthier than the general population). However, nonwhite men (in general, these were black men) had a significantly high SMR for chronic IHD (SMR, 1.47; 95% CI, 1.17–1.77) compared with the US general population. Such an increase did not appear in either race group for death from acute IHD. This finding was consistent with the results of a previous study (Matanoski et al 1990), but current data attributed the difference specifically to chronic IHD.

COX PROPORTIONAL HAZARD REGRESSIONS

Risk of IHD Based on Intensity of Styrene Exposure

Cox proportional hazard regressions were modeled for both acute and chronic IHD among active workers or workers who died while still employed. Among these active workers, the total duration of employment varied from less than 1 year to 40 years. We first looked at all active workers who had ever been employed prior to the time of death (Table 7, Employed > 0 Year). We then excluded those subjects whose time-dependent employment duration was less than 2 years before the time of death. In other words, we analyzed data for those workers whose time-dependent employment duration was 2 years or longer (Table 7, Employed ≥ 2 Years). Finally, we further excluded those subjects whose time-dependent employment duration was less than 5 years (Table 7, Employed ≥ 5 Years) and fit the same set of models. These three employment-duration groups were inclusive of each other.

Time-dependent TWA (ppm) during the most recent 2 years and TWA during the most recent 2 to 5 years were used as two variables of recent styrene or butadiene exposures. These two exposure variables were exclusive of each other. In addition to these exposure variables, the Cox models used age as the time scale, stratified by plant, and adjusted for race, birth year, and duration of employment.

Table 6. SMR for Acute and Chronic IHD in Male Workers Hired Between 1943 and 1982, by Race

Race	Disease	Observed Cases	Expected Cases[a]	Adjusted Expected Cases[b]	SMR[c]	95% CI
White	Acute IHD	260	241.89	298.37	87.14	75.79 – 98.49
	Chronic IHD	130	154.36	190.41	68.28	54.07 – 82.48
	All IHD	390	396.25	488.78	79.79	70.93 – 88.66
Nonwhite	Acute IHD	44	55.17	68.05	64.66	40.90 – 88.42
	Chronic IHD	64	35.20	43.42	147.38	117.64 – 177.12
	All IHD	108	90.37	111.47	96.89	78.32 – 115.45
All	Acute IHD	304	297.05	366.42	82.97	72.73 – 93.21
	Chronic IHD	194	189.57	233.83	82.97	70.15 – 95.78
	All IHD	498	486.62	600.25	82.97	74.97 – 90.97

[a] Expected case numbers are calculated based on US IHD mortality rates and observed person-years by race.

[b] Expected case numbers are adjusted by adding more person-years from unknown races based on known race proportions.

[c] Standardized mortality ratio compared with mortality rate (1940–1984) for US general population using adjusted expected case numbers.

Table 7. Risk of IHD Based on Intensity of Recent Styrene Exposure in Active Workers Stratified by Durations of Employment[a]

	Employed > 0 Year		Employed ≥ 2 Years		Employed ≥ 5 Years	
Exposure Variable[b]	RH	95% CI	RH	95% CI	RH	95% CI
Model 1: Acute IHD	**40 cases vs 571 noncases**		**36 cases vs 409 noncases**		**36 cases vs 325 noncases**	
Styrene TWA for recent 2 years	3.26	1.09 – 9.72	5.86	1.59 – 21.64	6.60	1.78 – 24.54
Styrene TWA for 2 years ago to 5 years	0.94	0.85 – 1.04	0.92	0.82 – 1.03	0.90	0.79 – 1.01
Model 2: Acute IHD	**40 cases vs 571 noncases**		**36 cases vs 409 noncases**		**36 cases vs 325 noncases**	
Styrene TWA for recent 2 years	2.34	0.72 – 7.57	4.99	1.07 – 23.34	4.27	0.84 – 21.79
Styrene TWA for 2 years ago to 5 years	0.98	0.87 – 1.11	0.95	0.82 – 1.09	0.94	0.81 – 1.10
Butadiene TWA for recent 2 years	1.05	0.98 – 1.14	1.02	0.92 – 1.14	1.07	0.94 – 1.23
Butadiene TWA for 2 years ago to 5 years	0.99	0.98 – 1.00	1.00	0.99 – 1.01	0.99	0.98 – 1.01
Model 3: Chronic IHD	**23 cases vs 573 noncases**		**23 cases vs 410 noncases**		**22 cases vs 326 noncases**	
Styrene TWA for recent 2 years	1.22	0.08 – 18.13	1.45	0.09 – 23.93	1.52	0.09 – 24.65
Styrene TWA for 2 years ago to 5 years	0.96	0.76 – 1.22	0.93	0.72 – 1.20	0.93	0.72 – 1.20
Model 4: Chronic IHD	**23 cases vs 573 noncases**		**23 cases vs 410 noncases**		**22 cases vs 326 noncases**	
Styrene TWA for recent 2 years	1.92	0.08 – 46.74	2.13	0.07 – 62.97	2.18	0.07 – 68.27
Styrene TWA for 2 years ago to 5 years	0.89	0.66 – 0.70	0.88	0.64 – 1.19	0.88	0.65 – 1.20
Butadiene TWA for recent 2 years	0.96	0.81 – 1.14	0.96	0.80 – 1.16	0.97	0.80 – 1.16
Butadiene TWA for 2 years ago to 5 years	1.01	0.99 – 1.02	1.01	0.99 – 1.02	1.01	0.99 – 1.02

[a] Using age as time scale, data were stratified by plant and controlled for race and birth year. Butadiene is adjusted in models 2 and 4.

[b] Employment duration weighted average concentrations in ppm.

The results shown in Table 7 are only for styrene and butadiene or other variables that were significantly associated with outcomes. Duration of employment, race, and birth year were not significant in these models and are not listed in Table 7. No models for the risks of chronic IHD showed any significant association between exposure to styrene or butadiene. Butadiene showed no association with acute or chronic IHD in any model.

Styrene TWA values for the most recent 2 years, however, resulted in significantly high relative hazard for IHD, ranging from 3.26 to 6.60 in the models using the three employment-duration cut points. For all active workers ever employed, the relative hazard of acute IHD was 3.26 (95% CI, 1.09–9.72). Excluding 4 cases and 62 noncases whose time-dependent employment durations were less than 2 years, the relative hazard was 5.86 (95% CI, 1.59–21.64). Excluding 84 additional noncases whose time-dependent employment durations were less than 5 years, the relative hazard was 6.60 (95% CI, 1.78–24.54) based on 36 eligible cases and 325 eligible noncases.

Risk of IHD from Cumulative Styrene Exposures

Active Workers We used the same three employment-duration cut points as in the risk analysis for recent exposures. Cumulative time-dependent ppm-years were used in examining chronic effect of exposure to styrene among active workers with different employment-duration cut points. Table 8 shows that cumulative exposures to styrene were also significantly associated with acute IHD. The risk was about 1.04-fold to 1.08-fold for each increase of 1 ppm-year in various models. This result suggests that high styrene concentrations in recent exposures were much more important contributors to risk than lower exposures of longer duration, although the latter were also associated with the risk of acute IHD mortality. Race was not associated with risk of either acute or chronic IHD for active workers.

Workers Who Left Employment Prior to Death Some workers in the study had left the plant shortly before death from IHD, while others had left employment decades before death from IHD or the end of follow-up. Data on exposures after termination were not available. Only death information was collected for the total follow-up period. Conclusions about the results of analyses on these workers should be guarded because of the possibility of exposure misclassifications. Using the same analysis models, risks of acute and chronic IHD among workers who had left their plants no more than 10 years before and workers who had left more than 10 years before are shown in Tables 9 and 10, respectively. Styrene and butadiene exposures showed no association with either acute or chronic IHD.

Table 8. Risk of IHD Based on Cumulative Styrene Exposure in Active Workers Stratified by Duration of Employment[a]

	Employed > 0 year		Employed ≥ 2 years		Employed ≥ 5 years	
Exposure Variable[b]	RH	95% CI	RH	95% CI	RH	95% CI
Model 1: Acute IHD	**40 cases vs 571 noncases**		**36 cases vs 409 noncases**		**36 cases vs 325 noncases**	
Styrene accumulated ppm-years	1.04	1.00 – 1.08	1.04	1.00 – 1.09	1.04	1.00 – 1.08
Model 2: Acute IHD	**40 cases vs 571 noncases**		**36 cases vs 409 noncases**		**36 cases vs 325 noncases**	
Styrene accumulated ppm-years	1.07	1.02 – 1.13	1.08	1.02 – 1.14	1.07	1.02 – 1.13
Butadiene accumulated ppm-years	1.00	0.99 – 1.00	1.00	1.00 – 1.00	1.00	1.00 – 1.00
Model 3: Chronic IHD	**23 cases vs 573 noncases**		**23 cases vs 410 noncases**		**22 cases vs 326 noncases**	
Styrene accumulated ppm-years	0.99	0.94 – 1.05	0.99	0.93 – 1.05	0.99	0.93 – 1.05
Model 4: Chronic IHD	**23 cases vs 573 noncases**		**23 cases vs 410 noncases**		**22 cases vs 326 noncases**	
Styrene accumulated ppm-years	0.98	0.90 – 1.07	0.98	0.90 – 1.07	0.98	0.90 – 1.07
Butadiene accumulated ppm-years	1.00	1.00 – 1.00	1.00	1.00 – 1.00	1.00	1.00 – 1.00

[a] Using age as time scale, data were stratified by plant and controlled for race and birth year. Butadiene is adjusted in models 2 and 4.

[b] Time-dependent cumulative ppm-years prior to the time of event.

Table 9. Risk of IHD Based on Cumulative Styrene Exposure in Workers Who Left Plant Up to 10 Years Before Event Stratified by Durations of Employment[a]

	Employed > 0 Year		Employed ≥ 2 Years		Employed ≥ 5 Years	
Exposure Variable[b]	RH	95% CI	RH	95% CI	RH	95% CI
Model 1: Acute IHD	**61 cases vs 769 noncases**		**44 cases vs 244 noncases**		**32 cases vs 129 noncases**	
Styrene accumulated ppm-years	0.98	0.93 – 1.04	0.97	0.91 – 1.03	0.98	0.92 – 1.05
Model 2: Acute IHD	**61 cases vs 769 noncases**		**44 cases vs 244 noncases**		**32 cases vs 129 noncases**	
Styrene accumulated ppm-years	0.99	0.93 – 1.06	0.98	0.92 – 1.04	0.99	0.93 – 1.07
Butadiene accumulated ppm-years	1.00	0.99 – 1.00	1.00	0.99 – 1.00	1.00	0.99 – 1.00
Model 3: Chronic IHD	**38 cases vs 774 noncases**		**32 cases vs 246 noncases**		**29 cases vs 129 noncases**	
Styrene accumulated ppm-years	1.00	0.95 – 1.05	0.98	0.93 – 1.04	0.98	0.93 – 1.04
Nonwhite race	3.35	1.68 – 6.67	3.53	1.63 – 7.62	4.30	1.92 – 9.66
Model 4: Chronic IHD	**38 cases vs 774 noncases**		**32 cases vs 246 noncases**		**29 cases vs 129 noncases**	
Styrene accumulated ppm-years	1.00	0.94 – 1.06	0.99	0.93 – 1.05	0.99	0.92 – 1.05
Butadiene accumulated ppm-years	1.00	0.99 – 1.00	1.00	0.99 – 1.00	1.00	0.99 – 1.00
Nonwhite race	3.39	1.68 – 6.84	6.50	2.60 – 16.29	4.48	1.92 – 10.45

[a] Using age as time scale, data were stratified by plant and controlled for race and birth year. Butadiene is adjusted in models 2 and 4.

[b] Time-dependent cumulative ppm-years prior to the time of event.

However, nonwhite race was significantly associated with chronic IHD in each model of workers who had left the plants. The association between race and chronic IHD seemed independent of duration of employment and of the time since the termination of jobs.

ESTIMATION OF RISKS FROM EXPOSURE TO AMBIENT STYRENE

On the basis of the exposure dose-response relation found in the analysis, each increase of 1 ppm in intensity of styrene concentration during the most recent 2 years of employment was associated with a 5.86-fold–increased risk of death from acute IHD ($\beta = 1.7688$) among active workers employed at least 2 years. Because the model showed the important exposure variable was intensity or TWA, independent of duration of exposure, the situation depicted by the model could mimic the mortality related to ambient air pollution. Results obtained with this model were used to estimate the risk of acute events in the general population.

Table 11 gives estimates for the risk of death from acute IHD for exposures to styrene at common ambient levels and at some extreme situations assuming a nonthreshold log linear dose-response model. For each increase of 10 $\mu g/m^3$ in ambient styrene, acute IHD mortality is estimated to increase by 0.4%; or for each 23 $\mu g/m^3$ increase, by 1%. At common levels, such as the levels reported for Los Angeles in spring and winter of 1984, the relative risk would increase at most by 0.1%. However, in some locations—for instance, in communities near reinforced plastic processing plants—ambient styrene levels could be so high that the relative risk of death from IHD would reach as high as 3.386-fold.

SMOKING DATA

Smoking has a well-known association with IHD and thus is an important confounding factor. In an early study, 424 subjects from eight plants were interviewed by phone as described in the Methods section. Of these 424 subjects, 69.1% were smokers and 49.2% smoked 20 cigarettes or more a day on average, despite the fact that smoking was restricted for these employees during working hours.

All 424 interviewees were examined for smoking history in relation to last job held. Figure 10 shows the distribution of smokers by division. (Table D.11 in Appendix D gives

Table 10. Risk of IHD Based on Cumulative Styrene Exposure in Workers Who Left Plant More Than 10 Years Before Event Stratified by Durations of Employment[a]

	Employed > 0 Year		Employed ≥ 2 Years		Employed ≥ 5 Years	
Exposure Variable[b]	RH	95% CI	RH	95% CI	RH	95% CI
Model 1: Acute IHD	**203 cases vs 590 noncases**		**53 cases vs 158 noncases**		**24 cases vs 67 noncases**	
Styrene accumulated ppm-years	0.98	0.90 – 1.06	0.96	0.86 – 1.07	0.97	0.86 – 1.10
Model 2: Acute IHD	**203 cases vs 590 noncases**		**53 cases vs 158 noncases**		**24 cases vs 67 noncases**	
Styrene accumulated ppm-years	0.99	0.90 – 1.08	0.96	0.86 – 1.08	0.98	0.86 – 1.12
Butadiene accumulated ppm-years	1.00	0.99 – 1.01	1.00	0.99 – 1.01	1.00	0.99 – 1.00
Model 3: Chronic IHD	**133 cases vs 600 noncases**		**36 cases vs 159 noncases**		**21 cases vs 67 noncases**	
Styrene accumulated ppm-years	0.95	0.87 – 1.04	0.95	0.84 – 1.08	0.94	0.81 – 1.08
Nonwhite race	2.24	1.54 – 3.27	4.24	1.92 – 9.36	4.37	1.34 – 14.30
Model 4: Chronic IHD	**133 cases vs 600 noncases**		**36 cases vs 159 noncases**		**21 cases vs 67 noncases**	
Styrene accumulated ppm-years	1.00	0.90 – 1.11	0.95	0.93 – 1.09	0.87	0.71 – 1.05
Butadiene accumulated ppm-years	0.99	0.98 – 1.00	0.98	0.96 – 1.00	0.96	0.94 – 1.00
Nonwhite race	2.29	1.57 – 3.34	6.50	2.60 – 16.29	19.21	2.84 – 130.21

[a] Using age as time scale, data were stratified by plant and controlled for race and birth year. Butadiene is adjusted in models 2 and 4.

[b] Time-dependent cumulative ppm-years prior to the time of event.

Table 11. Estimated Risk of Acute IHD from Exposure to Ambient Styrene (Based on Usual and Special Exposure Circumstances)

Circumstances	Styrene ($\mu g/m^3$)	Styrene (ppm)[a]	Relative Risk[b]	Reference
Usual				
Los Angeles CA, winter 1984	1.90 – 2.30	0.00045 – 0.00054	1.001 – 1.001	Hartwell et al 1987
Los Angeles CA, spring 1984	0.63 – 1.50	0.00015 – 0.00035	1.000 – 1.001	Hartwell et al 1987
Special				
Los Angeles CA, 1965	8.50 – 63.70	0.00200 – 0.01497	1.004 – 1.027	Mckay et al 1982
Vicinity of processors of unsaturated polyester resins in USA, as a function of distance and wind direction	0.29 – 2934.0	0.00007 – 0.68949	1.000 – 3.386	Mckay et al 1982

[a] Styrene at 1 mg/m^3 = 0.235 ppm.

[b] A relative hazard of 5.864/ppm was used in the risk estimation.

the ranges of IH ranks and geometric means of styrene in different subdivisions and work areas.) From the results there did not appear to be a direct relation between smoking and jobs having potentially high styrene exposures. For example, the highest proportion of nonsmokers and the lowest proportion of heavy smokers were in jobs in the Process/Production subdivision, which were given the maximum IH ranks and most of which entailed some exposure to styrene. The Warehouse, Shipping and Receiving subdivision was classified as having no exposed jobs, but workers in

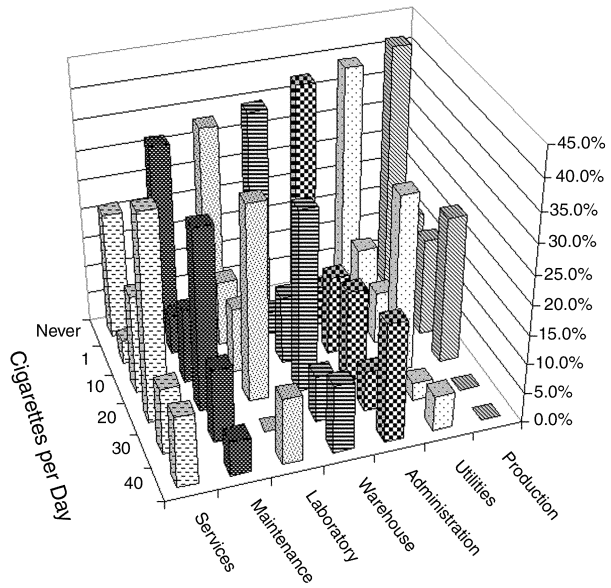

Figure 10. Smoking distribution based on subdivisions of last employment (424 subjects interviewed).

this subdivision actually had an intermediate ranking among all 424 subjects according to smoking history. Thus there was no obvious relation between job and smoking history that would suggest smoking history might confound the association between IHD and styrene exposure.

The smoking distribution also did not demonstrate any major differences by plant. Plant 6 had 50.0% heavy smokers compared with 45.8% in Plant 7. Because only 131 of the 424 workers interviewed were from the two study plants (72 from plant 6 and 59 from plant 7), the number of interviewed workers in the case-cohort study was too small to adjust for this confounder directly, and we assumed that smoking as a personal habit was not associated with styrene exposure concentration. Therefore, smoking does not explain the apparent association between styrene exposure and risk of acute IHD.

DISCUSSION

STUDY RESULTS AND PREVIOUS STUDIES

This study established a dose-response relation between styrene exposure and death from acute IHD. Standardized mortality ratio analysis results showed that the workers employed between 1943 and 1982, as a whole, had lower risk of death from acute and chronic IHD than the US general population. However, black workers had a higher risk of death from chronic IHD than that of the US general population. Because occupational populations tend to be healthier than the general population (the healthy worker effect), these external comparisons tend to underestimate the real risk of an exposure within the industry. Internal comparisons are needed to uncover the real risks of exposure among workers.

The results of this study, obtained using internal comparisons and multivariate time-dependent exposure analysis, showed an association between the intensity of recent styrene exposure and an increased risk of acute IHD mortality among active workers. For each ppm increase in styrene intensity, the risk of acute IHD mortality increased from 2.3- to 6.6-fold. For each ppm-year of increase in cumulative styrene exposure, the risk of acute IHD mortality increased 4% to 8%. Thus, risk of acute IHD mortality was more sensitive to the recent intensity of styrene exposure. These results establish measurement-based dose-response relations between levels of styrene exposure and acute IHD mortality.

Extensive efforts have been made to evaluate the potential reproductive, neurotoxic, genotoxic, and carcinogenic activities of styrene in vitro, in animals (Murata et al 1991; Edling et al 1993; Sorsa et al 1993; McConnell and Swenberg 1994; Phillips and Farmer 1994; Scott 1994; Sumner and Fennell 1994), and in humans (Downs et al 1987; Matanoski and Schwartz 1987; Matanoski et al 1990, 1997; Santos-Burgoa et al 1992; Sorsa et al 1993; Coggon 1994; Kogevinas et al 1994). However, the effects of styrene exposure on the cardiovascular system have not been emphasized.

Most previous occupational studies were SMR studies, usually with lower risks, in which the deaths from heart disease in the populations were compared with the US general population. However, elevated SMRs were often seen in subgroups such as blacks. Matanoski and colleagues (1990) conducted a study on a cohort of 12,110 workers in the styrene-butadiene polymer manufacturing industry (1943–1982) and found a significant excess SMR for IHD (SMR, 1.48; 95% CI, 1.23–1.76) among black workers. The reason for this excess was not investigated although it was suspected that minority workers might be heavily exposed to chemicals in the industry. In the current study, when an internal comparison was conducted (Table 9), the risk of IHD mortality among blacks was primarily due to chronic IHD and was not associated with styrene or butadiene exposure, but was associated with being a former worker. Another interesting phenomenon in the results of the current study was the increased risk of IHD mortality in workers with shorter employment durations. Bond and colleagues (1992) found a significant elevation of IHD mortality (SMR, 1.34; 95% CI, 1.04–1.71) among employees with exposure to styrene and ethyl benzene at

TWA concentrations of 5 ppm (21.3 mg/m^3) or higher in a cohort study among workers engaged in development or manufacture of styrene-based products. The risk was concentrated primarily among persons with duration of exposure that was short (< 1 year) to moderate (1 to 4 years). The same phenomenon occurred in another large epidemiologic occupational study. Wong and colleagues (1994) reported results based on a cohort of 15,826 workers in the reinforced plastics and composites industry where there were exposures to styrene monomer as well as other chemicals. Workers with the shortest duration of exposure to styrene had the highest SMR for IHD (129.4, $P < 0.05$), and SMRs decreased with increases in duration of employment: workers with employment durations of less than 1 year, 1 to 1.9 years, 2 to 4.9 years, 5 to 9.9 years, and 10 years or more had SMRs of 129.4, 113.8, 108.7, 85.8, and 85.6, respectively. Although these previous studies did not provide information on the risks related to acute IHD and chronic IHD separately, these deaths among short-term workers might have been due to acute IHD.

On the basis of our study results on the association of styrene and acute IHD, we conclude that only those who could survive acute IHD from a styrene exposure or tolerate an early high exposure to styrene would continue to work for a long period. As suggested above, individuals with compromised blood flow from existing arteriosclerosis would either die from the acute episode of IHD or leave the plant because of increased symptoms early in their employment, resulting in short work histories. Workers with long employment duration would be those individuals who worked in areas with low styrene exposure or perhaps those with healthier cardiovascular systems. These hypotheses need to be examined further in relation to incident events.

POSSIBLE MECHANISMS EXPLAINING ASSOCIATION BETWEEN STYRENE AND IHD

Heart disease is infrequently identified as a problem in toxicologic studies of styrene and other chemicals, possibly because the predisposing factors that exist in human populations are not found in most animal models. In fact, the animal species used for most of the studies may not represent the optimum model for studies of either acute or chronic cardiovascular disease. The mechanisms that might cause cardiovascular diseases are complicated and include (1) damage to barriers in the vascular system, (2) activation of leukocytes and platelets, (3) initiation of plaque formation, (4) stimulation of the inflammatory response, (5) kidney-related hypertension, and (6) direct damage to cardiac and blood vessel tissue. We hypothesized that styrene could have both acute and chronic impacts on risk of IHD, although the mechanisms have clearly not been established.

The results of this study indicate that the intensity of short-term styrene exposures poses a greater effect on risk of IHD mortality than long-term exposures. Styrene can be distributed with lipids to atherosclerotic plaques and other tissues with fat deposits; therefore, styrene or its metabolites have opportunities to cause changes in atherosclerotic plaques, for example, or may act directly on artery walls, leading to obstruction or narrowing of blood vessels, probably reversibly. The effects could be more marked in individuals with already compromised blood flow from arteriosclerosis. However, this study was designed only to examine a possible association between styrene exposure and IHD risk based on the hypothesis that there would be differences in effect with differences in exposure. It cannot go beyond suggesting a hypothesized mechanism. Direct studies, which focus on possible mechanisms to explain the association between styrene and cardiovascular disease, would be necessary to confirm the findings from epidemiologic studies.

IMPLICATIONS FOR MODELING RISKS BASED ON AMBIENT EXPOSURES

The major purpose of this study was to determine whether a substance like styrene, which is present in very small quantities in urban air on a normal day but can reach higher levels in special circumstances and could adhere to particulate matter, might explain a sudden increase in deaths from heart disease. The study focused on an occupational cohort for whom exposures were high. On average, levels of styrene in the ambient air would obviously be much lower than levels in industrial settings. However, the results do address whether air contaminants are actually associated with cardiovascular outcomes thought to explain most deaths related to changing particulate matter levels in ambient air.

Styrene is an example of a chemical that could attach to particulate matter and thus enter the lungs and circulatory system, possibly resulting in death. To accomplish this sequence, styrene would need to be associated with heart disease deaths at high doses as well as low doses. Further, the effect would be likely to manifest relatively soon after exposure. As pointed out previously, this study and some previous studies suggest styrene could have an acute IHD effect consistent with immediate changes in mortality related to changes in ambient air pollution. We should continue to consider that long-term exposure to styrene could also have an effect on heart disease that may be due to vessel damage from lipid changes. This sequence of

events, although not as relevant to the study of ambient air pollution, has been examined in this study.

The present study has also examined whether styrene itself could explain any of the mortality from air pollution and, if so, how large a risk it poses. According to our calculations, for each 10 $\mu g/m^3$ increase in ambient styrene, acute IHD mortality might increase 0.4%, or for each 23 $\mu g/m^3$ increase in ambient styrene, acute IHD mortality might increase 1%. The levels of styrene in ambient air are very low compared with those that have been recorded in these workplaces. Thus, calculated risks of death from IHD for the general public based on the actual exposures in some US cities are low. This is true even if one believes that the air measurements underrepresent the actual levels because they do not include styrene in aerosol form or adhered to particles. However, risks calculated on the basis of special circumstances were high. The relative risk could be as high as 3-fold.

First, air pollution risks are episodic and relate to changes in levels of pollution. Thus, at certain times styrene levels could be higher than the levels that have been calculated using an averaged result for ambient air over an extended period. Second, the mortality increase should occur for brief periods around times of heightened pollution that may only occur for a few months in a year. Possibly the only people at risk during the periods of high pollution are those who have underlying risk factors for cardiovascular disease. Third, the risk we measured in this study was specifically for death from IHD, whereas air pollution may also be followed by deaths from respiratory diseases. So acute IHD may constitute only a portion of the overall mortality risk from air pollution.

The important finding of this study is that a chemical found in ambient air and in industrial settings can be associated with an increased risk of heart disease. Relatively low industrial exposures to the chemical appear to result in a risk of acute events. The fact that this chemical is also one that can be adsorbed on particles provides a possible mechanism to explain why particulate matter might be related to IHD mortality. The point of this study was not to prove that styrene explains all the observed excess mortality associated with particulate air pollution. Rather, the intent was to test the theory that chemicals that might be attached to particles could be associated with increased mortality. Whether other chemicals in the outdoor and indoor environment may play similar roles needs to be investigated.

METHODOLOGIC ISSUES

Particular features of the study design, exposure assessment, and data analysis strengthen this study. First, for this study we developed a method to estimate exposure concentrations for unmeasured jobs based on relative exposures for the job and the concentration distribution parameters from the plant. The method enabled us to perform analysis to indicate a dose-response relation between styrene and acute IHD mortality based on individual measurements of exposure.

Second, this study used a case-cohort design. The case-cohort design combines the advantages of a cohort analysis, which allows analysis of time-dependent covariates, and a case-control study, which allows limitation of the number of subjects for whom complete covariates must be ascertained (Wacholder and Boivin 1987). Covariate information was collected on all cases and on a subset of the full cohort. With a modification of the variance correction, we could perform on a limited number of subjects the same type of analysis that would be possible in a full-cohort study. With this design, we were able to perform time-dependent analysis, which is very important when the follow-up is long and the outcome is an acute event. Comparisons of up-to-date exposures were made at each time point whenever a new case occurred during the 40-year follow-up. We did not use a nested case-control design because this design is not optimal for dealing with time-dependent covariates with a long follow-up period (Wacholder and Boivin 1987; Wacholder 1991; Ernster 1994).

Third, the dose-response relation was established using data from active workers. As pointed out previously, many case subjects in this cohort had terminated their jobs in the plant long before they died from IHD. Two potential difficulties caused concern: linking an acute event in later years to a job held decades earlier and obtaining exposure information for workers after they had left the plants. Only the analysis of active workers would not have these problems. This study used an analysis approach based on specified outcome time windows. The first outcome time window was death while employed among active workers. This approach allowed us to establish a dose-response relation between styrene and acute IHD mortality based on the data from active workers.

There were also some weaknesses in this study. IHD deaths rather than IHD incident events were used as cases. Because the cases were deaths, we did not know the real time relation between IHD onset and IHD death. A worker's exposure status might have changed after the onset of incident IHD but before the IHD death. It was difficult to choose appropriate exposure variables. Because of the concern about possible exposure misclassification, we did not use the last job as the exposure variable. Intensity of exposure for the recent 2 years was used to try to reduce

the possible impact from changing exposure status after incident IHD.

Using deaths rather than incident cases resulted in another problem, which was competing risks from other causes of death. For instance, exposure to styrene reportedly causes increased reaction time, sleepiness, and other neuropsychiatric symptoms and behavioral effects (Lorimer et al 1978; Cherry et al 1980; Flodin, 1989; Edling et al 1993). These effects might increase the risk of injury from exposure to styrene. If so, deaths from injuries could be an important competing risk for IHD. In other words, an incident IHD case might die of injury before he could die of a heart attack. A heart attack might also cause an injury resulting in death, but the death certificate could fail to record IHD as the underlying cause of death. If these assumptions are true, the risk outcomes in this study could be underestimated. A review of the time of death from injury with regard to employment status indicated that 20% of the injury deaths occurred while workers were still employed and thus potentially still actively exposed to styrene.

Another weakness was that race was missing for the noncases in Plant 7. Race was randomly assigned for each unknown based on the known race distribution of the plant workers. Multiple imputations used to test the consistency of the method showed that the different race assignments for each imputation did not influence the results of model fitting. Several reasons might explain why the race assignments did not influence the results:

- Only a small portion of subjects needed to be assigned race.
- All cases had known races, and only noncases had unknown races. Since the noncase group was much larger than the case group, race changes in only a few noncases would have less influence on risk measures than if race changes occurred in cases.
- Race was an independent factor related to styrene exposure.
- Unknown race was randomly assigned on the basis of race distribution and not on the basis of either styrene level or case status, so the assignment did not alter the relation between styrene and IHD risk.

A third weakness was that the study had several possible confounders: smoking, diet, blood pressure, physical activity, and coexisting chemicals. To be a confounder, the factor should be associated with exposure, styrene concentration, and outcome (IHD death). Smoking may be the most important risk factor associated with IHD death. The question was whether smoking or other factors in this population could be associated with styrene exposure. If they were not associated with the styrene exposure level, they should not have confounded the analysis. The results presented in Figure 10 show that smoking was not associated with styrene exposures. In fact, the proportion of smokers was smaller among workers with high styrene exposures than among those with lower styrene exposures. Therefore, the association observed in this study between styrene exposure and acute IHD mortality is not likely to be explained by smoking. We did not have personal information on diet, blood pressure, and physical activities; however, these factors have no intuitive association with styrene exposure.

Butadiene was the major coexisting chemical in the industry. Exposure to this chemical did have some association with styrene, and we did not know whether it had an association with IHD mortality. Therefore, we used individual information on exposure to this chemical to adjust the risk models for potential confounding. We used the same procedure to estimate exposure for butadiene as for styrene. A detailed concentration matrix was created by job, by plant, and by time. Exposure to butadiene for each individual was obtained by linking the detailed personal job history to the butadiene exposure concentration matrix. We included butadiene in each of the styrene analysis models for adjustment.

Results showed that butadiene did not confound the association between styrene and IHD death. In no model did butadiene appear as a significant risk factor for IHD death. Thus butadiene was not an important factor in explaining the increased risk of acute IHD in this population. Other chemicals might exist in low concentrations in the industry, but they would have to have had a direct relation to styrene exposure and IHD to be confounders. At present we know of no such chemical. Other exposures to styrene from background contamination and water could have occurred, but these exposures should be very low compared with occupational sources and should not have differed by job in the industry.

FUTURE STUDIES

Although the follow-up period of this study covered 40 years, it ended in 1982 when job history collection ended for the study population taken from previous studies. It would be helpful to extend the job history and exposure data to recent years to confirm the relation found in this study. The following possible studies would be the likely steps to investigate these interesting findings further:

- A continuation of this case-cohort study with follow-up extended to include events among active workers in recent years;

- A nested case-control or case-cohort study using incident IHD cases to target all defined acute IHD events with additional information on confounding factors such as detailed personal information on smoking, diet, disease history, and physical activities;
- A short-term prospective cohort study on volunteer workers using biomarkers and clinical and physical test results as outcomes, rather than IHD itself, to check the influence of monthly, daily, and hourly styrene concentration changes on short-term indicators related to IHD in humans; and
- An exposure assessment study of methods to detect styrene in ambient particulate matter and establish better indicators of actual styrene exposure dose and total dose.

All of these steps are necessary to define risks and exposures more precisely than is possible in a mortality study.

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APPENDIX A. Methods of Estimating Exposure in Unmeasured Jobs and Exposure Changes Over Time

BACKGROUND

In most occupational epidemiologic studies, exposure measurements are available for only a small fraction of the jobs and periods to be assessed. The problem of estimating pollutant exposures for unmeasured jobs in occupational studies is well recognized. Previous studies have tried the following methods to resolve this problem.

One commonly used method is for industrial hygienists to assign an estimated exposure to each unmeasured job or to give each job an IH rank. Exposure categories (high, medium, and low) or IH ranks (0 to 10) can be used as relative exposure indicators in risk analysis. One problem with this method is that it ignores potentially large variation in exposure concentrations for the same job among different plants. For instance, the actual exposure concentration level of a job with an IH rank 10 in a clean plant could be lower than that of a job with an IH rank 2 in a dirty plant. Another common method is to use the average pollutant exposure for the same job at other plants as the concentration for an unmeasured job. This method also ignores the variation in exposures by job among different plants. Utilizing the average exposure at other plants for a job within a specific plant may also alter the relative exposure by job within that plant.

A third method, which is not commonly used, is proportional interpolation (Theriault et al 1974). By this method, the exposure concentration for an unmeasured job in plant A can be estimated using the exposure concentration for the same job in plant B multiplied by the mean concentration of all measured jobs in plant A and divided by the mean concentration of all measured jobs in plant B. With this method, the value is weighted by the relative combined exposures of all jobs in plants A and B). Thus this method takes into account the variation of mean exposure concentrations among different plants. The disadvantage of this method is that it assumes distribution parameters, such as standard deviation, are the same in plants A and B, which is not true in most circumstances.

A more advanced method is deterministic modeling (Schneider et al 1991). If significant factors determining level of exposure can be identified and assessed, a deterministic model can be used to calculate the exposure. The advantage of this method is that it can be used without measurement data. The disadvantage is that it is likely to be less accurate than measurement-based estimation methods.

This appendix describes a newer method to estimate exposures for unmeasured jobs using *z* scores based on incomplete measurement data and IH ranks (Tao et al 1996). This method was used in this study and in a previous study on workers in the synthetic rubber industry (Matanoski et al 1997).

METHODS

Exposure Estimation for Unmeasured Jobs Using *z* Score

Basic Idea Behind z Scores A proportion that represents the difference between an observed value and the mean of all observed values divided by the standard deviation is a *z* score. The *z* score transformation is used to convert data from different sources with different magnitudes, ranges, and units into a unitless standard distribution with constant mean of 0 ± 1 SD. The *z* score shows a job's relative exposure level among all jobs in a plant and should be highly comparable among plants. The exposure concentration for an unmeasured job in a plant can be estimated from the distribution parameters of measured jobs in the same plant and the relative exposure level of the job (its *z* score—based on information from other sources).

Assumptions Exposure concentrations at all jobs in a plant are assumed to present a normal distribution either when direct measurements are used or when appropriate transformation is used to produce normality. The distribution can be calculated from a random sample of all jobs.

The absolute mean exposure concentrations vary widely among different plants in the same industry; however, the relative exposure concentrations among jobs within each plant in this study are assumed to be consistent with those in other plants within the same industry. Industrial hygienists' ranks are also assumed to indicate these relative exposure levels by job.

Procedure The first step in *z* score transformation is to convert all available exposure measurements and IH ranks for each job to *z* scores (equation 1). The measurement *z* score for a job in a plant is the observed value for the job minus the mean of all observed values in the plant, divided by the standard deviation. The IH rank *z* score is the IH rank for the job minus the mean of IH ranks for all jobs, divided by SD of IH ranks. The mean of both measurement and IH rank *z* scores should be 0 ± 1 SD.

$$Z_{ij} = \frac{X_{ij} - M_j}{SD_j} \quad (1),$$

where

i = 1, 2, 3, . . ., n, and n = total number of jobs,

j = 1, 2, 3, . . ., m, and m = total number of data sources,

Z_{ij} = z score for job i from source j,

X_{ij} = measured concentration value or IH rank of job i from source j,

M_j = mean of all X_{ij} from source j, and

SD_j = SD of X_{ij} distribution from source j.

Theoretically, *z* scores for the same job obtained from different data sources should be consistent, but they may vary in real data. Thus *z* scores need to be averaged across plants. The weighted-average *z* score for a job is the weighted average of all measurement and IH rank *z* scores for that job from all plants or data sources. Weights are assigned to the *z* scores depending on the source of the information. In equation 2, for example, the weight for a measurement *z* score is the number of measurements used in the *z* score calculation, while the weight for an IH rank *z* score is 1. More weight is given to the measurement data in this instance:

$$WAZ_i = \frac{\sum_{j=1}^{m} (Z_{ij} \cdot N_{ij}) + Zrank_i}{\sum_{j=1}^{m} N_{ij} + 1} \quad (2),$$

where

i = 1, 2, 3, . . ., n, and n = the total number of jobs,

j = 1, 2, 3, . . .,m, and m = the total number of data sources,

WAZ_i = weighted-average *z* score for job i in all data sources,

Z_{ij} = measurement *z* score for job i in plant j,

$Zrank_i$ = rank *z* score for job i, and

N_{ij} = number of measurements for job i in plant j.

Before calculating the **standard weighted average *z* score** for job i, note that WAZ_i may not conform to a standard normal distribution. Therefore, the *z* score for WAZ_i is obtained using the same transformation to create $SWAZ_i$.

To calculate the **estimated exposure values for a specific unmeasured job** in each plant, multiply the $SWAZ_i$ by the standard deviation of all measurements in that plant plus the mean measurements of the plant (equation 3).

$$E_{ij} = SWAZ_i \cdot SD_j + MEAN_j \quad (3),$$

where

i = 1, 2, 3, . . ., n, and n = the total number of jobs,

j = 1, 2, 3, . . ., m, and m = the total number of data sources,

E_{ij} = estimated concentration for job i in plant j,

$SWAZ_i$ = standard weighted average *z* score for job i in all data sources,

SD_j = SD of measurements for measured jobs in plant *j*, and

MEAN = mean concentration of measurements for measured jobs in plant *j*.

Estimated concentrations can be calculated for each job in each plant. If the estimated value is negative, 0 is used as the exposure value.

Estimating Exposure Change over Time Using Proportional Slope Method

Basic Idea Behind Use of Proportional Slope Because overall, concentrations of styrene have decreased over time, this method assumes that the concentration of the pollutant for a job is a function of calendar year. The function can be any kind, but the simplest is linear. Given a calendar year and the slope of the function (ppm decrease per year), the concentration for the year can be calculated. The slope for each job is proportionally correlated with the slope of the average concentration for all jobs because at any time during the follow-up, the relative level of exposure for all jobs is consistent. The ratio of a known concentration for a job in a year to the average concentration in the same year is used as the slope proportion coefficient of the job to the average of slope.

Assumptions For simplicity, we assume that the concentration of the pollutant for a job is a linear function of the calendar year. The linear assumption may not hold for some jobs, but it seems to fit the overall trend of decreasing concentrations. If the available data appear to require complex calculations such as stepwise functions, they could be written into the method.

At any time period during follow-up, the relative level of exposure for jobs is assumed to be consistent. That is, the relative relation of jobs to each other remains the same. This assumption may not hold true for a few jobs that underwent a disproportionate change in exposure level and thus shifted their relative positions in the exposure scales.

The slopes of exposure changes for different jobs may be different, but they are assumed to remain proportional to each other. For example, the higher the concentration for a job, the steeper the slope of ppm decreases. Jobs with 0 ppm exposure are assumed to remain at 0 exposure. Generally, this assumption may be true, but some jobs may undergo exposure changes that are not proportional to others.

Concentrations measured in recent years and those estimated by *z* score are assumed to be a valid basis of estimating unmeasured jobs.

Procedures According to our assumptions, the decreasing slope of concentration for each specific job is proportional to the average decreasing slope. This proportion can be determined by the ratio of a known concentration for that job in a year over the average concentration in the same year. Estimation of change (in ppm) over time for a job can be calculated using equation 4 or equation 5.

If

$$\mathrm{ppm}_{ij} = (j-a)\cdot k_i + \mathrm{ppm}_{ia}$$

$$k_i = \frac{\mathrm{ppm}_{ia}}{\mathrm{ppm}_{va}}\cdot k_v$$

then:

$$\mathrm{ppm}_{ij} = \frac{\mathrm{ppm}_{ia}}{\mathrm{ppm}_{va}}\cdot (j-a)\cdot k_v + \mathrm{ppm}_{ia} \qquad (4)$$

or:

$$\mathrm{ppm}_{ij} = \mathrm{ppm}_{ia}\left[\frac{(j-a)\cdot k_v}{\mathrm{ppm}_{va}} + 1\right] \qquad (5)$$

where

i = 1, 2, 3 . . ., m, for the ith job,

j = 0, 1, 2 . . ., n, for the jth year from the end of follow-up, and j = 0 means the last year of follow-up,

a = the year with known ppm from the end of the follow-up,

k_i = the slope of ppm decrease for the ith job,

k_v = the average slope of ppm decrease for all jobs,

ppm_{ij} = concentration in ppm for the ith job in the jth year,

ppm_{ia} = known concentration in ppm for the ith job in the ath year, and

ppm_{va} = average concentration in ppm for all jobs in ath year.

APPENDICES AVAILABLE ON REQUEST

The following appendices may be obtained by contacting the Health Effects Institute by mail (Charlestown Navy Yard, 120 Second Ave, Boston MA 02129-4533), fax (+1-617-886-9335), or email (*pubs@healtheffects.org*). Please provide both the Investigators' Report title and appendix title when requesting appendices.

Appendix B. Job Dictionary and Industrial Hygienists' Chemical Ranking for Styrene-Butadiene Polymer Manufacturing Industry

Appendix C. Observed, Estimated, and Combined Styrene Concentrations in Two Study Plants

Appendix D. Additional Tables for Styrene and IHD Case-Cohort Study

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ABBREVIATIONS AND OTHER TERMS

CI	confidence interval
EPA	Environmental Protection Agency (US)
ICD-8	*International Classification of Diseases, Eighth Revision*
IHD	ischemic heart disease (*ICD-8* codes 410 to 414)
IH	industrial hygienists
NIOSH	National Institute for Occupational Safety and Health
OR	odds ratio
OSHA	Occupational Safety and Health Administration (US)
PM_{10}	particulate matter 10 μm or smaller in aerodynamic diameter
ppm-year	parts per million × exposure duration in years
R^2	coefficient of determination for multivariate analysis
RH	relative hazard, produced by Cox proportional hazard models
SMR	standardized mortality ratio
TWA	time-weighted average
z score	deviation of a value from its mean divided by the standard deviation of that mean

INTRODUCTION

The purpose of Dr Matanoski's study was to investigate the association between styrene exposure and death from ischemic heart disease (IHD*) in styrene-exposed workers.† This investigation was important because findings from other occupational studies indicate a possible association (Matanoski et al 1990; Wong et al 1994). If supported, these indications may have implications for the general population because styrene (at much lower levels) is present in ambient air, partly as the result of motor vehicle fuel combustion. In the current report, the investigators suggest that results of their study might help to interpret previous findings of an association between particulate matter (PM) exposure and cardiovascular disease in time-series and cohort studies.

BACKGROUND

STYRENE OCCURRENCE AND EXPOSURE

Styrene, $C_6H_5CH=CH_2$, is a volatile liquid at room temperature and does not occur naturally. The compound is produced synthetically for use in a number of applications, including production of polystyrene or mixed polymers (butadiene-styrene and acrylonitrile-butadiene-styrene) found in plastics, synthetic rubber, resins, and insulators. Styrene is found in mobile source emissions (Miller et al 1994) and cigarette smoke (Wallace et al 1987; Miller et al 1994).

The highest exposures to styrene are occupational, primarily in reinforced plastics and synthetic rubber production, with the maximum levels in production of fiber-reinforced boats (World Health Organization 1983). Exposure levels vary widely, however. For example, Dobos (2000) reported exposures of 5.6 ppm to 150 ppm in three fiberglass boat manufacturing plants. In the synthetic rubber industry, which generally involves a closed polymerization process, exposures usually range from 20 to 50 ppm. However, higher peaks may occur during the cleaning, filling and maintenance of reaction vessels and during transport of liquid.

Styrene exposures in the general population are measured in parts per billion (World Health Organization 1983; Newhook and Caldwell 1993; Miller et al 1994). The ambient concentrations of styrene vary according a site's industrialization and the proximity to industrial sources. Ambient concentrations range from 0.08 ppb in rural areas to 0.317 ppb in sites close to industrial sources (Miller et al 1994). Styrene can also be taken into the body through ingestion. Potential sources are contaminated drinking water, styrene flavoring in ice cream and candy, alcoholic beverages, and residues in food containers (US Environmental Protection Agency [EPA] 1994; Tang et al 2000). Estimates of average daily oral intake are 0.2 to 1.2 µg/person (Newhook and Caldwell 1994).

REGULATION

In the United States, occupational exposure to styrene is regulated by the US Occupational Safety and Health Administration (OSHA). Present OSHA standards set the permitted exposure level at 100 ppm as an 8-hour time-weighted average (TWA) with a ceiling exposure of 200 ppm for any 5-minute period in 3 hours (OSHA 2001). However, a voluntary compliance program has been adopted by industries that use styrene to reduce exposure to 50 ppm TWA with a 100-ppm 15-minute ceiling (OSHA 2001). The recommendations of the National Institute of Occupational Safety and Health are 50 ppm as an 8-hour TWA with a 15-minute short-term exposure limit of 100 ppm (Centers for Disease Control and Prevention 1996). The American College of Government and Industrial Hygienists (2001) recommends a threshold limit value, established in 1994, of 50 ppm with a 100-ppm ceiling. The EPA does not regulate styrene levels in ambient air or water but has established an oral reference dose of 2×10^{-1} mg/kg/day for styrene and an inhalation reference concentration of 1 mg/m^3 (0.23 ppb) (EPA 2001). The reference dose and reference concentration are estimates of the daily exposure to the human population (including sensitive subgroups) likely to pose no appreciable risk of negative effects for an average lifetime.

* A list of abbreviations and other terms appears at the end of the Investigators' Report.

† Dr Matanoski's 1-year study, *Case Cohort Study on Styrene Exposure and Ischemic Heart Disease*, began in January 1999. Total expenditures were $109,139. The draft Investigators' Report from Matanoski and Tao was received for review in March 2000. A revised report, received in November 2000, was accepted for publication in December 2000. During the review process, the investigators had the opportunity to exchange comments and to clarify issues in both the Investigators' Report and the Review Committee's Critique.

METABOLISM

The main metabolic pathway for styrene involves oxidation by cytochrome P450 to an electrophilic epoxide, styrene-7,8-oxide. The epoxide is hydrolyzed to form phenylethylene glycol, which undergoes further metabolic transformation to yield mandelic acid, phenylglyoxylic acid, and a conjugation product, hippuric acid. Mandelic acid and phenylglyoxylic acid, the primary metabolites, can be measured in urine to monitor recent exposure to styrene (Sumner and Fennell 1994). Styrene can also undergo glutathione conjugation leading to the production of several mercapturic derivatives that are excreted in urine. These derivatives have been found in urine of occupationally exposed subjects although in much smaller amounts than urinary metabolites derived from styrene-7,8-oxide (Maestri et al 1999).

HEALTH EFFECTS

A number of studies have looked at health effects related to exposure to styrene or styrene oxide. End points included genotoxicity, cytotoxicity, carcinogenicity, neurotoxic effects, birth and reproductive effects, and IHD.

Cytotoxicity and Genotoxicity

Styrene oxide is reported to be cytotoxic and genotoxic (Karakaya et al 1997; Marczynski et al 1997, 2000) and to bind covalently to human plasma protein and hemoglobin (Yeowell-O'Connell et al 1996). A significant increase in DNA adducts (8-hydroxy-2-deoxyguanosine) have been found in the white blood cells of styrene-exposed workers (Marczynski et al 1997).

Carcinogenicity

In a review of eleven animal studies, McConnell and Swenberg (1994), found no convincing evidence for carcinogenicity although many studies were evaluated as inadequate in design or reporting and data analysis. Results from epidemiology studies are inconsistent. Matanoski and coworkers (1997) reported associations between styrene exposure and multiple myeloma, lymphosarcoma, and all lymphomas among styrene-exposed workers in styrene-butadiene rubber production. Although Delzell and colleagues (1996) and Maculoso and coworkers (1996) reported evidence of increased risk among workers in areas with relatively high exposure to styrene monomer, the results were not statistically significant. Dr Delzell has followed her earlier work with a study that is currently under review by HEI.

Neurotoxicity

Styrene has been associated with acute disturbances in the central and peripheral nervous system in both animals and humans (Matikainen et al 1993; Welp et al 1996; Chakrabarti 2000). Acute disturbances in humans, including neurobehavioral changes such as altered mood states (Challenor and Wright 2000) and impairment of memory, cognition, perceptual speed and color vision (Kishi et al 2000), are found at exposure levels as low as 50 ppm. Evidence for chronic neurotoxicity in humans is less conclusive (Rebert and Hall 1994).

Developmental and Reproductive Effects

Evidence for developmental and reproductive effects is inconsistent. In one review of several epidemiologic studies, no risk was reported among workers exposed to styrene in the reinforced-plastics industry, but one study did report excess spontaneous abortions in women whose work included the processing of polystyrene (Lindbohm 1993). Reported associations between exposure to styrene and low birth weight or reduced fertility were weakened by methodologic shortcomings.

Heart Disease

The association between styrene exposure and coronary artery disease has been examined by several investigators. Wong and coworkers (1994) found significant increases in mortality from hypertensive heart disease in styrene-exposed workers, but the significance of association decreased with increasing years of exposure to styrene. In a study of workers employed in styrene-butadiene polymer production, Matanoski and coworkers (1990) reported that the overall standard mortality ratio (SMR) was less than in the general population (0.81). However, the SMR for atherosclerotic heart disease in black workers was significantly higher than would be expected based on general population rates. Boffetta and coworkers (1998) reported an analysis of 21,784 styrene-exposed workers in eight European countries with less than 1 year of employment (short-term workers) and 19,117 workers with 1 or more years of employment (long-term workers). In both cohorts, short-term workers had a higher mortality from external (nondisease) causes. There was a nonsignificant increase in death from IHD among short-term workers and no increase in long-term workers.

CHARACTERISTICS OF IHD

IHD is a condition associated with coronary heart disease that causes an individual to be susceptible to myocardial ischemia, which results from an imbalance between

myocardial blood flow and the metabolic demands of the myocardium. The reduced blood flow reflects occlusion(s) of the coronary arteries as a result of progressive atherosclerosis. Vasospasm, thrombosis, or other circulatory changes can further decrease myocardial blood flow. One manifestation of IHD is angina pectoris, a condition characterized by chest pain, usually upon exertion although it may occur at rest (Venes and Thomas 1997). IHD is frequently asymptomatic. The acute effects of IHD are sudden death due to cardiac arrest or arrhythmia, or to acute myocardial infarction, in which lack of adequate blood supply to the myocardium permanently damages the myocardium (Venes and Thomas 1997). Chronic IHD may progressively damage the myocardium and lead to progressive heart failure.

Common risk factors for IHD include high blood cholesterol, high blood pressure, obesity, diabetes mellitus, and lifestyle factors such as tobacco smoking and physical inactivity. Blacks have more severe high blood pressure than whites and thus a higher risk of IHD.

TECHNICAL EVALUATION

AIMS AND OBJECTIVES

The overall objective of this study was to examine the possible association and exposure-response relation between styrene exposure and death from IHD in a group of workers employed in styrene-butadiene polymer manufacturing plants. The study had the following aims:

1. Conduct a case-cohort study of male workers in two synthetic styrene-butadiene rubber plants who were followed from 1943 to 1982.
2. Use measurement data and other exposure-related information to establish concentration matrices for styrene and butadiene by job, by plant, and for different periods of time.
3. Use individual job histories and corresponding exposure data for specific jobs at specific periods of time in order to establish time-dependent methods for identifying personal styrene exposures.
4. Explore possible associations between styrene exposure and IHD using multivariate proportional hazard models controlling for such possible confounders as butadiene exposure and demographic characteristics.
5. Use the association between styrene exposure and IHD established in the study to develop methods for estimating the risk of IHD from exposure to ambient styrene.

STUDY DESIGN

The case-cohort approach used to examine the association between styrene exposure and death from IHD allows a direct analysis of risk without the technical demands involved in assembling information on a full cohort. Styrene exposure was estimated from job histories, and death from IHD was based on the *International Classification of Diseases, Eighth Revision* (*ICD-8*) codes 410 to 414 recorded on the death certificates.

The facilities from which the subjects came were chosen because of the completeness of their work records. When no measurement data were available for specific jobs, however, exposure was estimated using a *z* score method (described in the text of the report and in more detail in the appendix to the report). This approach estimated exposure by job in the two study plants based on the relative exposure level of that job in similar plants and the parameters of measurement distribution in the study plant. The method is based on two important assumptions: (1) that exposure concentrations in all jobs in a plant are normally distributed; (2) that processing methods throughout the rubber processing industry are similar and have not changed appreciably. The latter assumption is supported by industrial hygiene observations (Burgess 1981). While basic techniques of styrene-butadiene rubber production have not changed appreciably since their induction in 1940, better formulations, process modifications, and engineering controls have lowered overall exposures (Naqvi 1998). Exposure variables in the current study included TWA exposure and cumulative exposure.

Confounding factors considered were age, race, date of birth, and exposure to butadiene. Cox regression analysis controlling for age, date of birth, and race was used to examine the relation between styrene exposure and risk of death from IHD. The exposure-response relation with cumulative exposure for active workers was used to estimate the lifetime effect of styrene exposure on IHD deaths at ambient levels recorded in various surveys.

STUDY METHODS

Case-Cohort Design

Cases were compared to a randomly selected subcohort of 15% (n = 997) of the entire cohort of 6,587 men employed from 1943 to1982 at two styrene-butadiene polymer manufacturing plants. A case could be either a worker who died during employment, or a former employee who had died during a specified time window. A case might or might not come from the subcohort. Any subject from the full cohort became a case if he had died from IHD within the designated time window for analysis. In Dr Matanoski's study,

cases (n = 498) were defined as all deaths from IHD, using *ICD-8* with codes 410 to 414. These codes include acute myocardial infarction (410); other acute and subacute forms of IHD (411); old myocardial infarction (412); angina pectoris (413); and other forms of chronic IHD (414).

Assignment of Exposure

Workers enrolled in Dr Matanoski's study worked in 166 of 579 possible jobs in the styrene-butadiene rubber industry. When it was necessary to estimate exposure, all available exposure measurements for a particular job within a particular facility were converted to a z score, a unitless number that represents the relative position of a particular measurement in a set of normally distributed measurements where the distribution values have a mean of zero and standard deviation of 1. A z score for a particular job provides information about the relative exposure of that job within a plant but does not specify the actual exposure level. In Dr Matanoski's study, the z score transformation was further refined to a weighted z score by using all available data for jobs from several plants and from several sources. The exposure for a particular period of time was determined from the slope of the concentration change for a particular job over time, using available data on manufacturing processes, engineering controls, and job descriptions. In general, the absolute value of exposure decreased over time, and the investigators assumed, unless otherwise known, that the decrease was linear.

Data Analysis

Because death might be associated with short-term or long-term exposures, a number of outcome time windows were used. To look at the short-term effect of exposure to styrene, active workers and only those who died from IHD while employed were considered cases. Three time windows were used for these cases: One included all active workers (range of time from less than 1 year to 40 years); a second excluded workers who had worked less than two years; a third excluded workers who had worked less than 5 years. The effects of longer term exposures were evaluated by two time windows: one for workers who had left the plant and died within 10 years after leaving, and a second for those who had left and died more than 10 years after leaving.

The Cox proportional hazards model was used to analyze risk. This model assumes that anything affecting a specified hazard does so by the same ratio at all times and permits analysis to determine the combined effect of a number of predictor variables. Exposure variables included TWA exposure and cumulative exposure. Potential confounding factors considered were age, race, date of birth, and butadiene exposure.

RESULTS

ASSESSMENT OF EXPOSURE

The distribution patterns for estimated and measured exposure concentrations of styrene were found to be similar, and the majority of measured exposures were below 0.2 ppm. On average, one of the two plants studied (plant 7) had higher concentrations of styrene than the other (plant 6). The correlation coefficient between styrene and butadiene measurements, the major copollutant in the facilities, was found to be low (R^2 = 0.16).

EXPOSURE TO STYRENE AND RISK OF DEATH FROM IHD

The SMR for the full cohort was lower than the US general population, demonstrating the healthy worker effect. However, a subcohort of nonwhite men who no longer worked at the plants had an elevated SMR of 1.47 (95% confidence interval [CI] 1.17–1.77).

No significant association between styrene or butadiene exposure and deaths from chronic IHD was seen using any of the models for risk. Models included such factors as age as a time scale; stratification by plant; and adjustment for race, birth year, and duration of employment.

Using Cox proportional hazard regressions for death from acute IHD among active workers, TWA exposure during the most recent two years of employment was found to be associated with a relative hazard ranging from 3.26 (95% CI 1.09–9.72) for all active workers ever employed to 6.60 (95% CI 1.78–24.54) for workers employed more than 5 years. The results suggest a 4% to 8% increase for each increase of 1 ppm-year of exposure.

The analyses were adjusted for a number of possible confounders: age, race, date of birth, and butadiene exposure. An analysis of smoking data taken from interviews of 424 subjects from all eight styrene-butadiene polymer plants indicated no correlation between smoking habits and styrene exposure. Based on this, the authors thought that smoking was an unlikely confounder.

ESTIMATION OF EFFECTS OF AMBIENT EXPOSURE

Using a nonthreshhold log linear dose-response model, Drs Matanoski and Tao estimated that for each increase of 10 $\mu g/m^3$ (2.3 ppb) in ambient styrene, risk of acute IHD mortality increases by 0.4%. Where communities are close to industrial facilities using styrene, ambient concentrations may be higher and the risks may be greater.

DISCUSSION

This study addresses an important question using historical occupational data not collected for this purpose. The case-cohort approach is appropriate and has been well designed and implemented. The study has inherent limitations in some areas, however: specifically, the potential for confounding, lack of specificity, and assumptions used in extrapolating the effects of styrene from environmental exposures.

RATIONALE

The authors present a rationale for the study, both in terms of previous occupational evidence for a relation between styrene exposure and IHD and a possible mechanism for effects. Because styrene can be distributed in fatty tissue (including atherosclerotic plaques composed of lipid-laden foam cells and extracelluar lipid deposits), the authors suggest that the acute health effects may be due to styrene altering the atherosclerotic plaques and leading to obstruction or narrowing of blood vessels. She also suggests that styrene and its metabolites may have chronic effects on lipid metabolism that increase the risk of plaque formation. Both proposed mechanisms must be regarded as speculative, however, because they are not based on established evidence.

METHODS

The *z* score method is a creative and effective way of developing relations among jobs and job categories to estimate missing exposure data. Irrespective of the model used to develop relations among jobs, however, single imputations of exposures fail to incorporate potentially important uncertainty. Multiple imputation should have been used. A strength of the analyses in this report is the stratification by plant to account for differences in characteristics of the two plants.

CONFOUNDING

Factors such as diet, smoking, blood pressure, physical activity, and job grade are risks for IHD and may be plausible explanations for the observed association between exposure to styrene and death from IHD. When relative risks are small, the impact of residual confounding is greater. More discussion on the extent of error that could be introduced by some of these confounders would have been useful. A specific concern for confounding is smoking. No individual-level data on smoking were available although the authors present indirect evidence suggesting that styrene exposure was not related to smoking.

SPECIFICITY

Investigators addressed the issue of specificity within the cardiac group by considering acute and chronic responses separately. However, they did not include analyses of other causes of death to test the specificity of the association when compared to all causes of mortality or to all cardiopulmonary mortality. This would have been an important extension of the study, using data that are already available. It would also have been informative to examine a negative control end point, such as death by trauma, which is unlikely to be associated with styrene exposure. Finally, details about other causes of death mentioned in the death certificates might have been informative.

EXTRAPOLATION TO AMBIENT ENVIRONMENT

Although this study of an occupational cohort reports statistically significant associations between mortality from IHD and styrene exposure, uncertainties relating to specificity, confounding, and plausibility of the proposed mechanism limit extrapolation to the ambient environment. Occupational exposures are in the ppm range whereas ambient exposures are generally about 1,000-fold lower, in the ppb range. Extrapolation to the ambient environment would be made more informative by discussing the uncertainties in extrapolation, providing confidence limits, and including a discussion of the theoretical relevance of results from an occupational cohort study such as this to the ambient situation.

SUMMARY AND CONCLUSIONS

Dr Matanoski and her colleagues have successfully carried out a difficult occupational cohort study with an appropriate and well-designed approach. They have found associations between styrene exposure and death from acute IHD. Although these results are statistically significant, uncertainties regarding the causality of the associations and extrapolation to the ambient environment are substantial. However, because the results may be relevant to the ambient environment, further research in this area is important. Occupational studies offer the best approach at present for understanding the adverse health effects of styrene, from ambient exposures as well as from higher ocupational exposures.

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