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# The mortality of cellulose fiber production workers

Cohen, Aaron J.

Boston University

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Thesis

# THE MORTALITY OF CELLULOSE FIBER PRODUCTION WORKERS

By

Aaron J. Cohen

A.S. Northeastern University, 1975

B.S. Northeastern University, 1982

M.P.H. Boston University School of Public Health, 1985

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Approved by

First Reader [redacted]

Kenneth J. Rothman, Dr.P.H.
Boston University School of Public Health

Second Reader [redacted]

Ann Aschengrau, Sc.D.
Assistant Professor of Public Health
(Epidemiology and Biostatistics)
Boston University School of Public Health

Third Reader [redacted]

Theodore Colton, Sc.D.
Professor of Public Health
(Epidemiology and Biostatistics)
Boston University School of Public Health

**Abstract**

This dissertation examines the relation between occupational exposure to the solvent methylene chloride and mortality in a cohort of cellulose fiber production workers. The first paper, entitled *The Mortality of Cellulose Fiber Production Workers*, presents the main results of the mortality follow-up of the cellulose fiber workers cohort through September 1, 1986. Mortality from neoplastic and non-neoplastic disease among cellulose fiber production workers is compared to that of the U.S. and local (county level) populations, while controlling for the effects of gender, race, calendar period, and age. Mortality from cancers of the lung, breast, and pancreas, and ischemic heart disease was less than expected. Excess mortality was observed for melanoma of the skin, cancer of the buccal cavity and pharynx, tumors of the liver and biliary tract, and accidental deaths. Three deaths from cancer of the bile ducts were observed (3 observed, 0.15 expected, SMR=20). This is the first known report of an association between exposure to methylene chloride and cancer of the bile ducts.

The second paper, entitled *Reassessment of Methylene Chloride Exposure in a Cohort of Cellulose Fiber Production Workers: Construction of an Exposure Scale and Analyses of Mortality*, presents the results of an attempt to quantify further the methylene chloride exposure of the cellulose fiber workers cohort using work histories and industrial hygiene data, with the goal of improving the accuracy of exposure classification and reducing misclassification. An exposure classification scheme comprising three categories of job groups was developed that allows deaths and person-time associated with the greatest exposure to be analyzed separately. Analyses of mortality from selected causes were

conducted using the exposure classification scheme, but their informativeness was limited by small numbers of deaths and residual exposure misclassification and they yielded little additional information.

The third paper, *Issues in Mortality Ascertainment in a Cohort of Cellulose Fiber Production Workers*, examines three methodologic issues related to mortality ascertainment that arose in the course of the follow-up of the cellulose fiber workers cohort. First, the use of the SSA decedent files as the primary source of vital status data in the absence of individualized follow-up was examined by comparing the completeness of separate follow-ups of the fiber workers cohort through June, 1977. Contrary to expectation, SSA follow-up compared favorably with individualized follow-up, providing reassurance that underascertainment is not a major concern for the interpretation of the results of the mortality analyses. Second, death certificates that have been collected by the company for purposes other than epidemiologic research were examined to determine their suitability as a data source for preliminary analyses of the mortality of occupational cohorts. Death certificates of cellulose fiber workers that were in the possession of the company were compared to the total group of certificates obtained by cohort follow-up. Death certificates on file with the employer did not accurately reflect the mortality of the cohort, indicating that analyses based solely upon this source of mortality data may be subject to considerable bias. Finally, differential accuracy of mortality ascertainment according to exposure status was as a potential source of bias in occupational cohort mortality studies. Differential completeness of mortality ascertainment related to exposure was observed when an attempt was made to expand

the cellulose fiber workers cohort to include workers who had not been exposed to methylene chloride. Race and length of employment appeared to be related to completeness of mortality ascertainment.

## Introduction

The main objective of the research presented herein is to study whether occupational exposure to the solvent methylene chloride causes increased mortality from certain neoplastic and non-neoplastic diseases. I addressed this question in a retrospective cohort study of textile workers exposed to methylene chloride in the manufacture of cellulose triacetate fiber. Methylene chloride is a chlorinated solvent, widely used in industrial applications and in consumer products. Animal experiments and an epidemiologic study have yielded evidence of the carcinogenic potential of methylene chloride. These results, coupled with the possibility of widespread human exposure, have focussed the attention of epidemiologists, toxicologists, and government regulators on the carcinogenic potential of methylene chloride in humans.

## Background

Methylene chloride ($CH_2Cl_2$), also known as dichloromethane or methylene dichloride, is produced commercially by the chlorination of methane or methyl chloride. The U.S. International Trade Commission estimates that U.S. production of methylene chloride in 1975 was 270 million kilograms (1).

Methylene chloride has many and diverse industrial and consumer applications. It is employed as a solvent in paint removers and degreasing agents, and in the manufacture of textiles, pharmaceuticals, and photographic film. It is used as an extractant in the

decaffeination of coffee and the production of spices, and as a propellant in spray cans (2).

The National Institutes of Occupational Safety and Health estimate that, as of 1976, 70,000 workers in the U.S. were exposed to methylene chloride in the work place (2), either in the production of methylene chloride itself, or in the production of consumer products. Because of its presence in consumer products, non-occupational sources of exposure may also occur.

The World Health Organization estimates that 80% of the estimated 570 million kilograms of methylene chloride produced worldwide is released into the atmosphere (3). In the U.S., methylene chloride has been detected in various water supplies and aquifers (2,4).

Two pathways for the metabolism of methylene chloride have been described in humans and other mammalian species (5). The multi- function oxidase, MFO, pathway produces carbon monoxide as a byproduct of methylene chloride metabolism, and is saturated at methylene chloride concentrations of 500 parts per million (ppm). A second metabolic pathway for methylene chloride, the glutathione-S-transferase (GST) pathway was described by Ahmed and Anders (6). This pathway produces formaldehyde as a byproduct of methylene chloride metabolism. Metabolic intermediates produced by the GST pathway are considered to be carcinogenic (5), and this pathway has been

demonstrated to be active in in-vitro studies of several organ systems, including lung, liver and pancreas, in several rodent species and in humans. The GST pathway is non-saturable, and is responsible for the metabolism of methylene chloride at levels exceeding 500 ppm. Methylene chloride, or its metabolites, is excreted by the lungs, in the urine, and in stool.

Interest in the carcinogenic potential of methylene chloride has been stimulated by the results of bioassays conducted by the National Toxicology Program (NTP) (7). These studies yielded evidence of the carcinogenicity of methylene chloride in mice and rats continuously exposed to 2,000 ppm of methylene chloride for two years. The mice developed excess lung and liver tumors, the rats developed excess mammary tumors, non-neoplastic hepatic changes, and fibrotic changes of the bile ducts. Toxicologists have interpreted these results as consistent with the observation of greater levels of GST activity in the mouse, despite the induction of mammary tumors in the rat. The implications of these results for human carcinogenesis are not clear, due to lack of knowledge of the comparative pharmacokinetics of methylene chloride in the different species (2,5).

While the attention of scientists has focussed most recently on the carcinogenicity of methylene chloride, it was its neurologic and cardiovascular effects that first aroused scientific interest. Interest in the health effects of methylene chloride dates from the late 19th century. Early investigators administered methylene chloride vapor to dogs and

described its anesthetic effects, as well as its deleterious neurologic effects, such as tremors and seizure activity, at high doses (8). In the first half of the 20th century these observations were repeated in several other species including humans (9). During this period, methylene chloride was employed in clinical anesthesia practice, particularly in obstetric anesthesia, because it produced anesthesia without loss of consciousness or muscle tone (10). Case reports and anecdotal writings from this era describe the effects of acute occupational exposure to methylene chloride vapor, ranging from lightheadedness (11) to death (12).

Formal scientific investigation of the health effects of methylene chloride began in the 1970s. Fodor and Winneke (13) observed impaired responses to auditory and visual stimuli in volunteer subjects exposed to 300 to 800 ppm concentrations of methylene chloride relative to their performance at 0 ppm. Winneke (14) exposed volunteers to concentrations of methylene chloride between 317 and 751 ppm for three to four hours and observed impaired responses to auditory and visual stimuli, and impaired performance of psychomotor tasks, relative to volunteers exposed to between 50 and 100 ppm. Stewart (15) exposed subjects to concentrations of methylene chloride from 213 to 986 ppm for a maximum duration of two hours. He observed deleterious changes in electroencephalographic patterns evoked in response to visual stimuli.

Stewart's study also provided the first experimental evidence of the effect of methylene chloride on oxyhemoglobin saturation. In one subject Stewart observed that after exposure to 213 ppm of methylene chloride for one hour carboxyhemoglobin rose from 0.4% to 1.75%. After discontinuation of exposure carboxyhemoglobin continued to rise, reaching a maximum of 2.4% three hours after exposure had ceased. Stewart reproduced this pattern in other subjects and observed that the peak concentrations of carboxyhemoglobin, both during and after exposure, were proportional to methylene chloride concentration and duration of exposure. Elevations of carboxyhemoglobin were maintained for greater than 24 hours after cessation of exposure. Stewart (16-18) conducted additional experiments and observed a direct relation between carboxyhemoglobin levels and duration of exposure to 250 ppm of methylene chloride in non-smoking men (16) and women (17). Women experienced higher levels of carboxyhemoglobin at each duration. Stewart (18) also observed that exposure of subjects to a 4:1 mixture of methylene chloride (216 to 788 ppm) and methanol resulted in prolonged elevation of carboxyhemoglobin relative to those exposed to methylene chloride alone.

Although most experimental studies administered methylene chloride as a vapor, at least one investigation demonstrated that methylene chloride could be absorbed through intact skin at room temperature and subsequently detected both in blood and in expired air (19). Dermal contact resulted in a burning sensation, and, after ten minutes, numbness. A white scale and exudate were also observed.

There have been two major epidemiologic studies of occupational cohorts exposed to methylene chloride. Ott et al. (20) assembled a cohort of workers exposed to methylene chloride in the production of cellulose triacetate fiber. The study comprised 1,271 workers at the plant who held jobs that entailed exposure to methylene chloride. The study identified 54 deaths during the period from January 1, 1954 through June 30, 1977. Compared with mortality in the United States population, this study found that workers died more frequently from accidental causes. There was no increased risk of death from ischemic heart disease. Seven cancer deaths were observed in the cohort, but there was no excess (observed minus expected) of more than one death from any particular type of cancer. While cohort members were exposed to high levels of methylene chloride (median eight hour time-weighted exposures of 60-690 parts per million), the cohort consisted of relatively young people who had accrued little follow-up time in the lengthy induction periods considered necessary for occupational carcinogens to produce neoplastic disease.

Hearne, et al. (21) assembled and followed a cohort of workers exposed to methylene chloride in the production of photographic film. Among 1,013 workers, 176 deaths were observed for the period 1964 through 1984. There were no excess deaths from cancers of the liver or lung, nor from accidents or ischemic heart disease; however, an increase in mortality from cancer of the pancreas was reported (SMR=2.5, based on 8 observed pancreatic cancer deaths). These workers were exposed to lower average concentrations

of methylene chloride than the cohort studied by Ott (26-100 ppm, on average), but had been followed for a longer period since the start of exposure.

**Contents of the Thesis**

The thesis comprises three papers:

The first paper, entitled *The Mortality of Cellulose Fiber Production Workers*, presents the main results of the mortality follow-up of the cellulose fiber workers cohort through September 1, 1986. Mortality from neoplastic and non-neoplastic disease among cellulose fiber production workers is compared to that of the U.S. and local (county level) populations, while controlling for the effects of gender, race, calendar period, and age. In these analyses exposure to methylene chloride is represented by employment in the plant, and the relations between mortality from selected causes and duration of employment and time since first employment are examined.

The second paper, entitled *Reassessment of Methylene Chloride Exposure in a Cohort of Cellulose Fiber Production Workers: Construction of an Exposure Scale and Analyses of Mortality*, presents the results of an attempt to quantify further the methylene chloride exposure of the cellulose fiber workers cohort using work histories and industrial hygiene data, with the goal of improving the accuracy of exposure classification and reducing misclassification. Work histories and industrial hygiene data are used to construct an exposure scale. Analyses of mortality which measure the effect of exposure to different levels of exposure are presented for selected causes of death.

The third paper, *Issues in Mortality Ascertainment in a Cohort of Cellulose Fiber Production Workers*, examines three methodologic issues related to mortality ascertainment that arose in the course of the follow-up of the cellulose fiber workers cohort. In this paper I examine: 1) the use of the SSA decedent files as the primary source of vital status data in the absence of individualized follow-up, 2) the use of death certificates that have been collected by the company for purposes other than epidemiologic research as a data source for preliminary analyses of the mortality of occupational cohorts, and 3) differential accuracy of mortality ascertainment according to exposure status as a potential source of bias in occupational cohort mortality studies.

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# THE MORTALITY OF CELLULOSE FIBER PRODUCTION WORKERS

**Abstract**

We examined the mortality of a cohort of 1,271 employees of a cellulose fiber production facility in the Southeastern United States. Cohort members were employed for at least three months between January 1, 1954 and January 1, 1977 in jobs that entailed exposure to the solvent, methylene chloride. Mortality of the cohort was ascertained through September 1, 1986: 122 deaths were observed. Mortality from cancers of the lung, breast, and pancreas, and ischemic heart disease was less than expected. Excess mortality was observed for melanoma of the skin, cancer of the buccal cavity and pharynx, tumors of the liver and biliary tract, and accidental deaths. Three deaths from cancer of the bile ducts were observed (3 observed, 0.15 expected, SMR = 20).

## Introduction

Methylene chloride, also known as dichloromethane, is a chlorinated solvent widely used in industrial applications such as metal cleaning, electronics, and chemical processing. Methylene chloride is also used in consumer products as a constituent of aerosol propellants and paint removers, and as an extractant in the decaffeination of coffee (1). A study in the early 1970s demonstrated a deleterious effect of methylene chloride inhalation on arterial oxygen content, stimulating research interest in a possible relation between methylene chloride exposure and ischemic heart disease (2). More recently, bioassays have yielded evidence of the carcinogenicity of methylene chloride in mice and rats (1,3). The results from laboratory studies of animals focused attention on the possible carcinogenic effects of methylene chloride exposure in humans.

There have been two major epidemiologic studies of occupational cohorts exposed to methylene chloride. Ott et al. (4) assembled a cohort of workers exposed to methylene chloride in the production of cellulose triacetate fiber. The study comprised 1,271 workers who held jobs that entailed exposure to methylene chloride. The study identified 54 deaths during the period from January 1, 1954 through June 30, 1977. Compared with mortality in the United States population, this study found that cellulose fiber production workers died more frequently from accidental causes. There was no increased risk of death from ischemic heart disease. Seven cancer deaths were observed in the cohort, but there was no excess (observed minus expected) of more than one death from any particular type of cancer. While cohort members were exposed to high

levels of methylene chloride (median eight hour time-weighted exposures of 60-690 parts per million), the cohort consisted of relatively young people who had accrued relatively little follow-up time.

Hearne, et al. (5) assembled and followed a cohort of workers exposed to methylene chloride in the production of photographic film. Among 1,013 workers, 176 deaths were observed for the period 1964 through 1984. There were no excess deaths from cancers of the liver or lung, nor from accidents or ischemic heart disease; however, an increase in mortality from cancer of the pancreas was reported (SMR = 2.5, based on 8 observed pancreatic cancer deaths). These workers were exposed to lower average concentrations of methylene chloride than the cohort studied by Ott (26-100 ppm, on average), but had been followed for a longer period since the start of exposure.

To measure the effect of methylene chloride exposure on mortality we performed a retrospective cohort study of workers exposed to methylene chloride in the production of cellulose fiber at a plant in the Southeastern United States. The cohort was originally assembled by Ott, et al., and followed by them through 1977 (4). We extended the follow-up of this cohort for an additional nine to ten years, that is, through September 1, 1986.

## Methods

**Study Population.** The cohort comprises 1,271 workers who were employed for at least three months between January 1, 1954 and January 1, 1977 in jobs that entailed exposure to methylene chloride.

We obtained data tapes from the original investigators that contain the names, Social Security numbers, birth dates, race, gender, vital status as of June 30, 1977, and cause of death for those who died for all of the cohort members. The data also include work history information for all cohort members as of June 30, 1977 (described in more detail below).

We obtained computer tapes of company personnel and benefits records and used them to determine the employment status of cohort members as of September 1, 1986. We wrote computer programs that matched the cohort roster to the data tapes provided by the personnel and benefits departments to obtain the date of most recent employment and to verify the date of hire as recorded in the data of the original study. We obtained information on last place of residence known to the company from benefits records. This information was available for approximately fifty percent of cohort members.

Ott, et al. did not verify the completeness of the cohort. Since the completion of Ott's study the work history records used to assemble the cohort have been discarded making

verification impossible for workers who terminated employment before 1979. We obtained from the plant work history records for 955 employees who terminated on or after January 1, 1979: among these were 119 cohort members. We identified 11 workers who met criteria but were not on the roster. This yields an estimate of 89.1% for the completeness of the cohort. The validity of this estimate depends on there being no relation between completeness and date of termination.

**Exposure Characterization.** Cellulose fiber production took place in two production areas, or "blocks"; two types of cellulose fiber (diacetate and triacetate) were produced in both areas at different times. Consequently, at a given time, methylene chloride levels were higher in whichever area was producing cellulose triacetate fiber. Methylene chloride was the major solvent exposure for employees in the cellulose triacetate production process, but methanol also was used in a ratio of approximately one part methanol to ten parts methylene chloride. In addition, employees were exposed to acetone in the production of cellulose diacetate. There are no data that indicate the block in which an employee worked or whether an employee worked in the cellulose triacetate or cellulose diacetate process at a particular time.

Investigators from the Dow Chemical Company, under whose auspices the cohort had first been assembled and studied (4), provided us with a report of an industrial hygiene survey of the extrusion and preparation areas conducted in 1977, when the cohort was assembled (6). The Dow survey revealed concentrations of methylene chloride in the

preparation and extrusion areas ranging from 1 to 1,700 ppm (8 hour time-weighted average or TWA), with a median of 190 ppm. Acetone exposures ranged from 10 to 1,600 ppm (TWA), and methanol was found in concentrations of 3 to 140 ppm (TWA). Short-term exposure levels in 1977 showed vapor concentrations in the work environment reaching levels of 3,400 ppm methylene chloride, 4,140 ppm acetone, and 380 ppm methanol (6). Respirators were not used before November, 1983. The plant produced cellulose triacetate from 1954 until the end of 1986.

Since monitoring data were unavailable for most employees, areas, and times of employment, Ott and his colleagues used work history records in an attempt to identify the most heavily exposed employees for inclusion in the cohort. According to documentation provided by Dow, the cohort includes employees who worked for at least three months in any of ten jobs considered to entail substantial methylene chloride exposure (Table 1).

**Mortality Ascertainment.** The follow-up of the cohort was extended through September 1, 1986 by submitting names and Social Security numbers of its members to both the Social Security Administration (SSA) and the National Death Index (NDI). The entire roster was submitted for follow-up, including those determined by the original investigators to have died during the original follow-up period. After matching the cohort roster to the lists of deaths provided by the SSA and NDI using name and Social Security number, the death certificates were requested from the appropriate state. The

company Medical Department also provided a number of death certificates that were in its files.

We identified 122 deaths in the cohort from 1954 through 1986, an increment of 68 deaths since June, 1977, the date of the last follow-up of the cohort. We obtained death certificates for 97% of the decedents (118/122). There was high concordance in mortality ascertainment between NDI and SSA, with 49 of 54 deaths since 1979 being identified by both sources. Four deaths, however, were identified only by NDI and one death was identified only by SSA. A nosologist reviewed the death certificates and assigned codes to the underlying cause of death and contributing causes of death in accordance with the 9th revision of the International Classification of Diseases (7). Employees not identified as deceased were assumed to be living at the end of the follow-up period (9/1/86).

**Analysis.** The effect of exposure on mortality controlling for the effects of age, calendar period, gender, and race was measured by computing standardized mortality ratios (SMRs) (8). Person-years of follow-up and observed deaths were cross-classified by:

- Five year age categories between 20 and 85+ years of age
- Five year calendar period categories between 1954 and 1986
- Two gender categories
- Two race categories: white and nonwhite

We derived expected numbers of deaths using the age-, calendar period-, gender-, and race-specific mortality rates of the U.S. population and the population of York County, SC, where most cohort members reside. Rates for neoplastic diseases were available from 1950 through 1985. Rates for non-neoplastic diseases were available from 1960 through 1985. We used the 1960 rates for the period from 1954 to 1959 for non-neoplastic causes of death. We used the 1985 rates for 1986 experience for all causes of death.

The Occupational Cohort Mortality Analysis Program (OCMAP) (9), developed by the University of Pittsburgh, was used to apportion the person-time, derive the expected number of deaths, and compute SMRs.

We used the calculator program of Rothman and Boice (10) to calculate exact confidence intervals for the SMR based on a Poisson error model.

**Results**

Table 2 shows the vital status of the original cohort as of 1977 by gender and race, as reported by Ott et al. (4) and as we determined. The nearly identical distributions of cohort members by race and gender indicate that the data that we received were the same as those used in the earlier report. We identified 54 deaths through June 1977, as did Ott, et al., though the gender and race distributions of deaths differed slightly, and we identified an additional cancer death.

The bulk of the person-time experience of the cohort through 1986 is concentrated below 50 years of age (Table 3) where expected mortality from most causes is low. This distribution of person-time is due to the fact that 49% of the cohort was hired after 1960, and 72% of the employees were hired under the age of 30 (Table 4).

A total of 122 deaths were observed in the cohort through September 1, 1986. This is nearly the same as the number of deaths expected based on U.S. rates, but about 20 fewer deaths than expected based on York County rates (Table 5). The difference between the two reference populations in the number of expected deaths is due largely to higher death rates from heart disease in the Southeastern U.S. Five death certificates (4.1%) could not be located.

Tables 6-9 show the observed and expected deaths and SMRs stratified by race and then gender. Total mortality was lower for Nonwhites and women regardless whether expected numbers were derived from U.S. or York County rates.

Table 10 presents SMRs and 95% confidence intervals for diseases for which an excess or deficit of at least one death was observed and diseases that were associated with methylene chloride exposure in previous studies (e.g., pancreatic cancer). Among the neoplasms, elevated SMRs were observed for buccal cavity and pharynx (2 deaths observed/0.87 deaths expected, SMR=2.3), biliary passages and liver (4 deaths observed/0.70 deaths expected, SMR=5.7) and melanoma (2 deaths observed/0.88

deaths expected, SMR=2.3). Deficits in mortality were observed for cancer of the respiratory system (8 deaths observed/10.1 deaths expected, SMR=0.79), breast (2 deaths observed/3.3 deaths expected, SMR=0.60), and pancreas (1 death observed/1.5 deaths expected, (SMR=0.65).

Among non-cancer causes of death, we observed excess deaths from accidents (21 deaths observed/12.8 deaths expected, SMR=1.7), and hypertension without heart disease (2 deaths observed/0.63 deaths expected, SMR=3.2). Accidental death accounted for the greatest absolute excess mortality. Ten deaths were caused by motor vehicle accidents (Table 11). Deficits in mortality were observed for death from cerebrovascular disease (5 deaths observed/8.9 deaths expected, SMR=0.56), ischemic heart disease (31 deaths observed/34.4 deaths expected, SMR=0.90), and non-malignant respiratory disease (4 deaths observed/6.0 deaths expected, SMR=0.67).

We examined the relationship of mortality to time since first employment and duration of employment for ischemic heart disease, lung cancer and cancer of the liver and biliary tract. The only evidence of excess mortality from lung cancer was among those workers with less than ten years employment and less than twenty years since first employment (SMR=2.2, Observed=3) (Table 12). No excess mortality (defined as O-E>=1) from ischemic heart disease was observed at any level of time since first employment or duration of employment. Among employees with greater than ten years employment and

greater than twenty years since first employment, we observed 4 deaths from liver and biliary tract cancer with 0.35 deaths expected (SMR = 11.55) (Table 13).

When computing confidence intervals for the SMR it is generally assumed that the sampling variability of the mortality rates from the general population is small relative to the sampling variability of the rates in the cohort. For this reason, the population rates are considered to be known quantities rather than random variables and do not contribute to the variance of the SMR in the standard statistical analyses (Ref.8, pp.65-72). The confidence intervals presented above were calculated under this assumption. However, because the SMRs were constructed using reference rates from the county of residence the usual assumption concerning the variability of the reference rates may be less tenable than if rates from the U.S. population had been employed. To determine whether the contribution of the reference rates to the variance of the SMR could be ignored in computing confidence intervals, we calculated the components of the approximate variance of the log SMR for liver and biliary cancer (SMR = 5.75) contributed by the observed deaths (N = 4) and the expected deaths (based on 69 deaths in York County, SC between 1954 and 1985) (29). The overall variance of the log SMR for liver and biliary cancer is 0.284, to which the county rates contribute 0.034 and the cohort rates contribute 0.250. Approximate 95% confidence bounds on the SMR based upon the approximate variance of 0.284 are 2.0 and 16.3. The contribution of the reference rates to the total variance of the log SMR for liver and biliary cancer is nearly an order of magnitude less than that of the cohort rates and accounting for it in the

computation of confidence intervals does not appreciably affect the interpretation of the results.

Because of the association between employment and cancer of the liver and biliary passages, we attempted to verify the cause of death indicated on the death certificate by obtaining the medical records of the decedents. Two deaths (cases 1 and 3) were cholangiocarcinomas of the extrahepatic bile ducts, one case (case 4) was a cholangiocarcinoma of the intrahepatic duct (Table 14). For case 2, no medical record was obtained. However, this was the only case in which an autopsy had been performed, and the autopsy results may have informed the death certificate diagnosis of adenocarcinoma of the liver.

Since the York County and U.S. reference rates combine cancer of the liver with cancer of the biliary passages, we could not use these data to compute the number of deaths expected from cancer of the biliary tract alone. Age-, race-, and sex-specific mortality rates for biliary cancer (ICD-8 codes 155.5, 156.1-156.9) for the years 1973-77 are available from the Surveillance, Epidemiology and End Results (SEER) program for the geographic areas included in the SEER network (11), and were used to estimate the number of deaths expected from biliary cancer. We could not adjust for calendar time because mortality rates for this type of cancer are unavailable for the 1950s and 1960s. These data provided an estimate of 0.15 deaths expected from biliary cancer, yielding an SMR of 20 (95% confidence interval = 5.2, 56).

**Discussion**

We conducted a retrospective cohort study of the mortality of textile workers exposed to methylene chloride. The cohort was originally assembled in 1977, and according to the eligibility criteria, should have included the employees most heavily exposed to methylene chloride between 1954 and 1977. We verified that the data we received were the same data used in the earlier report (4), and determined that the original cohort membership was underascertained by approximately 11%.

We used the SSA, NDI, and plant records to ascertain the mortality of the cohort, but did not attempt to locate all cohort members individually; consequently, ascertainment may not have been complete, particularly among women and non-whites (14). Several factors may mitigate the extent of underascertainment. We were able to replicate closely the mortality ascertainment of the previous study, which suggests that mortality ascertainment through 1977 using SSA files produced results comparable with previous efforts to locate and contact individual cohort members. We used the decedent files of the NDI in addition to SSA files and plant records to extend ascertainment until September, 1986. Several studies have demonstrated that mortality follow-up through NDI results in nearly complete ascertainment (12-14).

Extending mortality ascertainment of the cohort through 1986 added 68 deaths for a total of 122 deaths, and provided more information about mortality in relation to exposures that occurred in the more distant past. While the study provided little

evidence of exposure-related excess mortality for most causes of death, we observed a large relative excess of mortality for cancer of the biliary tract, a malignancy not previously reported to be associated with exposure to methylene chloride, acetone or methanol in animals or humans.

Although there is no animal model for methylene chloride-induced biliary cancer, inhalation of 2,000 ppm methylene chloride for two years produced lung and liver tumors in mice (1,15,16), and mammary tumors in rats (3). The difference between species in susceptibility to a carcinogenic effect of methylene chloride may be explained in part by differences in the way methylene chloride is metabolized. Two pathways have been described for the metabolism of methylene chloride in mammalian species: the multi-function oxidase (MFO) pathway and the glutathione-s-transferase (GST) pathway (16,17). Utilization of these pathways is dose-dependent, since the MFO pathway is saturated at about 500 ppm, while the GST pathway is non-saturable (16). It has been hypothesized that the greater carcinogenic effect in mice may be due to the fact that mice, in whom the GST pathway is more active than in other species, metabolize methylene chloride at a much greater rate. Nevertheless, methylene chloride produced mammary neoplasms in the rat, as well as non-neoplastic liver pathology and fibrosis of the biliary tract (3). There is little information with which to compare the pharmacokinetics of methylene chloride in the biliary tracts of rats and humans. Thus, the implications of the bioassays for the potential carcinogenicity of methylene chloride in the human biliary tract are unclear.

Cancer of the biliary tract in humans has not been previously associated with methylene chloride exposure. As of 1977, there were no biliary cancer deaths reported in this cohort (4). In the most recent follow-up of a cohort of photographic film manufacturing workers, Hearne et al. (5) found no deaths from cancer of the liver or biliary tract (0.8 deaths were expected for these sites combined based on New York State death rates) (T. Hearne, personal communication). However, average exposures to methylene chloride in the textile workers cohort appear to have been considerably higher than the exposure levels reported by Hearne. If methylene chloride causes bile duct tumors, it may do so at levels of exposure experienced by the textile workers cohort but not the photographic film manufacturing workers cohort. Alternatively, the different gender distributions in the two cohorts may explain the discrepancy. The photographic cohort is exclusively male, whereas this cohort is mostly female. Two of the three biliary cancer deaths were women. Hernberg, et al. (18) observed increased mortality from biliary cancer among women exposed to chlorinated solvents but not among men.

The excess deaths from bile duct cancer might have been caused by other risk factors for these cancers, although biliary cancer is not well studied and few risk factors have been identified. Heavy consumption of alcohol is related to cirrhosis and liver cancer in the U.S., but not to bile duct tumors (19). Cancer of the bile ducts is associated with a medical history of chronic ulcerative colitis and gallstones, and in Asia with parasitic infestation (19,20). The latter cause seems unlikely in this cohort, and the former causes cannot be formally evaluated in this study, although none of these factors was noted on

the medical records of the three cases of biliary cancer. Use of oral contraceptives are associated with liver tumors (19), and there have been reports of cholangiocarcinoma in two women aged 21 and 29 years with a history of oral contraceptive use (21,22). However, oral contraceptive use is common in young women and a possible relation between oral contraceptives and cholangiocarcinoma has not been studied epidemiologically, so the existence of a causal relation and its possible induction time remain unknown. Of the three cholangiocarcinomas in this cohort, two occurred among women aged 47 and 60 years (Table 13).

This cohort experienced no excess mortality from ischemic heart disease which is in agreement with results reported for the photographic industry cohort. Thus, the effect of methylene chloride on arterial oxygen content does not appear to have any adverse effect on mortality from ischemic heart disease.

We failed to observe the association between methylene chloride exposure and death from pancreatic cancer that was reported recently for the photographic industry cohort (8 deaths observed/3.9 deaths expected, SMR=2.1) (23). Seven of the eight deaths from pancreatic cancer observed in the photographic industry cohort occurred more than thirty years since first employment. The cellulose fiber cohort, on the other hand, has contributed only about six percent of its total person-time to this category of induction time. It may be that longer periods of follow-up will be required to observe an effect of exposure on pancreatic cancer mortality. The absence of a pancreatic cancer excess in

this cohort does not, therefore, necessarily represent a discrepancy with the findings in the photographic cohort.

We observed excess mortality from cancer of the buccal cavity and pharynx, a finding not in evidence among the photographic film workers (5). Smoking and alcohol, acting alone or in tandem (24), have been observed to cause relative increases of cancer of the buccal cavity and pharynx of greater magnitude than the two-fold excess observed in this study and could, therefore, explain this result if cohort members were heavy consumers of alcohol. However, no excess deaths were seen for other diseases related to smoking and alcohol consumption (e.g. lung cancer, cirrhosis).

The evidence of a possible etiologic relation for melanoma of the skin is sparse. No deaths from melanoma were reported in the photographic film manufacturing cohort (5). Cutaneous exposure to methylene chloride results in a burning sensation and the chemical can penetrate intact skin (25). U.S. counties in which chemical industries are located have shown increased rates of melanoma (26). A study of cancer risk in relation to occupation revealed a two-fold increase in the incidence of melanoma in men employed in the spinning, weaving, and finishing of textiles (27). However, none of these studies addresses directly the issue of methylene chloride exposure in relation to melanoma.

The excess deaths in this cohort from accidental causes may be of interest in light of the neurobehavioral effects of methylene chloride (28). However, the current study did not take into account the effects of many other risk factors for accidents (e.g., alcohol consumption, mileage driven), and cannot be assumed to provide an accurate assessment of the effect of methylene chloride on accidental deaths.

In summary, the strongest association observed in this study was an excess of mortality from cancer of the bile ducts. This result was not observed in a previously studied cohort occupationally exposed to lower concentrations of methylene chloride (5). We found no excess of mortality from pancreatic cancer. If methylene chloride causes pancreatic cancer, it may do so after long induction times not yet experienced by the vast majority of textile workers included in this cohort.

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TABLE 1

Job Titles Used to Assemble the Cohort

- Doffer
- Jet Wiper
- Mixing and Press Operator
- Charge Room Operator
- Staple Operator
- Extrusion Machine Cleaner
- Extrusion Floor Buffer
- Extrusion Vacuum Cleaner Operator
- Extrusion Mechanical Service
- Extrusion Janitor/Janitress

TABLE 2

Vital Status Through 1977
by Gender and Race

| | Ott, et al.[1] | | | Verification | | |
|---|---|---|---|---|---|---|
| | Dead | Alive | Total | Dead | Alive | Total |
| Men | | | | | | |
| White | 37 | 450 | 487 | 39 | 449 | 488 |
| Non-white | 6 | 58 | 64 | 6 | 58 | 64 |
| Women | | | | | | |
| White | 11 | 604 | 615 | 9 | 605 | 614 |
| Non-white | 0 | 105 | 105 | 0 | 105 | 105 |
| TOTAL | 54 | 1217 | 1271 | 54 | 1217 | 1271 |

[1] Ott MG, Skory LK, Holder BB et al. Health evaluation of employees occupationally exposed to methylene chloride. Scand J Work Environ Health 1983;9(suppl 1):1-16.

TABLE 3

Age at Hire, Age at Death and Age Distribution of Person-Time in the Cohort Through 1986

| Age Group | -----Number in Category----- At Hire | At Death | Person-years Contributed |
|---|---|---|---|
| ≤ 19 | 228 | 0 | 202.0 |
| 20-24 | 437 | 2 | 2,028.5 |
| 25-29 | 253 | 5 | 3,756.1 |
| 30-34 | 185 | 4 | 4,691.5 |
| 35-39 | 118 | 7 | 4,818.9 |
| 40-44 | 38 | 15 | 4,551.3 |
| 45-49 | 7 | 23 | 3,946.9 |
| 50-54 | 3 | 16 | 2,900.6 |
| 55-59 | 1 | 23 | 1,743.6 |
| 60-64 | 1 | 15 | 844.1 |
| 65-69 | 0 | 9 | 336.9 |
| 70-74 | 0 | 3 | 116.1 |
| 75-79 | 0 | 0 | 22.5 |
| 80-84 | 0 | 0 | 1.2 |
| 85+ | 0 | 0 | 0 |
| TOTAL | 1,271 | 122 | 29,960.2 |

TABLE 5

Observed and Expected Numbers of Deaths Through 9/1/86[1]

| Cause of Death | Observed | Expected[2] | SMR[2] | Expected[3] | SMR[3] |
|---|---|---|---|---|---|
| All Causes of Death | 122 | 122.39 | 1.00 | 141.94 | 0.86 |
| Tuberculosis | 0 | 0.29 | ---- | 0.41 | ---- |
| All Malignant Neoplasms | 28 | 33.24 | 0.84 | 32.88 | 0.85 |
| Neoplasms | | | | | |
| Buccal Cavity & Pharynx | 2 | 0.84 | 2.39 | 0.87 | 2.31 |
| Digestive Organs & Peritoneum | 7 | 7.10 | 0.99 | 6.81 | 1.03 |
| Esophagus | 0 | 0.66 | ---- | 0.73 | ---- |
| Stomach | 0 | 1.02 | ---- | 0.79 | ---- |
| Large Intestine | 2 | 2.54 | 0.79 | 2.60 | 0.77 |
| Rectum | 0 | 0.61 | ---- | 0.33 | ---- |
| Biliary Passages & Liver | 4 | 0.53 | 7.54 | 0.70 | 5.75 |
| Pancreas | 1 | 1.41 | 0.71 | 1.54 | 0.65 |
| All Other Digestive Organs | 0 | 0.24 | ---- | 0.06 | ---- |
| Respiratory System | 8 | 9.61 | 0.83 | 10.42 | 0.77 |
| Larynx | 0 | 0.33 | ---- | 0.17 | ---- |
| Bronchus, Trachea, Lung | 8 | 9.15 | 0.88 | 10.11 | 0.79 |
| All Other Respiratory | 0 | 0.13 | ---- | 0.12 | ---- |
| Breast | 2 | 3.87 | 0.52 | 3.32 | 0.60 |
| All Uterine Cancers | 0 | 1.15 | ---- | 1.06 | ---- |
| Cervix Uteri | 0 | 0.80 | ---- | 0.80 | ---- |
| Other Female Genital Organs | 2 | 1.11 | 1.81 | 1.03 | 1.95 |
| Prostate | 0 | 0.69 | ---- | 0.76 | ---- |
| Testes & Other Male Genital | 0 | 0.15 | ---- | 0.10 | ---- |
| Kidney | 0 | 0.68 | ---- | 0.47 | ---- |
| Bladder & Other Urinary Tract | 1 | 0.43 | 2.35 | 0.37 | 2.72 |
| Malignant Melanoma of the Skin | 2 | 0.65 | 3.07 | 0.88 | 2.28 |
| Eye | 0 | 0.02 | ---- | 0.04 | ---- |
| Central Nervous System | 1 | 1.20 | 0.83 | 1.52 | 0.66 |
| Thyroid Gland & Other Endocrine | 0 | 0.14 | ---- | 0.16 | ---- |
| Bone | 0 | 0.12 | ---- | 0.09 | ---- |
| All Lymphatic & Hematologic | 2 | 3.19 | 0.63 | 2.92 | 0.69 |
| Lymphosarcoma & Reticulosarcoma | 0 | 0.58 | ---- | 0.66 | ---- |
| Hodgkins Disease | 0 | 0.46 | ---- | 0.25 | ---- |
| Leukemia & Aleukemia | 1 | 1.24 | 0.80 | 1.12 | 0.90 |
| All Other Lymphopoietic System | 1 | 0.91 | 1.09 | 0.90 | 1.11 |
| All Other Malignant Neoplasms | 1 | 2.40 | 0.42 | 2.18 | 0.46 |
| Benign Neoplasms | 0 | 0.54 | ---- | 0.54 | ---- |
| Diabetes Mellitus | 0 | 2.00 | ---- | 2.58 | ---- |
| Cerebrovascular Disease | 5 | 5.79 | 0.86 | 8.90 | 0.56 |
| All Heart Disease | 34 | 37.90 | 0.90 | 47.23 | 0.72 |
| Rheumatic Heart Disease | 1 | 0.93 | 1.07 | 1.08 | 0.93 |
| Ischemic Heart Disease | 31 | 27.95 | 1.11 | 34.33 | 0.90 |
| Chronic Disease of Endocardium | 0 | 0.81 | ---- | 0.64 | ---- |
| Hypertension with Heart Disease | 1 | 0.89 | 1.12 | 0.91 | 1.10 |
| All Other Heart Disease | 1 | 4.76 | 0.21 | 7.01 | 0.14 |
| Hypertension w/o Heart Disease | 2 | 0.39 | 5.17 | 0.62 | 3.20 |
| Non-Malignant Respiratory Disease | 4 | 5.84 | 0.69 | 6.04 | 0.66 |
| Influenza & Pneumonia | 3 | 2.07 | 1.45 | 2.07 | 1.45 |
| Bronchitis, Emphysema, Asthma | 0 | 1.37 | ---- | 1.77 | ---- |
| Bronchitis | 0 | 0.21 | ---- | 0.05 | ---- |
| Emphysema | 0 | 0.87 | ---- | 1.44 | ---- |
| Asthma | 0 | 0.31 | ---- | 0.28 | ---- |
| Other Non-Malignant Resp. Disease | 1 | 2.32 | 0.43 | 2.12 | 0.47 |

**(Table continues on next page)**

TABLE 5 continued

Observed and Expected Number of Deaths Through 9/1/86[1]

| Cause of Death | Observed | Expected[2] | SMR[2] | Expected[3] | SMR[3] |
|---|---|---|---|---|---|
| Ulcer of Stomach & Duodenum | 0 | 0.52 | ---- | 0.82 | ---- |
| Cirrhosis of Liver | 4 | 4.82 | 0.83 | 4.13 | 0.97 |
| Nephritis & Nephrosis | 0 | 1.11 | ---- | 1.90 | ---- |
| All External Causes of Death | 28 | 18.53 | 1.51 | 22.03 | 1.27 |
| Accidents | 21 | 10.77 | 1.95 | 12.77 | 1.64 |
| Motor Vehicle Accidents | 10 | 5.73 | 1.74 | 6.59 | 1.52 |
| All Other Accidents | 11 | 5.02 | 2.19 | 6.16 | 1.79 |
| Suicides | 3 | 4.15 | 0.72 | 4.86 | 0.62 |
| Homicides & Other External | 4 | 3.25 | 1.23 | 3.96 | 1.01 |
| All Other Causes of Death | 12 | 12.98 | 0.92 | 16.00 | 0.75 |

[1] Total = 1271 persons, 29,960.2 person-years.

[2] Expected deaths calculated from U.S. rates.

[3] Expected deaths calculated from York County, S.C. rates.

TABLE 6

Observed and Expected Numbers of Deaths
Through 9/1/86[1], Whites

| Cause of Death | Observed | Expected[2] | SMR[2] | Expected[3] | SMR[3] |
|---|---|---|---|---|---|
| All Causes of Death | 110 | 106.71 | 1.03 | 120.86 | 0.91 |
| Tuberculosis | 0 | 0.19 | — | 0.29 | — |
| All Malignant Neoplasms | 27 | 30.25 | 0.89 | 29.64 | 0.91 |
| Neoplasms | | | | | |
| Buccal Cavity & Pharynx | 2 | 0.71 | 2.82 | 0.78 | 2.56 |
| Digestive Organs & Peritoneum | 6 | 6.30 | 0.95 | 5.87 | 1.02 |
| Esophagus | 0 | 0.48 | — | 0.51 | — |
| Stomach | 0 | 0.87 | — | 0.60 | — |
| Large Intestine | 2 | 2.35 | 0.85 | 2.44 | 0.82 |
| Rectum | 0 | 0.56 | — | 0.28 | — |
| Biliary Passages & Liver | 3 | 0.47 | 6.43 | 0.64 | 4.67 |
| Pancreas | 1 | 1.27 | 0.79 | 1.29 | 0.77 |
| All Other Digestive Organs | 0 | 0.21 | — | 0.04 | — |
| Respiratory System | 8 | 8.69 | 0.92 | 9.54 | 0.84 |
| Larynx | 0 | 0.28 | — | 0.13 | — |
| Bronchus, Trachea, Lung | 8 | 8.29 | 0.97 | 9.29 | 0.86 |
| All Other Respiratory | 0 | 0.12 | — | 0.11 | — |
| Breast | 2 | 3.67 | 0.55 | 3.06 | 0.65 |
| All Uterine Cancers | 0 | 1.02 | — | 0.88 | — |
| Cervix Uteri | 0 | 0.71 | — | 0.65 | — |
| Other Female Genital Organs | 2 | 1.06 | 1.88 | 0.92 | 2.17 |
| Prostate | 0 | 0.57 | — | 0.58 | — |
| Testes & Other Male Genital | 0 | 0.15 | — | 0.09 | — |
| Kidney | 0 | 0.63 | — | 0.45 | — |
| Bladder & Other Urinary Tract | 1 | 0.39 | 2.58 | 0.34 | 2.97 |
| Malignant Melanoma of the Skin | 2 | 0.64 | 3.10 | 0.87 | 2.29 |
| Eye | 0 | 0.02 | — | 0.04 | — |
| Central Nervous System | 1 | 1.15 | 0.87 | 1.41 | 0.71 |
| Thyroid Gland & Other Endocrine | 0 | 0.13 | — | 0.16 | — |
| Bone | 0 | 0.11 | — | 0.09 | — |
| All Lymphatic & Hematologic | 2 | 2.95 | 0.68 | 2.71 | 0.74 |
| Lymphosarcoma & Reticulosarcoma | 0 | 0.55 | — | 0.63 | — |
| Hodgkins Disease | 0 | 0.43 | — | 0.25 | — |
| Leukemia & Aleukemia | 1 | 1.15 | 0.87 | 1.06 | 0.95 |
| All Other Lymphopoietic System | 1 | 0.83 | 1.21 | 0.78 | 1.29 |
| All Other Malignant Neoplasms | 1 | 2.13 | 0.47 | 1.94 | 0.52 |
| Benign Neoplasms | 0 | 0.49 | — | 0.44 | — |
| Diabetes Mellitus | 0 | 1.69 | — | 2.10 | — |
| Cerebrovascular Disease | 4 | 4.70 | 0.85 | 6.63 | 0.60 |
| All Heart Disease | 29 | 33.87 | 0.86 | 40.95 | 0.71 |
| Rheumatic Heart Disease | 1 | 0.86 | 1.16 | 0.91 | 1.10 |
| Ischemic Heart Disease | 27 | 25.53 | 1.06 | 30.45 | 0.89 |
| Chronic Disease of Endocardium | 0 | 0.70 | — | 0.55 | — |
| Hypertension with Heart Disease | 0 | 0.60 | — | 0.39 | — |
| All Other Heart Disease | 1 | 3.94 | 0.25 | 6.03 | 0.17 |
| Hypertension w/o Heart Disease | 2 | 0.25 | 8.03 | 0.17 | 12.03 |
| Non-Malignant Respiratory Disease | 4 | 5.06 | 0.79 | 5.30 | 0.76 |
| Influenza & Pneumonia | 3 | 1.66 | 1.80 | 1.65 | 1.82 |
| Bronchitis, Emphysema, Asthma | 0 | 1.25 | — | 1.68 | — |
| Bronchitis | 0 | 0.19 | — | 0.04 | — |
| Emphysema | 0 | 0.81 | — | 1.39 | — |
| Asthma | 0 | 0.25 | — | 0.25 | — |
| Other Non-Malignant Resp. Disease | 1 | 2.09 | 0.48 | 1.90 | 0.53 |

(Table continues on next page)

TABLE 6 continued

Observed and Expected Numbers of Deaths
Through 9/1/86[1], Whites

| Cause of Death | Observed | Expected[2] | SMR[2] | Expected[3] | SMR[3] |
|---|---|---|---|---|---|
| Ulcer of Stomach & Duodenum | 0 | 0.46 | — | 0.68 | — |
| Cirrhosis of Liver | 4 | 4.13 | 0.97 | 3.69 | 1.08 |
| Nephritis & Nephrosis | 0 | 0.86 | — | 1.58 | — |
| All External Causes of Death | 25 | 15.48 | 1.62 | 18.57 | 1.35 |
| Accidents | 19 | 9.36 | 2.03 | 11.00 | 1.73 |
| Motor Vehicle Accidents | 9 | 5.11 | 1.76 | 5.65 | 1.59 |
| All Other Accidents | 10 | 4.25 | 2.36 | 5.33 | 1.88 |
| Suicides | 3 | 3.93 | 0.76 | 4.62 | 0.65 |
| Homicides & Other External | 3 | 1.86 | 1.62 | 2.55 | 1.18 |
| All Other Causes of Death | 11 | 10.66 | 1.03 | 12.71 | 0.87 |

[1] Total = 1102 persons, 27,114.6 person-years.

[2] Expected deaths calculated from U.S. rates.

[3] Expected deaths calculated from York County, S.C. rates.

TABLE 7

Observed and Expected Numbers of Deaths
Through 9/1/86[1], Nonwhites

| Cause of Death | Observed | Expected[2] | SMR[2] | Expected[3] | SMR[3] |
|---|---|---|---|---|---|
| All Causes of Death | 12 | 15.68 | 0.77 | 21.08 | 0.57 |
| Tuberculosis | 0 | 0.10 | — | 0.12 | — |
| All Malignant Neoplasms | 1 | 2.99 | 0.33 | 3.24 | 0.31 |
| Neoplasms | | | | | |
| Buccal Cavity & Pharynx | 0 | 0.13 | — | 0.09 | — |
| Digestive Organs & Peritoneum | 1 | 0.80 | 1.25 | 0.94 | 1.06 |
| Esophagus | 0 | 0.17 | — | 0.21 | — |
| Stomach | 0 | 0.15 | — | 0.19 | — |
| Large Intestine | 0 | 0.19 | — | 0.16 | — |
| Rectum | 0 | 0.05 | — | 0.05 | — |
| Biliary Passages & Liver | 1 | 0.06 | 15.67 | 0.05 | 18.78 |
| Pancreas | 0 | 0.14 | — | 0.25 | — |
| All Other Digestive Organs | 0 | 0.02 | — | 0.02 | — |
| Respiratory System | 0 | 0.92 | — | 0.88 | — |
| Larynx | 0 | 0.05 | — | 0.04 | — |
| Bronchus, Trachea, Lung | 0 | 0.86 | — | 0.83 | — |
| All Other Respiratory | 0 | 0.01 | — | 0.01 | — |
| Breast | 0 | 0.20 | — | 0.25 | — |
| All Uterine Cancers | 0 | 0.13 | — | 0.18 | — |
| Cervix Uteri | 0 | 0.09 | — | 0.14 | — |
| Other Female Genital Organs | 0 | 0.04 | — | 0.11 | — |
| Prostate | 0 | 0.12 | — | 0.18 | — |
| Testes & Other Male Genital | 0 | 0.00 | — | 0.00 | — |
| Kidney | 0 | 0.05 | — | 0.02 | — |
| Bladder & Other Urinary Tract | 0 | 0.04 | — | 0.03 | — |
| Malignant Melanoma of the Skin | 0 | 0.00 | — | 0.00 | — |
| Eye | 0 | 0.00 | — | 0.00 | — |
| Central Nervous System | 0 | 0.05 | — | 0.11 | — |
| Thyroid Gland & Other Endocrine | 0 | 0.00 | — | 0.00 | — |
| Bone | 0 | 0.01 | — | 0.00 | — |
| All Lymphatic & Hematologic | 0 | 0.23 | — | 0.21 | — |
| Lymphosarcoma & Reticulosarcoma | 0 | 0.03 | — | 0.03 | — |
| Hodgkins Disease | 0 | 0.03 | — | 0.00 | — |
| Leukemia & Aleukemia | 0 | 0.09 | — | 0.06 | — |
| All Other Lymphopoietic System | 0 | 0.08 | — | 0.13 | — |
| All Other Malignant Neoplasms | 0 | 0.26 | — | 0.23 | — |
| Benign Neoplasms | 0 | 0.05 | — | 0.10 | — |
| Diabetes Mellitus | 0 | 0.31 | — | 0.49 | — |
| Cerebrovascular Disease | 1 | 1.09 | 0.92 | 2.27 | 0.44 |
| All Heart Disease | 5 | 4.03 | 1.24 | 6.28 | 0.80 |
| Rheumatic Heart Disease | 0 | 0.07 | — | 0.17 | — |
| Ischemic Heart Disease | 4 | 2.43 | 1.65 | 3.88 | 1.03 |
| Chronic Disease of Endocardium | 0 | 0.11 | — | 0.09 | — |
| Hypertension with Heart Disease | 1 | 0.29 | 3.48 | 0.52 | 1.92 |
| All Other Heart Disease | 0 | 0.82 | — | 0.98 | — |
| Hypertension w/o Heart Disease | 0 | 0.14 | — | 0.46 | — |
| Non-Malignant Respiratory Disease | 0 | 0.78 | — | 0.74 | — |
| Influenza & Pneumonia | 0 | 0.40 | — | 0.42 | — |
| Bronchitis, Emphysema, Asthma | 0 | 0.13 | — | 0.09 | — |
| Bronchitis | 0 | 0.01 | — | 0.02 | — |
| Emphysema | 0 | 0.05 | — | 0.05 | — |
| Asthma | 0 | 0.06 | — | 0.03 | — |
| Other Non-Malignant Resp. Disease | 0 | 0.23 | — | 0.22 | — |

(Table continues on next page)

TABLE 7 continued

Observed and Expected Numbers of Deaths
Through 9/1/86[1], Nonwhites

| Cause of Death | Observed | Expected[2] | SMR[2] | Expected[3] | SMR[3] |
|---|---|---|---|---|---|
| Ulcer of Stomach & Duodenum | 0 | 0.06 | --- | 0.14 | --- |
| Cirrhosis of Liver | 0 | 0.69 | --- | 0.43 | --- |
| Nephritis & Nephrosis | 0 | 0.26 | --- | 0.32 | --- |
| All External Causes of Death | 3 | 3.06 | 0.98 | 3.46 | 0.87 |
| Accidents | 2 | 1.41 | 1.42 | 1.78 | 1.13 |
| Motor Vehicle Accidents | 1 | 0.63 | 1.60 | 0.94 | 1.07 |
| All Other Accidents | 1 | 0.77 | 1.29 | 0.83 | 1.20 |
| Suicides | 0 | 0.22 | --- | 0.24 | --- |
| Homicides & Other External | 1 | 1.40 | 0.72 | 1.41 | 0.71 |
| All Other Causes of Death | 1 | 2.33 | 0.43 | 3.29 | 0.30 |

[1] Total = 169 persons, 2,845.5 person-years.

[2] Expected deaths calculated from U.S. rates.

[3] Expected deaths calculated from York County, S.C. rates.

TABLE 8

Observed and Expected Numbers of Deaths
Through 9/1/86[1], Males

| Cause of Death | Observed | Expected[2] | SMR[2] | Expected[3] | SMR[3] |
|---|---|---|---|---|---|
| All Causes of Death | 93 | 82.74 | 1.12 | 99.89 | 0.93 |
| Tuberculosis | 0 | 0.22 | — | 0.31 | — |
| All Malignant Neoplasms | 17 | 18.80 | 0.90 | 19.53 | 0.87 |
| Neoplasms | | | | | |
| Buccal Cavity & Pharynx | 1 | 0.65 | 1.54 | 0.65 | 1.54 |
| Digestive Organs & Peritoneum | 4 | 4.61 | 0.87 | 4.43 | 0.91 |
| Esophagus | 0 | 0.55 | — | 0.66 | — |
| Stomach | 0 | 0.72 | — | 0.51 | — |
| Large Intestine | 1 | 1.46 | 0.69 | 1.62 | 0.62 |
| Rectum | 0 | 0.40 | — | 0.14 | — |
| Biliary Passages & Liver | 2 | 0.32 | 6.18 | 0.33 | 6.15 |
| Pancreas | 1 | 0.94 | 1.06 | 1.07 | 0.93 |
| All Other Digestive Organs | 0 | 0.15 | — | 0.03 | — |
| Respiratory System | 6 | 7.26 | 0.83 | 8.10 | 0.74 |
| Larynx | 0 | 0.28 | — | 0.13 | — |
| Bronchus, Trachea, Lung | 6 | 6.89 | 0.87 | 7.89 | 0.76 |
| All Other Respiratory | 0 | 0.09 | — | 0.07 | — |
| Breast | 0 | 0.02 | — | 0.08 | — |
| All Uterine Cancers | 0 | 0.00 | — | 0.00 | — |
| Cervix Uteri | 0 | 0.00 | — | 0.00 | — |
| Other Female Genital Organs | 0 | 0.00 | — | 0.00 | — |
| Prostate | 0 | 0.69 | — | 0.76 | — |
| Testes & Other Male Genital | 0 | 0.15 | — | 0.10 | — |
| Kidney | 0 | 0.49 | — | 0.42 | — |
| Bladder & Other Urinary Tract | 1 | 0.34 | 2.95 | 0.34 | 2.94 |
| Malignant Melanoma of the Skin | 2 | 0.38 | 5.23 | 0.58 | 3.47 |
| Eye | 0 | 0.01 | — | 0.00 | — |
| Central Nervous System | 0 | 0.72 | — | 0.88 | — |
| Thyroid Gland & Other Endocrine | 0 | 0.07 | — | 0.09 | — |
| Bone | 0 | 0.08 | — | 0.07 | — |
| All Lymphatic & Hematologic | 2 | 1.95 | 1.03 | 1.77 | 1.13 |
| Lymphosarcoma & Reticulosarcoma | 0 | 0.36 | — | 0.30 | — |
| Hodgkins Disease | 0 | 0.28 | — | 0.12 | — |
| Leukemia & Aleukemia | 1 | 0.74 | 1.36 | 0.73 | 1.36 |
| All Other Lymphopoietic System | 1 | 0.57 | 1.75 | 0.61 | 1.64 |
| All Other Malignant Neoplasms | 1 | 1.45 | 0.69 | 1.36 | 0.74 |
| Benign Neoplasms | 0 | 0.28 | — | 0.34 | — |
| Diabetes Mellitus | 0 | 1.16 | — | 1.49 | — |
| Cerebrovascular Disease | 4 | 3.48 | 1.15 | 6.04 | 0.66 |
| All Heart Disease | 31 | 29.94 | 1.04 | 36.86 | 0.84 |
| Rheumatic Heart Disease | 1 | 0.47 | 2.11 | 0.47 | 2.13 |
| Ischemic Heart Disease | 28 | 22.87 | 1.22 | 27.35 | 1.02 |
| Chronic Disease of Endocardium | 0 | 0.55 | — | 0.47 | — |
| Hypertension with Heart Disease | 1 | 0.60 | 1.66 | 0.58 | 1.74 |
| All Other Heart Disease | 1 | 3.38 | 0.30 | 5.38 | 0.19 |
| Hypertension w/o Heart Disease | 2 | 0.26 | 7.65 | 0.42 | 4.77 |
| Non-Malignant Respiratory Disease | 3 | 4.05 | 0.74 | 4.31 | 0.70 |
| Influenza & Pneumonia | 3 | 1.40 | 2.14 | 1.33 | 2.26 |
| Bronchitis, Emphysema, Asthma | 0 | 0.95 | — | 1.50 | — |
| Bronchitis | 0 | 0.15 | — | 0.05 | — |
| Emphysema | 0 | 0.67 | — | 1.26 | — |
| Asthma | 0 | 0.13 | — | 0.19 | — |
| Other Non-Malignant Resp. Disease | 0 | 1.64 | — | 1.45 | — |

**(Table continues on next page)**

TABLE 8 continued

Observed and Expected Numbers of Deaths
Through 9/1/86[1], Males

| Cause of Death | Observed | Expected[2] | SMR[2] | Expected[3] | SMR[3] |
|---|---|---|---|---|---|
| Ulcer of Stomach & Duodenum | 0 | 0.39 | ---- | 0.67 | ---- |
| Cirrhosis of Liver | 2 | 3.29 | 0.61 | 3.03 | 0.66 |
| Nephritis & Nephrosis | 0 | 0.71 | ---- | 1.20 | ---- |
| All External Causes of Death | 22 | 13.30 | 1.66 | 16.17 | 1.36 |
| Accidents | 18 | 7.93 | 2.27 | 9.61 | 1.87 |
| Motor Vehicle Accidents | 9 | 4.05 | 2.22 | 4.72 | 1.91 |
| All Other Accidents | 9 | 3.86 | 2.33 | 4.87 | 1.85 |
| Suicides | 1 | 2.73 | 0.37 | 3.42 | 0.29 |
| Homicides & Other External | 3 | 2.36 | 1.27 | 2.79 | 1.07 |
| All Other Causes of Death | 9 | 7.87 | 1.14 | 10.79 | 0.83 |

[1] Total = 551 persons, 13,302.9 person-years.

[2] Expected deaths calculated from U.S. rates.

[3] Expected deaths calculated from York County, S.C. rates.

TABLE 9

Observed and Expected Numbers of Deaths
Through 9/1/86[1], Females

| Cause of Death | Observed | Expected[2] | SMR[2] | Expected[3] | SMR[3] |
|---|---|---|---|---|---|
| All Causes of Death | 29 | 39.65 | 0.73 | 42.05 | 0.69 |
| Tuberculosis | 0 | 0.07 | — | 0.10 | — |
| All Malignant Neoplasms | 11 | 14.44 | 0.76 | 13.35 | 0.82 |
| Neoplasms | | | | | |
| Buccal Cavity & Pharynx | 1 | 0.19 | 5.30 | 0.22 | 4.59 |
| Digestive Organs & Peritoneum | 3 | 2.49 | 1.21 | 2.40 | 1.25 |
| Esophagus | 0 | 0.10 | — | 0.06 | — |
| Stomach | 0 | 0.30 | — | 0.28 | — |
| Large Intestine | 1 | 1.08 | 0.93 | 0.98 | 1.02 |
| Rectum | 0 | 0.22 | — | 0.18 | — |
| Biliary Passages & Liver | 2 | 0.21 | 9.67 | 0.37 | 5.39 |
| Pancreas | 0 | 0.47 | — | 0.47 | — |
| All Other Digestive Organs | 0 | 0.09 | — | 0.02 | — |
| Respiratory System | 2 | 2.34 | 0.85 | 2.32 | 0.86 |
| Larynx | 0 | 0.05 | — | 0.04 | — |
| Bronchus, Trachea, Lung | 2 | 2.26 | 0.89 | 2.23 | 0.90 |
| All Other Respiratory | 0 | 0.04 | — | 0.05 | — |
| Breast | 2 | 3.85 | 0.52 | 3.24 | 0.62 |
| All Uterine Cancers | 0 | 1.15 | — | 1.06 | — |
| Cervix Uteri | 0 | 0.80 | — | 0.80 | — |
| Other Female Genital Organs | 2 | 1.11 | 1.81 | 1.03 | 1.95 |
| Prostate | 0 | 0.00 | — | 0.00 | — |
| Testes & Other Male Genital | 0 | 0.00 | — | 0.00 | — |
| Kidney | 0 | 0.19 | — | 0.05 | — |
| Bladder & Other Urinary Tract | 0 | 0.09 | — | 0.03 | — |
| Malignant Melanoma of the Skin | 0 | 0.27 | — | 0.30 | — |
| Eye | 0 | 0.00 | — | 0.04 | — |
| Central Nervous System | 1 | 0.48 | 2.07 | 0.64 | 1.57 |
| Thyroid Gland & Other Endocrine | 0 | 0.06 | — | 0.08 | — |
| Bone | 0 | 0.05 | — | 0.03 | — |
| All Lymphatic & Hematologic | 0 | 1.24 | — | 1.15 | — |
| Lymphosarcoma & Reticulosarcoma | 0 | 0.21 | — | 0.35 | — |
| Hodgkins Disease | 0 | 0.18 | — | 0.12 | — |
| Leukemia & Aleukemia | 0 | 0.51 | — | 0.38 | — |
| All Other Lymphopoietic System | 0 | 0.34 | — | 0.29 | — |
| All Other Malignant Neoplasms | 0 | 0.95 | — | 0.82 | — |
| Benign Neoplasms | 0 | 0.27 | — | 0.20 | — |
| Diabetes Mellitus | 0 | 0.84 | — | 1.09 | — |
| Cerebrovascular Disease | 1 | 2.31 | 0.43 | 2.86 | 0.35 |
| All Heart Disease | 3 | 7.95 | 0.38 | 10.37 | 0.29 |
| Rheumatic Heart Disease | 0 | 0.46 | — | 0.61 | — |
| Ischemic Heart Disease | 3 | 5.09 | 0.59 | 6.98 | 0.43 |
| Chronic Disease of Endocardium | 0 | 0.25 | — | 0.17 | — |
| Hypertension with Heart Disease | 0 | 0.29 | — | 0.33 | — |
| All Other Heart Disease | 0 | 1.37 | — | 1.63 | — |
| Hypertension w/o Heart Disease | 0 | 0.13 | — | 0.21 | — |
| Non-Malignant Respiratory Disease | 1 | 1.79 | 0.56 | 1.73 | 0.58 |
| Influenza & Pneumonia | 0 | 0.67 | — | 0.74 | — |
| Bronchitis, Emphysema, Asthma | 0 | 0.42 | — | 0.27 | — |
| Bronchitis | 0 | 0.06 | — | 0.00 | — |
| Emphysema | 0 | 0.19 | — | 0.18 | — |
| Asthma | 0 | 0.17 | — | 0.10 | — |
| Other Non-Malignant Resp. Disease | 1 | 0.68 | 1.48 | 0.68 | 1.48 |

**(Table continues on next page)**

TABLE 9 continued

Observed and Expected Numbers of Deaths
Through 9/1/86[1], Females

| Cause of Death | Observed | Expected[2] | SMR[2] | Expected[3] | SMR[3] |
|---|---|---|---|---|---|
| Ulcer of Stomach & Duodenum | 0 | 0.13 | — | 0.14 | — |
| Cirrhosis of Liver | 2 | 1.54 | 1.30 | 1.10 | 1.82 |
| Nephritis & Nephrosis | 0 | 0.41 | — | 0.71 | — |
| All External Causes of Death | 6 | 5.24 | 1.15 | 5.86 | 1.02 |
| Accidents | 3 | 2.84 | 1.06 | 3.16 | 0.95 |
| Motor Vehicle Accidents | 1 | 1.68 | 0.60 | 1.87 | 0.53 |
| All Other Accidents | 2 | 1.16 | 1.72 | 1.29 | 1.55 |
| Suicides | 2 | 1.42 | 1.41 | 1.44 | 1.39 |
| Homicides & Other External | 1 | 0.89 | 1.12 | 1.17 | 0.86 |
| All Other Causes of Death | 3 | 5.11 | 0.59 | 5.22 | 0.58 |

[1] Total = 720 persons, 16,657.3 person-years.

[2] Expected deaths calculated from U.S. rates.

[3] Expected deaths calculated from York County, S.C. rates.

TABLE 10

Observed and Expected Numbers of Deaths from Selected Causes
Through 9/1/86

| | Obs. | Exp.[1] | SMR | 95% C.I.[2] |
|---|---|---|---|---|
| All Causes | 122 | 141.94 | 0.86 | 0.71, 1.03 |
| Neoplasms: | | | | |
| Buccal Cavity/Pharynx | 2 | 0.87 | 2.31 | 0.39, 7.60 |
| Biliary Passages & Liver | 4 | 0.70 | 5.75 | 1.82, 13.78 |
| Melanoma | 2 | 0.88 | 2.28 | 0.38, 7.51 |
| Bronchus, Trachea & Lung | 8 | 10.11 | 0.79 | 0.37, 1.50 |
| Breast | 2 | 3.32 | 0.60 | 0.10, 1.99 |
| Pancreatic | 1 | 1.54 | 0.65 | 0.03, 3.20 |
| Accidents | 21 | 12.77 | 1.64 | 1.05, 2.47 |
| Hypertension Without Heart Disease | 2 | 0.62 | 3.20 | 0.54, 10.66 |
| Cerebrovascular Disease | 5 | 8.90 | 0.56 | 0.21, 1.25 |
| Ischemic Heart Disease | 31 | 34.33 | 0.90 | 0.62, 1.27 |
| Non-malignant Respiratory Disease | 4 | 6.04 | 0.66 | 0.21, 1.60 |
| Suicides | 3 | 4.86 | 0.62 | 0.16, 1.68 |

[1] Expected deaths calculated from York County, S.C. rates.

[2] Exact confidence intervals calculated by mid-p method.
(Miettinen OS. Comment. J Amer Stat Assn 1974; 69:380-2)

TABLE 11

Distribution of Accidental Deaths by Type of Accident

| Type of Accident | Number of Deaths |
|---|---|
| Motor Vehicle | 10 |
| Occupant | 6 |
| Driver | 5 |
| Passenger | 0 |
| Unspecified | 1 |
| Pedestrian | 1 |
| Unspecified | 3 |
| Home-Related | 4 |
| Fire | 3 |
| Other | 1 |
| Medication-Related | 2 |
| Drowning | 1 |
| Boating | 1 |
| Firearm | 1 |
| Unspecified | 2 |
| TOTAL | 21 |

TABLE 12

Observed and Expected[1] Deaths from Cancer of the Bronchus, Trachea and Lung Through 9/1/86, by Time Since First Employment and Duration of Employment

| Time Since First Employment | Measure | Duration of Employment (years) < 10 | 10+ | Total |
|---|---|---|---|---|
| < 20 years | Observed | 3 | 0 | 3 |
| | Expected | 1.40 | 1.42 | 2.82 |
| | Person-years | 16,511 | 5,583 | 22,094 |
| | SMR | 2.15 | 0 | 1.06 |
| | 95% C.I.[2] | (0.56, 5.8) | (0, 2.1) | (0.27, 2.9) |
| 20+ years | Observed | 3 | 2 | 5 |
| | Expected | 2.28 | 5.01 | 7.29 |
| | Person-years | 3,195 | 4,671 | 7,866 |
| | SMR | 1.32 | 0.40 | 0.79 |
| | 95% C.I. | (0.34, 3.6) | (0.07, 1.3) | (0.25, 1.5) |
| TOTAL | Observed | 6 | 2 | 8 |
| | Expected | 3.68 | 6.44 | 10.11 |
| | Person-years | 19,706 | 10,254 | 29,960 |
| | SMR | 1.63 | 0.31 | 0.79 |
| | 95% C.I. | (0.66, 3.4) | (0.05, 1.0) | (0.37, 1.5) |

[1] Expected deaths calculated from York County, S.C. rates.

[2] Exact confidence intervals calculated by mid-p method.
(Miettinen OS. Comment. J Amer Stat Assn 1974; 69:380-2)

TABLE 13

Observed and Expected[1] Deaths from Biliary Tract and Liver Cancer
Through 9/1/86, by Time Since First Employment
and Duration of Employment

| Time Since First Employment | Measure | ----------Duration of Employment (years)---------- < 10 | 10+ | Total |
|---|---|---|---|---|
| < 20 years | Observed | 0 | 0 | 0 |
| | Expected | 0.09 | 0.09 | 0.18 |
| | Person-years | 16,511 | 5,583 | 22,094 |
| | SMR | 0 | 0 | 0 |
| | 95% C.I.[2] | (0, 33.29) | (0, 33.29) | (0, 16.64) |
| 20+ years | Observed | 0 | 4 | 4 |
| | Expected | 0.17 | 0.35 | 0.52 |
| | Person-years | 3,195 | 4,671 | 7,866 |
| | SMR | 0 | 11.55 | 7.69 |
| | 95% C.I. | (0, 17.62) | (3.63, 27.57) | (2.44, 18.56) |
| TOTAL | Observed | 0 | 4 | 4 |
| | Expected | 0.26 | 0.44 | 0.70 |
| | Person-years | 19,706 | 10,254 | 29,960 |
| | SMR | 0 | 9.09 | 5.74 |
| | 95% C.I. | (0, 11.52) | (2.89, 21.93) | (1.82, 13.78) |

[1] Expected deaths calculated from York County, S.C. rates.

[2] Exact confidence intervals calculated by mid-p method.
(Miettinen OS. Comment. J Amer Stat Assn 1974; 69:380-2)

TABLE 14

Deaths From Liver and Biliary Tract Cancer
by Type of Tumor

| Case | Sex | Age | ICD | Cause | Autopsy | Medical Rec. Confirmation[1] |
|---|---|---|---|---|---|---|
| (1) | M | 59 | 156.2 | Cholangiocarcinoma of Ampulla of Vater | No | Yes |
| (2) | M | 67 | 155.2 | Adenocarcinoma of Liver | Yes | No |
| (3) | F | 60 | 156.1 | Cholangiocarcinoma of Hepatic and Common Bile Ducts | No | Yes |
| (4) | F | 47 | 155.1 | Cholangiocarcinoma of Common Bile Duct | No | Yes |

[1] Medical records are provided by plant medical department.

# REASSESSMENT OF METHYLENE CHLORIDE EXPOSURE IN A COHORT OF CELLULOSE FIBER PRODUCTION WORKERS: CONSTRUCTION OF AN EXPOSURE SCALE AND ANALYSES OF MORTALITY

**Abstract**

We attempted to improve the characterization of methylene chloride exposure for the Celriver cohort using work history and industrial hygiene data that are available for the cohort. Complete work histories exist for employees who terminated after 1979 and work history abstracts covering the period of employment through 1977 exist for all cohort members. Industrial hygiene measurements document wide variation in methylene chloride exposure among jobs held by cohort members. Exposure also varied among employees with identical job titles who produced different types of cellulose fiber. Work history data contain information about job title but not about production process. We developed an exposure classification scheme comprising three categories of job groups. This scheme allows deaths and person-time associated with the greatest exposure to be analyzed separately. We conducted analyses of mortality from selected causes using the exposure classification scheme, but the informativeness of these analyses was limited by small numbers of deaths and residual exposure misclassification.

## Introduction

In two mortality studies of a cohort of cellulose triacetate production workers (1,2) employment served as a marker of occupational exposure to the solvent methylene chloride; however, industrial hygiene data (3) indicate that methylene chloride exposure varied among cohort members. The use of employment as a surrogate of methylene chloride exposure must, inevitably, have resulted in the misclassification of actual methylene chloride exposure in the cohort. Most plausibly, this misclassification would have affected equally decedents and non-decedents, and produce a bias in the direction of observing no effect of methylene chloride exposure on mortality. To understand better the possible effects of exposure to methylene chloride on the mortality of the cohort, we evaluated the feasibility of improving exposure estimation by using existing work history records and industrial hygiene data to construct an exposure scale for methylene chloride.

## The cellulose fiber workers cohort.

The cohort, originally assembled by Dow Chemical Company investigators, comprises 1,271 workers employed in a plant in the Southeastern United States that produced cellulose triacetate fiber using methylene chloride (1). Cohort members held certain jobs in the preparation and extrusion areas of the plant for at least three months between January 1, 1954 and January 1, 1977 (Table 1); these jobs were thought by the original investigators to entail exposure to the highest concentrations of methylene chloride.

Dow Chemical Company investigators conducted an industrial hygiene survey of the extrusion and preparation areas conducted in 1977 when the cohort was assembled (3). The Dow survey revealed concentrations of methylene chloride in the preparation and extrusion areas ranging from 1 to 1,700 ppm (TWA), with a median of 190 ppm. Acetone exposures ranged from 10 to 1,600 ppm (TWA), and methanol was found in concentrations of 3 to 140 ppm (TWA). Short-term exposure levels in 1977 showed vapor concentrations in the work environment reaching levels of 3,400 ppm methylene chloride, 4,140 ppm acetone, and 380 ppm methanol (3). Respirators were not used before November, 1983. The plant produced cellulose triacetate from 1954 until the end of 1986.

The mortality of this cohort has been studied twice. Ott et al. (1) identified 54 deaths in this cohort during the period 1954 through 1977. Compared with mortality in the U.S. population, Ott et al. found that workers died more frequently from accidental causes. There were no excess deaths from ischemic heart disease. Only seven cancer deaths were observed in the cohort, and there was no excess of more than one death from any particular type of cancer. The most recent follow-up identified 122 deaths in the cohort through September 1, 1986 (2). The investigators compared mortality rates for the cohort with mortality rates for the United States population and the population of York County, South Carolina. The greatest relative increase in mortality was seen for cancer of the liver and biliary passages, with four deaths observed and less than one death

expected. Of these four deaths, the diagnosis for three decedents was confirmed by medical records as cancer of the biliary tract (cholangiocarcinoma). These three decedents were employed in jobs that entailed exposure to the highest concentrations of methylene chloride for approximately 28 years, 20 years, and less than one year. The data also revealed excess mortality from cancers of the buccal cavity and pharynx, and melanoma. Deficit mortality was seen for cancers of the respiratory system, breast and pancreas. Among non-cancer causes of death, excess mortality was seen from accidents and hypertension without heart disease, whereas deficits were apparent for cerebrovascular disease, ischemic heart disease, non-malignant respiratory disease and suicide.

**Development of an exposure classification scheme.**

The feasibility of developing an exposure classification scheme depends on 1) the availability of work history data by person and time period, and 2) the accuracy with which existing work history data provide information about exposure to methylene chloride. We therefore evaluated these separate components to determine whether a classification scheme could be constructed.

**Sources of work history data.**

Existing work history data are derived from travel cards maintained by the plant for each employee. The travel cards list each job held by the employee including lay-off or

furlough periods, and the dates that each job was held. However, owing to the historical plant policy of purging records after five years, travel cards are not available for the entire cohort. Fortunately, Dow Chemical Company investigators made abstracts of the travel cards in 1977 before they were destroyed. In addition, we recovered and transcribed travel cards for workers who terminated employment between 1979 and 1985. Consequently, there exist two sources of job history data for the cohort:

1) Abstracts of the travel cards made in conjunction with the Dow Chemical Company study (All (1,271) cohort members).
2) Transcriptions of the travel cards (119 cohort members who terminated after 1979).

**Abstracts of the travel cards.** Dow investigators abstracted certain elements of the work history from the travel cards for all members of the cohort. These data span the period from the date of hire to the date of termination or June 30, 1977 (the closing date for the Dow study), whichever date occurred first.

Each line of the abstracted work history comprises three elements: a numeric code that denotes a job or job category in which the cohort member was employed, the month and year that the person began work in that job or job category, and the start and stop dates that of employment in that job or category.

The abstracts contain several types of inaccuracies not found in the travel cards:

1) Jobs with different exposure levels were combined under one code (Table 2). Of the ten jobs considered by Dow investigators to entail substantial exposure to methylene chloride, five jobs were assigned separate codes: doffer, jet wiper, mixing and press operator, charge room operator, and staple operator. The five remaining exposed jobs were all assigned a single code (extrusion machine cleaner, extrusion mechanical service, extrusion vacuum cleaning operator, extrusion floor buffer, and extrusion janitor/janitress). Industrial hygiene data indicate that machine cleaners were exposed to higher levels of methylene chloride (510 ppm) than either janitors (160 ppm) or mechanical service operators (130 ppm).(3)

2) Furloughs (lay-offs) and terminations after which the employee was rehired were assigned the code corresponding to the preceding job. This approach overestimates duration of employment in the most recent job and, when the job entails exposure to methylene chloride, duration of exposure. Tables 3 and 4 illustrate how this error has resulted in ten and eleven month overestimates of duration of exposure for two employees. The worker whose history is depicted in Table 3 was terminated for 10 months in 1955-56: this time was coded by Dow investigators as time spent working as an extrusion doffer. Furlough periods in 1961 and 1963 were coded as

time employed in the job held before each furlough for the worker depicted in Table 4.

3) Each job on the travel card was not coded. Table 3 presents an example in which three jobs (jet assembler, extrusion mechanical service, and jet wiper) were not coded. It is not clear why these jobs were not coded, or the extent to which errors of this type are present in the abstracts.

**Transcriptions of the travel cards.** We located in Personnel Department records travel cards for a group of 955 hourly employees who terminated between January 1, 1979 and December 31, 1985. These records contained for each employee information on name, Social Security number, and the start and stop dates for each job held listed in chronological order. We coded the work histories from the travel cards for the 119 cohort members who terminated employment between 1979 and 1985. The records that resulted are verbatim representations of the travel cards, and include each job title, including furloughs, and the dates that each job was held.

**Completeness of work history data**

A work history abstract or a work history transcription exists for each cohort member. For 796 cohort members who terminated prior to January 1, 1979, only an abstracted version of work history data through June, 1977 is available. For 119 cohort members

who terminated after 1979 there is both a work history abstract that covers the period from January, 1954 through June, 1977 and a work history transcription that covers the period from date of hire to date of termination.

We attempted to assemble complete work histories for cohort members who remained actively employed through September 1, 1986, the closing date of the most recent follow-up study (2). While initially it appeared that complete work histories would be available for active employees, it became apparent upon closer inspection of the records that gaps of up to eight years existed for greater than ten percent of the records. These gaps begin in July, 1977, the last date in the work history abstracts. We decided not to attempt to construct work histories beyond June, 1977 for the active employees.

In summary, work history data appear to provide reasonably complete information about the titles and durations of jobs held by all cohort members through June, 1977 and for 119 cohort members who terminated employment between January 1, 1979 and December 31, 1985.

**Accuracy with which work histories indicate exposure to methylene chloride**

The feasibility of using work history data to characterize methylene chloride exposure depends on the accuracy with which job titles indicate exposure to methylene chloride. In particular, we considered the variation in exposure that is captured by job title (i.e.,

among employees with different jobs), as well as the residual variation in exposure (i.e., among employees with the same job).

**Variation in exposure among employees with different jobs.** Data from the industrial hygiene survey conducted at the plant in 1977-1978 by Dow Chemical(3) provide quantitative estimates of methylene chloride exposure for certain jobs held by cohort members. The Dow industrial hygiene survey data indicate that exposure varied widely among jobs (Table 5). For example, maximum eight hour time-weighted average exposures were substantially greater for mixing and press operators (900 ppm) and for doffers and jet wipers (580, 690 ppm) than for extrusion janitors or extrusion mechanical service operators (130, 160 ppm).

**Variation in exposure among employees with the same job.** Cellulose fiber production took place in two production areas, or "blocks," and two types of cellulose fiber (diacetate and triacetate) were produced in both areas at different times. Consequently, at a given time, methylene chloride levels were higher in whichever area was producing cellulose triacetate fiber (Table 6). For example, in 1977, when triacetate was produced in Block 2, doffers in Block 2 had higher methylene chloride exposures (320-690 ppm) than doffers in Block 1 (<1-350 ppm). However, in July through October of 1972 (4), doffers in Block 1 often experienced higher levels of methylene chloride exposure (573-690 ppm) than doffers in Block 2 (370-486 ppm) (Table 7). Thus, there appears to be

variation in exposure over time among employees who held the same job. Travel cards provide no indication of whether an employee worked in the cellulose triacetate or cellulose diacetate process.

**Measurement of exposure.** Employees who held the same jobs had different solvent exposures depending on whether they were producing cellulose triacetate fiber or cellulose diacetate fiber. Cellulose triacetate was produced using methylene chloride and methanol, whereas cellulose diacetate production used acetone. The available data allow one to improve methylene chloride exposure characterization, but not to distinguish the separate effects of methylene chloride, methanol, and acetone because, with few exceptions, job titles that entailed high methylene chloride exposure when triacetate fiber was produced also entailed high acetone exposures when diacetate fiber was produced. No data are available about the type of fiber that each employee produced. Methanol was always used together with methylene chloride.

**Construction of an exposure scale.**

To characterize more accurately the methylene chloride exposure of the cohort members requires work history information and the ability to link these data with methylene chloride exposure levels. Work history transcriptions and/or abstracts exist for each cohort member. Both the abstracts and transcriptions identify job titles and durations, although the abstracts exaggerate the duration of exposure for some employees.

According to the industrial hygiene survey conducted by Dow, exposure varied substantially for different jobs. However, the measurements made by Dow do not cover every job and time period of interest. Only certain preparation and extrusion jobs were monitored extensively, such as doffers, jet wipers, and charge room operators. No measurements appear to have been made for other jobs, such as extrusion floor buffer and extrusion vacuum cleaner operator. In addition, all measurements were made from September, 1977 to February, 1978, and may not reflect conditions during other periods. Nevertheless, the job rankings based on Dow exposure measurements correspond to potential exposure estimated from job descriptions. Since exposure varied for employees with the same job, it is difficult to assign to each job a particular exposure level or a range of exposures over the entire study period. It seems reasonable, however, to assume that the relative ranking of jobs remained stable. Therefore, we can use work history records to characterize methylene chloride exposures.

**Proposed classification scheme.** Since each cohort member has a work history record, and job titles are a major determinant of exposure, we developed an exposure classification scheme that classifies job titles into three groups (Table 8). The essential feature of this scheme is that it allows the deaths and person-time associated with the greatest methylene chloride exposure to be analyzed separately from the remainder of the cohort's experience. The category of greatest exposure includes all jobs in the industrial hygiene report associated with maximum eight hour time-weighted average

methylene chloride exposures of 500 ppm or greater. We chose 500 ppm as the lower boundary for this category because this is the concentration at which the multifunction oxidase (MFO) pathway becomes saturated, and at concentrations greater than 500 ppm methylene chloride is metabolized increasingly by the glutathione-S-transferase (GST) pathway, which is considered to be the source of potentially carcinogenic metabolites (5). An eight hour time-weighted average exposure of 500 ppm is also the permissible exposure limit specified for methylene chloride by the Occupational Safety and Health Administration (6). The intermediate exposure category includes jobs associated with maximum methylene chloride exposures less than 500 ppm and other jobs in preparation and extrusion, including those for which no measurements were made. Despite their exposure to levels greater than 500 ppm, extrusion machine cleaners were included in the intermediate category to make the exposure scheme compatible with the work history abstracts, which group machine cleaners with jobs associated with less exposure. The least exposed category comprises all other jobs (e.g., jobs in the textile area and grounds workers).

**Analyses**

We conducted analyses to estimate the effect of methylene chloride exposure through June, 1977 on mortality through September 1, 1986. While these analyses do not address explicitly the effects of exposure sustained subsequent to June, 1977, it appears, from

anecdotal information and from limited industrial hygiene data, that this approach will account for the periods in which the heaviest exposures took place.

We characterized the methylene chloride exposure of each cohort member through June 1977 using the system described above. We performed separate analyses for subcohorts defined by maximum level of exposure to methylene chloride experienced through June, 1977. We identified the maximum level of exposure experienced by each cohort member (Table 8) as of June, 1977, and apportioned person-years of follow-up and deaths following the start of maximal exposure through September 1, 1986 within categories of age, calendar period, race, and gender.

This exposure scheme is derived from time-weighted average exposures which can be achieved in different ways. For instance, workers in the preparation area (mixing and press and charge room operators) experienced a combination of intermediate exposures and unusually high excursion or peak exposures, whereas doffers experienced more consistent exposures (3). To assess the effect of high peak exposures, the mortality of preparation area workers was analyzed separately.

**Results**

Seventy-two percent (N=913) of the cohort members held a job in the highest exposure category prior to June, 1977, and the remaining (N=358) cohort members held jobs that

entailed at least intermediate level exposure. Tables 9 and 10 present SMRs and 95% confidence intervals for those who attained the highest exposure level and for those who attained only the intermediate level, respectively. The SMRs at the two exposure levels may be compared directly, since the age and calendar period-specific distributions of person-time are very nearly identical for each exposure level. We observed a deficit in total mortality (59 deaths observed/76.16 deaths expected, SMR=0.76) among those with the greatest exposure due primarily to deficits in heart disease mortality.

We also observed deficits in mortality from lung cancer and ischemic heart disease among workers with the greatest exposures. Those workers with, at most, intermediate level exposures also experienced no excess mortality from lung cancer. A single excess death from ischemic heart disease was observed among workers with intermediate level exposures. Total mortality for those workers with, at most, intermediate level exposure was close to expected (SMR=0.98).

The excess mortality from accidental causes is concentrated among those with, at most, intermediate level exposure (13 deaths observed/5.61 deaths expected, SMR=2.3).

Two cancers of the liver and biliary tract occurred at each exposure level. Two cancers of the biliary tract occurred at the highest level and one biliary tract cancer occurred at the intermediate level. Therefore, contrary to the impression given by the comparison of

the SMRs for cancers of the biliary passages and liver, the observed rates at each exposure level are of comparable magnitude.

Since each of the three employees who died of biliary cancer terminated employment after 1979, we were able to use their travel cards to examine further their exposure histories including post-1977 exposure. The durations of employment in a job classified as entailing the greatest exposure to methylene chloride were 33 years, and less than 1 year. The duration of employment in an intermediate level job of the biliary cancer death in that category was 21 years. We also compared the frequency and durations of all job titles for the three biliary cancer deaths with the remaining 116 employees who terminated since January 1, 1979 (Table 11). No job title was common to all three cases, and, for jobs held for at least a year, no job title was shared by any of the cases.

Two deaths from ovarian cancer had been observed in the cohort (2). Both of these deaths occurred among women who had been exposed at the highest level (2 deaths observed/0.93 deaths expected, SMR=2.16).

Eleven deaths occurred among the 89 workers who had held jobs in the preparation area where peak exposures were the greatest (Table 12); fourteen deaths were expected based upon 2,069 person-years of observation (SMR=0.78). Only a single death from

neoplastic disease, lung cancer, was observed. We observed a single excess death from ischemic heart disease (5 deaths observed/3.91 deaths expected, SMR = 1.28).

**Discussion**

We evaluated the feasibility of improving the characterization of methylene chloride exposure for a cohort of cellulose fiber production workers. We evaluated the sources of work history data that are available for the cohort, and the extent to which they include information about exposure to methylene chloride. Complete work histories exist for employees who terminated after 1979 and work history abstracts covering the period of employment through 1977 exist for all cohort members. Industrial hygiene measurements document wide variation in methylene chloride exposure among jobs held by cohort members. Exposure also varied among employees with identical job titles who produced different types of cellulose fiber. Work history data contain information about job title but not about production process. Consequently, it is not possible to determine an employee's exposure at a particular time. However, it is reasonable to assume that the most heavily exposed employees worked in certain jobs. Therefore, we developed an exposure classification scheme comprising three categories of job groups. This scheme allows deaths and person-time associated with the greatest exposure to be analyzed separately.

We examined the mortality of the cohort through September 1, 1986 in relation to their methylene chloride exposure through June, 1977 using the classification scheme that we had devised. Our previous analyses of the mortality of the cohort through September 1, 1986 had revealed excess mortality from cancers of the biliary tract, cancer of the buccal cavity and pharynx, melanoma, and accidental causes. Deficits had been observed for cancer of the lung and ischemic heart disease, causes of mortality for which a relation with methylene chloride had been hypothesized (2). We reasoned that analyses that used the exposure classification scheme would result in a net reduction in exposure misclassification from the approach used in the prior analysis (2), because this scheme distinguishes between levels of methylene chloride exposure.

If the maximum level of exposure to methylene chloride is directly related to mortality then we would expect to see excess mortality concentrated among workers exposed to the greatest levels of methylene chloride. Reexamination of the cohort's mortality using an exposure scheme based upon maximum level of exposure did not corroborate this hypothesis. The mortality rates for cancers of the biliary tract, buccal cavity and pharynx, and melanoma were approximately equal for workers with maximum exposures at the intermediate and highest levels. Excess mortality from accidental causes was concentrated among those with, at most, intermediate level exposures. Deficits in lung cancer mortality were observed at both exposure levels, corroborating the previous

analyses (2). The results for ischemic heart disease mortality provide no evidence of excess mortality concentrated among those with the greatest exposure.

The potential for considerable misclassification of exposure to methylene chloride remains under this exposure classification scheme. The absence of data on whether cohort members worked in the cellulose triacetate or cellulose diacetate process assures that some misclassification of methylene chloride exposure will remain in this, or any, exposure classification scheme that relies on either of the currently available sources of work history data. Under this scheme the highest exposure category includes job titles (doffers and jet wipers) that entailed wide ranges of exposure; therefore, some lower exposure person-time will inevitably be misclassified as higher exposure experience. If heavy methylene chloride exposure does effect mortality, then this misclassification will bias the SMR for the greatest exposed subcohort to the null.

In the industrial hygiene survey (3) only certain preparation and extrusion jobs were monitored extensively. For other jobs, no measurements were made, or few measurements were made under a limited range of conditions. The most extensive industrial hygiene measurements were made for jobs that we assigned to the highest exposure category, such as doffers, and jet wipers (Table 5). For certain jobs that we assigned to the intermediate exposure category , e.g., janitors, mechanical service

operators, and jet assemblers few measurements were made and those measurements were in Block 1 only. It seems unlikely that these jobs would have been confined to one production area; therefore, the true range of exposure may have been understated. For certain jobs classified as exposed by Dow investigators, such as extrusion floor buffer and extrusion vacuum cleaner operator, no measurements appear to have been made; therefore, the true range of exposure for these jobs is unknown, though it is assumed to be low in the industrial hygiene survey. The observation of greater mortality among those who worked only in jobs classified as intermediate exposure would be consistent with either an effect of intermediate exposure or misclassification of exposure.

The current data do not allow one to distinguish the separate effects of methylene chloride, methanol, and acetone. Methylene chloride exposures always occurred in the presence of methanol, and methanol concentrations were directly proportional to methylene chloride concentrations. The highest acetone levels were in jobs that entailed exposure to the greatest levels of methylene chloride. Therefore, while neither methanol nor acetone have been observed to have independent carcinogenic effects, observed effects would be consistent with the independent effect of either chemical or their interactive effect.

The small size and relative youthfulness of the cohort (2) have resulted in few deaths from any specific condition through September 1, 1986, and presented a major obstacle

to any more refined mortality analyses. As the cohort ages and more deaths occur, the classification scheme that we have developed may be able to be used to greater effect.

**References**

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**Table 1**

**Job Titles Used to Assemble the Celriver Cohort**

- Doffer
- Jet Wiper
- Mixing and Press Operator
- Charge Room Operator
- Staple Operator
- Extrusion Machine Cleaner
- Extrusion Floor Buffer
- Extrusion Vacuum Cleaner Operator
- Extrusion Mechanical Service
- Extrusion Janitor/Janitress

**Table 2**
**Coding System for Work History Abstracts**

| Job Title | Job Code |
|---|---|
| Jet Wiper* | 12 |
| Extrusion Doffer* | 13 |
| Mixing & Press Operator* | 22 |
| Charge Room Operator* | 23 |
| Staple Operator* | 33 |
| Textile Department (all jobs) | 41 |
| Jet Assembler | 61 |
| Physical Analysis Lab | 62 |
| Bobbin Buffer, Bobbin Stores Operator, Bobbin Stores Service Operator, Cloth Cutter, Transport Cleaning & Repair | 71 |
| Cellulose Department (all jobs) | 81 |
| Air Conditioner Cleaning/Repair Operator | 101 |
| Electrician | 105 |
| Machinist | 109 |
| Pipefitter | 115 |
| Welder | 118 |
| Other Jobs (utility) | 132 |
| CC Mechanical Service | 141 |
| Extrusion Machine Cleaner*, Extrusion Mechanical Service*, Extrusion Vacuum Cleaner Operator*, Extrusion Floor Buffer*, Extrusion Janitor/Janitress* | 151 |
| Jobs not otherwise specified | 199 |

* Indicates jobs used by Ott to select the cohort

**Table 3**

**Comparison of a Work History Transcription and a Work History Abstract**

| TRANSCRIPTION | | ABSTRACT | |
|---|---|---|---|
| JOB TITLE | DATES | CODE[a] | DATES |
| Extrusion Doffer[b] | 09/09/49 - 09/22/55 | 13 | 09/49 - 06/77 |
| Terminated | 09/23/55 - 07/16/56 | | |
| Extrusion Doffer[b] | 07/17/56 - 01/19/60 | | |
| Jet Assembly--Extrusion[c] | 01/20/60 - 04/09/60 | | |
| Extrusion Doffer[b] | 04/10/60 - 03/19/73 | | |
| Extrusion Mechanical Service[b,c] | 03/20/73 - 05/13/73 | | |
| Extrusion Doffer[b] | 05/14/73 - 02/23/74 | | |
| Jet Wiper--Extrusion[b,c] | 02/24/74 - 03/11/74 | | |
| Extrusion Doffer[b] | 03/12/74 - 05/13/84 | | |
| Terminated | 05/14/84 | | |

[a] Ott Study Codes Key
13 - Doffer

[b] Exposed to methylene chloride according to the study by Ott et al. Scandinavian Journal of Work, Environment, and Health 1983;9 (Suppl. 1):1-16.

[c] The coding scheme devised by Ott included separate codes for Jet Assemblers (61), Extrusion Mechanical Service (151), and Jet Wiper (12). However, in this case these jobs were given the code for doffer (13).

**Table 4**

**Comparison of a Work History Transcription and a Work History Abstract**

| TRANSCRIPTIONS | | ABSTRACTS | |
|---|---|---|---|
| JOB TITLE | DATES | CODE[a] | DATES |
| Extrusion Mechanical Service[b] | 01/12/60 - 08/24/61 | 151 | 01/60 - 11/63 |
| Furloughed | 08/25/61 - 11/19/61 | | |
| Textile Mechanical Service | 11/20/61 - 12/03/61 | | |
| Extrusion Mechanical Service[b] | 11/04/61 - 05/02/63 | | |
| Furloughed | 05/03/63 - 11/21/63 | | |
| Textile Mechanical Service | 11/22/63 - 10/31/64 | 41 | 11/63 - 11/64 |
| Extrusion Mechanical Service[b] | 11/01/64 - 11/23/74 | 151 | 11/64 - 06/77 |
| Furloughed | 11/24/74 - 01/26/75 | | |
| Extrusion Mechanical Service[b] | 01/27/75 - 07/07/81 | | |
| Terminated | 07/08/81 | | |

[a] Ott Study Codes Key
- 151 - Extrusion Machine Cleaner,Extrusion Mechanical Service Extrusion Vacuum Cleaning Operator,Extrusion Floor Buffer, Extrusion Janitor/Janitress
- 41 - Textile Department - all jobs

[b] Exposed to methylene chloride according to the study by Ott et al.Scandinavian Journal of Work, Environment, and Health 1983;9 (Suppl. 1):1-16.

**Table 5**

**Ranges of Eight Hour Time-Weighted Average Solvent Exposure for Selected Jobs[a]**

| Job Title | # of workers monitored | $CH_2Cl_2$[b] (ppm) | Methanol (ppm) | Acetone (ppm) |
|---|---|---|---|---|
| Doffer | 97 | <1-690 | <3-50 | 20-1570 |
| Jet Wiper | 35 | 60-580 | 3-60 | 40-1600 |
| Staple Operator | 19 | 60-470 | 5-40 | 10-1100 |
| Extrusion Janitor | 2 | 130, 160 | 5, 9 | 980, 1140 |
| Extrusion Mechanical Service | 2 | 120, 130 | 5, 7 | 980, 1160 |
| Charge Room Operator | 18 | 10-1700 | <3-140 | 10-800 |
| Mixing/Press Operator | 4 | 230-900 | 30-110 | 10-60 |

[a] Data from: Williams PR, Bronson JM, Rapp DE et al. " A comprehensive industrial hygiene survey for exposure to airborne methylene chloride , methanol and acetone vapors, oil mist and carbon monoxide concentrations , at the Celanese Fibers Company, Celco plant, Narrows, West Virginia, and Celriver plant, Rock Hill, South Carolina, From September, 1977 to February, 1978." Dow Chemical, September 12, 1978. Table 2.

[b] Methylene chloride

**Table 6**

**Ranges of Eight Hour Time-Weighted Average Solvent Exposures for Doffers and Jet Wipers by Block[a]**

| | Doffer | | Jet Wiper | |
|---|---|---|---|---|
| | Block 1 | Block 2 | Block 1 | Block 2 |
| $CH_2Cl_2$ (ppm) | <1-350 | 320-690 | 60-230 | 240-580 |
| Methanol (ppm) | <3-30 | 20-50 | 3-10 | 20-60 |
| Acetone (ppm) | 570-1570 | 20-680 | 590-1600 | 40-550 |

[a] Data from: Williams PR, Bronson JM, Rapp DE et al. " A comprehensive industrial hygiene survey for exposure to airborne methylene chloride , methanol and acetone vapors, oil mist and carbon monoxide concentrations , at the Celanese Fibers Company, Celco plant, Narrows, West Virginia, and Celriver plant, Rock Hill, South Carolina, From September, 1977 to February, 1978." Dow Chemical, September 12, 1978. Table 2.

**Table 7**

**$CH_2Cl_2$ Monitoring Data - Latter Half of 1972[a]**

| | Methylene Chloride (ppm) by Month | | | | | |
|---|---|---|---|---|---|---|
| Job Title/Location | July | August | September | October | November | December |
| Doffer/Block 1 | 597 | 690 | 573 | 559 | 468 | 622 |
| Doffer/Block 2 | 461 | ----- | 486 | 370 | 868 | 721 |
| Jet Wiper/Block 1 | 756 | ----- | ----- | ----- | ----- | ----- |
| Jet Wiper/Block 2 | 361 | 614 | ----- | 566 | ----- | 562 |

[a] Data provided by Norman Culbertson, Superintendent of Environmental and Industrial Hygiene and Safety, Hoechst Celanese Celriver Plant.

**Table 8**

**Methylene Chloride Exposure Classification Scheme**

Greatest Exposure

- Doffer (<1-690)*
- Jet Wiper (60-580)*
- Press & Mix Operator (230-900)*
- Charge Room Operator (10-1700)*

Intermediate Exposure

- Staple Operator (60-470)*
- Janitor/Janitress (130, 160)*
- Extrusion Mechanical Service (120, 130)*
- Extrusion Machine Cleaner (510)*
- Jet Assembler (10-90)*
- Extrusion Floor Buffer, Extrusion Vacuum Cleaner Operator NA**
- Other Jobs in Preparation or Extrusion NA**

Least Exposure

- All Other Jobs NA**

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* Indicates the range of methylene chloride levels as reported in: Williams PR, Bronson JM, Rapp DE et al. Dow Chemical, September 12, 1978. Table 2.

** Indicates that data were not available.

**Table 9**

**Observed and Expected Numbers of Deaths from Selected Causes**
**Through 9/1/86**
**Greatest Exposure**

| | Obs. | Exp.[1] | SMR | 95% C.I.[2] |
|---|---|---|---|---|
| All Causes | 59 | 76.16 | 0.76 | 0.59, 0.99 |
| Neoplasms: | | | | |
| Buccal Cavity/Pharynx | 1 | 0.46 | 2.19 | 0.11, 10.72 |
| Biliary Passages & Liver | 2 | 0.45 | 4.43 | 0.75, 14.68 |
| Melanoma | 1 | 0.53 | 1.89 | 0.09, 9.31 |
| Bronchus, Trachea & Lung | 4 | 5.38 | 0.74 | 0.24, 1.79 |
| Breast | 1 | 2.97 | 0.34 | 0.02, 1.66 |
| Pancreatic | 0 | 0.80 | 0.00 | 0.00, 3.75 |
| Accidents | 8 | 6.78 | 1.18 | 0.55, 2.24 |
| Hypertension Without Heart Disease | 0 | 0.23 | 0.00 | 0.00, 13.03 |
| Cerebrovascular Disease | 2 | 4.28 | 0.47 | 0.08, 1.54 |
| Ischemic Heart Disease | 13 | 17.02 | 0.76 | 0.43, 1.27 |
| Non-malignant Respiratory Disease | 3 | 3.15 | 0.95 | 0.24, 2.59 |
| Suicides | 3 | 2.86 | 1.05 | 0.27, 2.86 |

[1] Expected deaths calculated from York County, S.C. rates.

[2] Exact confidence intervals calculated by mid-p method.
(Miettinen OS. Comment. J Amer Stat Assn 1974; 69:380-2)

**Table 10**

**Observed and Expected Numbers of Deaths from Selected Causes Through 9/1/86 Intermediate Exposure**

| | Obs. | Exp.[1] | SMR | 95% C.I.[2] |
|---|---|---|---|---|
| All Causes | 63 | 64.15 | 0.98 | 0.76, 1.26 |
| Neoplasms: | | | | |
| Buccal Cavity/Pharynx | 1 | 0.40 | 2.50 | 0.13, 12.33 |
| Biliary Passages & Liver | 2 | 0.24 | 8.25 | 1.40, 27.53 |
| Melanoma | 1 | 0.34 | 2.98 | 0.15, 14.51 |
| Bronchus, Trachea & Lung | 4 | 4.69 | 0.85 | 0.27, 2.06 |
| Breast | 1 | 0.32 | 3.10 | 0.16, 15.41 |
| Pancreatic | 1 | 0.74 | 1.36 | 0.07, 6.67 |
| Accidents | 13 | 5.61 | 2.32 | 1.29, 3.86 |
| Hypertension Without Heart Disease | 2 | 0.39 | 5.18 | 0.86, 16.94 |
| Cerebrovascular Disease | 3 | 4.56 | 0.66 | 0.17, 1.79 |
| Ischemic Heart Disease | 18 | 17.06 | 1.06 | 0.65, 1.64 |
| Non-malignant Respiratory Disease | 1 | 2.86 | 0.35 | 0.02, 1.72 |
| Suicides | 0 | 1.89 | 0.00 | 0.00, 1.59 |

[1] Expected deaths calculated from York County, S.C. rates.

[2] Exact confidence intervals calculated by mid-p method. (Miettinen OS. Comment. J Amer Stat Assn 1974; 69:380-2)

## Table 11

**Duration of Employment in Jobs Held by Biliary Cancer Cases and Other Cohort Members Who Terminated Since January 1, 1979**

| | Ever | | ≥ 1 yr. | | ≥ 10 yr. | |
|---|---|---|---|---|---|---|
| | Cases N=3 (%) | Others N=116 (%) | Cases N=3 (%) | Others N=116 (%) | Cases N=3 (%) | Others N=116 (%) |
| Doffer[1] | 2 (67) | 69 (60) | 1 (33) | 52 (45) | 1 (33) | 31 (27) |
| Jet Assembler | 1 (33) | 1 (1) | 0 (0) | 1 (1) | 0 (0) | 0 (0) |
| Jet Wiper[1] | 1 (33) | 23 (20) | 0 (0) | 21 (18) | 0 (0) | 15 (13) |
| P.A. Lab Operator | 1 (33) | 3 (3) | 1 (33) | 2 (2) | 1 (33) | 0 (0) |
| Extrusion Mechanical Service Operator[1] | 2 (67) | 19 (16) | 1 (33) | 18 (16) | 1 (33) | 13 (11) |
| Textile Mechanical Service Operator | 1 (33) | 8 (7) | 1 (33) | 3 (3) | 0 (0) | 2 (2) |

[1] Characterized by Ott et al. as exposed.

## Table 12

**Observed and Expected Numbers of Deaths from Selected Causes Through 9/1/86 Preparation Area Jobs**

| | Obs. | Exp.[1] | SMR | 95% C.I.[2] |
|---|---|---|---|---|
| All Causes | 11 | 14.18 | 0.78 | 0.41, 1.35 |
| Bronchus, Trachea, & Lung | 1 | 1.17 | 0.85 | 0.04, 4.22 |
| Accidents | 1 | 1.48 | 0.68 | 0.03, 3.33 |
| Cerebrovascular Disease | 1 | 0.75 | 1.33 | 0.07, 6.58 |
| Ischemic Heart Disease | 5 | 3.91 | 1.28 | 0.47, 2.83 |
| Suicides | 1 | 0.54 | 1.84 | 0.09, 9.13 |
| Other | 2 | 1.46 | 1.37 | 0.23, 4.53 |

[1] Expected deaths calculated from York County, S.C. rates.

[2] Exact confidence intervals calculated by mid-p method. (Miettinen OS. Comment. J Amer Stat Assn 1974; 69:380-2)

# ISSUES IN MORTALITY ASCERTAINMENT IN A COHORT OF CELLULOSE FIBER PRODUCTION WORKERS

**Abstract**

In this paper we examine three issues concerning the ascertainment of mortality in occupational cohorts using data from the mortality follow-up of a cohort of 1,271 cellulose fiber production workers exposed to methylene chloride: 1) the use of the SSA decedent files as the primary source of vital status data in the absence of individualized follow-up, 2) the use of death certificates that have been collected by the company for purposes other than epidemiologic research as a data source for preliminary analyses of the mortality of occupational cohorts, and 3) differential accuracy of mortality ascertainment according to exposure status as a potential source of bias in occupational cohort mortality studies. In this cohort, contrary to expectation, SSA follow-up compared favorably with individualized follow-up. Death certificates on file with the employer did not accurately reflect the mortality of the cohort. Differential completeness of mortality ascertainment related to exposure was observed when an attempt was made to expand the cohort to include workers who had not been exposed to methylene chloride. Race and length of employment appeared to be related to completeness of mortality ascertainment.

## Introduction

Complete ascertainment of mortality is an important determinant of the informativeness of retrospective cohort mortality studies of infrequent causes of death, such as rare malignancies, when the number of cases is small. A recent retrospective cohort study (1) of the mortality of cellulose fiber production workers exposed to methylene chloride provided an opportunity to examine three issues in mortality ascertainment that arise in such studies. Therefore this study had three objectives:

1) **To examine the performance of the SSA decedent files as the primary source of vital status data in the absence of individualized follow-up.** The method of choice for the ascertainment of vital status is individualized follow-up of each cohort member via personal contact with the cohort member or a relative, through the use of data sources such as motor vehicle registries, and by the use of mortality registries such as the Social Security Administration (SSA) or, for deaths since 1979, the National Death Index (NDI) (2). However, in the interest of reducing the length or cost of the study, investigators sometimes choose to ascertain mortality using less rigorous approaches. In the most recent study of the cellulose fiber production workers cohort, cohort members were not followed individually to ascertain their mortality, but rather the cohort roster was submitted to both the SSA and NDI and all cohort members not identified

as dead from these sources were considered to be alive as of the end of the study. The investigators acknowledged the possibility that mortality had been underascertained, citing several studies (3,4) that found rates of underascertainment of known deaths by NDI and SSA to be on the order of 10 to 20 percent. In this paper we compare the completeness of mortality ascertainment using the decedent files of the SSA with the results achieved using individualized follow-up plus the SSA.

2) **To examine the characteristics of death certificates that have been collected by the company for purposes other than epidemiologic research with respect to their use as a data source for preliminary analyses of the mortality of occupational cohorts.** As a preliminary step in the epidemiologic investigation of a suspected occupational hazard, death certificates collected by company medical or benefits departments for administrative or other purposes are sometimes analyzed to determine whether there is evidence of excess mortality from selected causes of death. The preliminary analysis may take the form of a simple count of deaths from selected causes, or a "proportional mortality" study, in which the proportion of deaths from a given cause is compared to an expected proportion derived from general population data. If the preliminary analysis shows evidence of excess mortality then a cohort or case-control

study may be planned. The rationale behind this approach is that the death certificates collected by the company constitute a sample that accurately represents the distribution of the deaths that would be observed in a cohort assembled from among the employees. In this paper we examine the validity of this approach, using data from the cellulose fiber production workers cohort.

3) **To describe an example of differential accuracy of mortality ascertainment according to exposure status and to examine its causes and its potential to produce bias in occupational cohort mortality studies.** The cellulose fiber workers cohort was restricted to employees who had worked for at least three months in jobs that entailed exposure to methylene chloride; therefore, its mortality could be compared only with an "external" population of people who did not work at the plant (e.g., the population of York County, SC) (2). A general population is the standard type of comparison population in occupational epidemiology. Experience has shown, however, that employed populations often have more favorable mortality experience than populations that include unemployed people, presumably because healthy people are preferentially selected for employment, the "healthy worker effect" (5). Much of the bias due to the healthy worker effect can be avoided by making "internal" comparisons

between exposed and unexposed workers within the cohort. It is, however, essential that the completeness of mortality ascertainment not differ between the exposed and unexposed subcohorts; such differences could produce spurious positive or negative associations. In this paper we describe an example of such differential ascertainment.

## Methods

### Study Populations

**The original cellulose fiber production workers cohort.** The original cellulose fiber production workers cohort ("original cohort") was assembled by Dow Chemical Company investigators, and comprises 1,271 workers who were engaged in the production of cellulose fiber at a plant in the Southeastern United States. Cohort members were required to have worked for at least three months between January 1, 1954 and June 1, 1977 in jobs that entailed exposure to the solvent, methylene chloride. The original cohort is predominately white and approximately half of its members are women (Table 1). Ott, et al. (6) studied the mortality of the cohort through June 1977 ("Dow Study"). We recently extended the follow-up of the original cohort through September 1, 1986 ("Current Study").

**The expanded cellulose fiber workers cohort.** To enable internal comparisons, we expanded the original cellulose fiber workers cohort. The expanded cellulose fiber workers cohort ("expanded cohort") comprises hourly workers at the Rock Hill plant employed for at least three months between January 1, 1954 and September 1, 1986, who were not included in the original cellulose fiber workers cohort. Thus, the expanded cohort includes workers who were exposed after 1977 ("additional exposed"), as well as workers who did not hold jobs that entailed exposure to methylene chloride for at least three months before 1977 ("unexposed").

We assembled the expanded cohort using records from Personnel and Benefits Departments. Temporary clerical staff hired by the company abstracted from card files in the Personnel Department name, Social Security number, gender, dates of hire and termination and last job held for people who terminated employment since the plant opened in 1948. We obtained from the Benefits department a data tape of employees who terminated after 1966 or who were actively employed as of September 1, 1986. These data files contained name, Social Security number, date of birth, date of termination, gender, race, and employment status as of September 1, 1986. For active employees, we used a recently established automated data base to provide data on race, gender, job title as of September 1, 1986, and date of hire. We identified from these sources 7,998 employees not included in the original cohort. After excluding employees who worked less than three months, for whom dates of hire and termination were

unavailable, who terminated before January 1, 1954, and who were not hourly employees, the expanded cohort available for analysis comprised 5,220 employees.

In the past, complete personnel files were not retained by the plant for employees who had been terminated for more than five years. Instead, certain items of information were abstracted onto file cards that were used to assemble the expanded cohort. Apparently, however, file cards were not available for every employee. Eighteen per cent (234 people) of the original cellulose fiber workers cohort were not identified in the files of either the Personnel or Benefits Departments. Later, a sample of these 234 subjects was submitted to the Personnel Department, and the staff was able to locate about 25% of them. We infer that the personnel records available to us were incomplete, and that some underascertainment also occurred due to omission of existing records. If underascertainment was related to exposure then rate ratio and rate difference measures could be biased. If underascertainment was not related to exposure then rate difference measures would be biased towards the null and rate ratio measures would not be biased.

The abstracted personnel cards used to assemble the expanded cohort did not contain complete information on birth date, age or race, nor were detailed work histories available for employees who had been terminated for more than five years. Data on race were missing for 2,634 members of the cohort, data on gender were missing for 63

members, first names were unavailable for 1,232 people, and date of birth was missing for 3,011 subjects. Complete data on name, age, race, and gender were available for all original cohort members, these data having been obtained in 1977 from original records, that have since been destroyed. In summary, the records available to assemble the expanded cohort did not contain as much information as the records used to assemble the original cohort.

Since the Social Security Administration can provide the years when Social Security numbers were obtained, date of birth can be determined from the Social Security number if the age at which subjects received their Social Security numbers is known (7). These dates were known for members of the original cohort, and we used this information to estimate birth dates for employees not included in the original cohort. For 16 subjects for whom this procedure produced an estimated age at hire of less than 14 years, the minimum age at hire in the early days of the plant's operation, we corrected the age at hire to be 14.

**Characterization of exposure of the expanded cohort to methylene chloride.** For the expanded cohort, exposure to methylene chloride was classified from the last job held, as obtained from the abstract of the personnel record for terminated employees, or from automated data files for active employees. Exposure classification was conducted under the direction of the Environmental and Industrial Hygiene Department for subjects

identified through Personnel files, or by our staff for subjects identified from Benefits files. All questions that arose with respect to our coding of jobs also were referred to the Environmental and Industrial Hygiene Department. The person-time contributed by employees in the expanded cohort was classified as exposed if their most recent job was held for at least three months and if it indicated substantial exposure to methylene chloride. The job titles characterized by plant representatives as involving substantial methylene chloride exposure were very similar to the job titles used for the same purpose by Dow investigators. For 234 original cohort members, and 40 employees who were not included in the original cohort, an exposure code could not be assigned because the most recent job held was unavailable for these subjects. Table 2 presents the number of subjects, deaths and person-years in the original cellulose fiber workers cohort and the expanded cohort, including the additional exposed and the unexposed. Approximately 93% of the person-time experience contributed by the expanded cohort was classified as unexposed.

Since exposure status for the expanded cohort was classified according to each employee's last job held, it is possible that a subject's assigned exposure status could be partly in error. For example, consider a hypothetical subject who worked for twenty years in an exposed job before transferring to an unexposed job one year before termination. For this person, all 21 years of employment would have been classified as unexposed based on his last job, when in fact only 5% of that time was unexposed. To

estimate the magnitude of this type of error, we examined the representativeness of the last job among employees with complete work history information. We located in Personnel Department records complete work histories for a group of 955 hourly employees who terminated between 1979 and 1985. Twenty of these employees had not been identified from other data sources. The work history records contained for each employee information on name, Social Security number, and the start and stop dates for each job held listed in chronological order. These records constituted a source of more accurate exposure information against which we could contrast the accuracy of exposure classification using only the last job.

**Mortality Ascertainment.**

**Dow Study.** Dow Chemical Company investigators followed the original cellulose fiber workers cohort through June 30, 1977 (6). Dow investigators used company records to ascertain those currently working or receiving retirement benefits, as well as any decedents on file with the company. The vital status of terminated employees was sought first by means of telephone and mail contact, and motor vehicle registration records. The names and Social Security numbers of cohort members whose status had not been ascertained from company records or personal tracing were submitted to the SSA. Those not identified as deceased by the SSA were considered lost to follow-up, and treated as either alive or deceased in separate analyses. The Dow Chemical Company made available to us a tape containing data from their study. These data

include for each cohort member the Social Security number, first name, last name, date of death, and the underlying cause of death coded according to the Eighth Revision of the International Classification of Diseases. The death certificates obtained by the Dow investigators were unavailable, so that neither the correct coding of the cause of death nor the presence of other causes of death on the certificate could be examined.

**Current Study.** We ascertained the mortality of both the original and expanded cohorts through September 1, 1986 (1). Mortality ascertainment was conducted using the decedent files of the Social Security Administration (SSA) and, for deaths occurring since 1979, the National Death Index (NDI). When we extended the follow-up of the original cohort through September 1, 1986 we submitted the entire cohort roster to the SSA, including those identified as deceased in the Dow study. We did not submit to NDI the names of 1,232 members of the expanded cohort who did not meet NDI requirements because the first name was unknown, and three subjects were not submitted to the NDI or the SSA because the last name was unknown. For 150 expanded cohort members for whom we obtained two last names, and for 1,382 women for whom maiden names were available, we submitted these subjects to the SSA under each name. No subjects were submitted to NDI under multiple names because of the additional cost involved. Finally, the Medical Department provided us with all of the death certificates that had already been acquired by the plant Medical and Benefits Departments.

Lists of potential matches identified by the SSA or NDI were compared to the cohort roster. A cohort member was considered to have been identified as deceased by either mortality registry if both the first and last name (or maiden name, in the case of female cohort members) and social security number from the cohort roster matched the information provided by SSA or NDI. Cohort members not identified as deceased were considered to be alive as of the end of the follow-up period. In the case of deaths identified by NDI, death certificates were requested from the state in which the death was recorded. In the case of deaths identified by the SSA, certificates were requested from the state where the Social Security claim was filed. Because the plant is located in South Carolina near the North Carolina border, death certificates initially requested in one state but not found there, were requested of the other state. A nosologist who was unaware of the research hypothesis coded the primary and contributing causes of death listed on the death certificates according to the 9th Revision of the International Classification of Diseases (8). We opted to code to the 9th ICD revision rather than to the revision in effect at time of death for the sake of simplicity.

## Analyses and Results

**Completeness of mortality ascertainment in the original cohort: individualized follow-up plus SSA vs. SSA.** We compared the vital status of the original cohort through June, 1977 ascertained by Dow investigators via individual follow-up and SSA submission with vital status through June, 1977 ascertained by us via SSA submission (Table 1). Both

follow-ups revealed a total of 54 deaths. However, the original follow-up ascertained 37 deaths among white males and 11 deaths among white females, whereas 39 deaths among white males and 9 deaths among white females were observed in the later follow-up. This discrepancy results from the identification of different decedents in each follow-up. Each follow-up identified three individuals who were not identified as deceased by the other follow-up (Table 3). Two of the three decedents identified in only the earlier follow-up were female (females comprised 56% of all deaths in the cohort), whereas two of the three deaths identified in only the later follow-up were male.

Seven additional discrepancies were observed between the results of the two follow-ups (Table 3). In three cases the underlying cause of death in the Dow study was noted as a contributing cause in our study.

Table 4 presents the numbers of deaths from various causes through June 1977 found by each follow-up. In general, the two follow-ups produced very similar results. The Dow study identified seven deaths from cancers, whereas the most recent follow-up identified eight. The additional cancer death was a cancer of the central nervous system (ICD 191.9). The later follow-up identified a death from ovarian cancer (ICD 183.0) that had been classified in the original follow-up as a death from a malignancy of unspecified primary site (ICD 199.0). Both causes of death, unspecified primary site and ovarian cancer, appeared on the death certificate that obtained by the later follow-up. It is not

possible to determine whether the discrepant attribution of cause of death is due to differences in coding between coders in each follow-up or to different death certificates having been obtained.

**Characteristics of death certificates obtained by the company.** The follow-up of the original cohort through September 1, 1986 identified 122 deaths (1). The company Medical Department was in possession of the death certificates of 44 (31%) cohort members who died on or before September 1, 1986. We compared the characteristics of the deaths known to the company with those of the total deaths. In contrast to the total group of deaths in the original cohort, those deaths known to the Medical Department were more likely to be male (86% vs. 78%), and to have worked for the company for at least ten years (96% vs. 57%). All of the deaths known to the Medical Department died in either North or South Carolina, whereas 8% of all deaths in the cohort were registered in states other than North or South Carolina.

The Medical Department had in its possession 11 of 28 (39%) death certificates of cohort members who died of cancer. All four deaths from cancer of the liver and biliary tract were known to the Medical Department. However, none of the eight lung cancer deaths nor either of the deaths from ovarian cancer (coded as ICD 183.0) was on file with the Medical Department. Death certificates were on file with the Medical

Department for 14 of 31 (45%) cohort members who died from ischemic heart disease, and for 7 of 21 (33%) who died of accidental causes.

**Expansion of the cellulose fiber workers cohort: differential completeness of mortality ascertainment.** The purpose of expanding the cellulose fiber workers cohort was to increase the size of the original cohort, and to assemble an unexposed population for internal comparisons. Our approach to the analysis was two-fold: first, we planned to compare the mortality of the exposed portion of the expanded cohort (the additional exposed) with the U.S. and York County, South Carolina populations, and then we planned to combine the additional exposed with the original cohort to conduct internal comparisons among exposed and unexposed workers.

The effect of exposure on mortality controlling for the effects of age, calendar period, gender, and race was measured by computing standardized mortality ratios (SMRs) (9). Person-years of follow-up and observed deaths were cross-classified by:

- Five year age categories between 20 and 85+ years of age
- Five year calendar period categories between 1954 and 1986
- Two gender categories
- Two race categories: white and nonwhite

We derived expected numbers of deaths using the age-, calendar period-, gender-, and race-specific mortality rates of the U.S. population and the population of York County, SC, where most cohort members reside. Rates for neoplastic diseases were available from 1950 through 1985. Rates for non-neoplastic diseases were available from 1960 through 1985. We used the 1960 rates for the period from 1954 to 1959 for non-neoplastic causes of death. We used the 1985 rates for 1986 experience for all causes of death. The Occupational Cohort Mortality Analysis Program (OCMAP)(10), developed by the University of Pittsburgh, was used to apportion the person-time, derive the expected number of deaths and compute SMRs.

Table 6 presents observed and expected deaths and SMRs for the additional exposed based on York County rates. People whose race was unknown were classified first as white and then as nonwhite, so that two SMRs are presented for each cause of death. 18 deaths were observed in 6,623 person-years. Depending on the classification of people of unknown race, these data show an overall SMR from all causes of 0.41 to 0.57; deaths from cerebrovascular disease and heart disease contribute approximately half of these deficits.

Analysis of the additional exposed revealed a large overall deficit of mortality not evident in the original cohort, (i.e., the mortality rate was only slightly more than half of the expected rate). This deficit also was present in the unexposed portion of the

expanded cohort (Table 5). Subjects of unknown race were coded as white for this analysis. We observed 293 deaths in 91,500 person years with an overall SMR of 0.57. Decreased risks are apparent in all major categories of causes of death, including deaths from malignant neoplasms (SMR=0.67), deaths from heart disease (SMR=0.57), and external causes of death (SMR=0.51). These results appear to indicate underascertainment of deaths in the expanded cohort. Therefore, we explored further differences between the original cohort and the expanded cohort before combining these groups and conducting internal comparisons.

One possible explanation for the deficit relates to underascertainment of terminees. We could not locate personnel records for 18% of the original cohort, the majority of whom were terminees. We infer that personnel cards also were missing for other terminees who were not in the original cohort. Presumably, active employees were ascertained more completely from recently installed automated data files. Therefore, employees active at the end of the study may be more likely than terminees to appear in the expanded cohort, and they also are known to be alive. A cohort that preferentially includes people because they are alive will have an unusually favorable mortality experience. Therefore, incomplete records for terminees could be responsible for underascertainment of deaths in the expanded cohort. If this hypothesis were correct, the mortality deficits should not be apparent if we exclude active employees from the analysis.

We evaluated this hypothesis by computing SMRs for five major categories of death among terminees. For these analyses, mortality follow-up of employees begins at the date of termination rather than the date of hire. Table 7 shows the observed and expected numbers of deaths and SMRs for five categories of death in terminees of known race. While the deficit is ameliorated among the additional exposed, it is accentuated among the unexposed. Therefore, this hypothesis does not fully explain the observed deficits.

Another possible explanation for the mortality deficit in the expanded cohort is that the mortality searches conducted by the SSA and the NDI may not have been able to ascertain deaths in the expanded cohort as thoroughly as in the original cohort. We considered three specific reasons for underascertainment relating to differences between the original cohort and expanded cohort with regard to gender and race composition, duration of employment, and completeness of information. Deaths among women and blacks are less likely to be ascertained by both NDI and SSA than deaths among white males (4). Even in the original cohort, the SMR for all-cause mortality is lower for nonwhites (SMR = 0.57) than it is for whites (SMR = 0.91). If the proportional representation of women and/or blacks was greater among the expanded cohort than the original cohort, this might explain the discrepancy between cohorts in mortality ascertainment. We examined gender and race distributions in the two subcohorts. Whereas the gender distributions were identical, the race distributions show that

nonwhites comprise a larger proportion of the expanded cohort relative to the original cohort (Table 8). This imbalance would exist even if all of the subjects of unknown race were white.

Workers with less than one year of employment are often excluded from occupational cohorts, in part because they constitute a mobile group whose vital status is thought to be difficult to ascertain accurately. In Table 9, we present the distribution of the two cohorts by duration of employment. The expanded cohort has proportionally more subjects with less than one year of employment than the original cohort.

Lastly, the ability to identify deaths in the cohort from the NDI and SSA files depends in part on the amount of descriptive information available for the cohort. The records used to assemble the expanded cohort did not contain all of the information that was available from the records that were used to assemble the original cohort. The missing demographic data for the expanded cohort may be the most important source of noncomparability with the original cohort.

## Discussion

**Comparison of individualized follow-up plus SSA submission with SSA submission only.** We compared the performance of SSA submission plus individualized follow-up versus SSA submission alone on the completeness of vital status ascertainment through 1977 in

a cohort of cellulose fiber production workers. The results obtained by the two approaches were found to be quite similar, indicating that important underascertainment of mortality in the original cohort from 1954 through 1977 in the most recent study was unlikely. Since several studies have documented the satisfactory performance of the NDI with respect to completeness of ascertainment of mortality (3,4,11), it is unlikely that important underascertainment of mortality occurred for any interval during the risk period of the current study.

Curb, et al. (4) found that women in the Southern part of the United States were at particular risk of underascertainment of mortality by the SSA. The observation in our study that of the three deaths not ascertained by SSA submission alone two were women, is consistent with the finding of Curb, et al.

**Characteristics of death certificates obtained by the company.** The results of this study indicate that those death certificates on file with the employer may not provide neither complete nor a representative account of the mortality of occupational cohorts. It is of particular interest that certain causes of death, such as lung cancer and ovarian cancer, were missed entirely, while other causes of death, such as liver and biliary cancer, were ascertained completely. Further the study results indicate that the proportional distribution of causes of death in such samples cannot be expected to reflect the distribution of causes of death in the cohort.

**Differential completeness of mortality ascertainment.** Since deaths appear to have been ascertained more completely for the original cohort, and the original cohort contains most of the employees classified as exposed to methylene chloride, internal comparisons of the mortality rates between the exposed and the unexposed workers in the expanded cohort would have been biased. Specifically, internal comparison would erroneously have found excess deaths among employees exposed to methylene chloride simply because deaths were ascertained more completely for this group. An analysis that combined the original cohort with the additional exposed and compared this group with an external population would tend to underestimate the magnitude of any real excess that might exist, because mortality is underascertained in the additional exposed.

Owing to concerns about substantial mortality deficits in the expanded cohort, combined with the knowledge that a substantial amount of data from personnel records is unavailable for this group, we did not combine the exposed portion of the expanded cohort with the original cohort, nor did we conduct internal comparisons. In consideration of these limitations of the expanded cohort, and the fact that the additional exposed contributed only 18 deaths to the total cohort, it is doubtful that further analyses of the expanded cohort would enhance appreciably the informativeness of the analyses of the original cohort.

Our attempt to expand the cellulose fiber workers cohort to enable internal comparisons indicates that investigators should consider the possibility that low SMRs for total mortality and for important subgroups of causes of death may indicate differential completeness of mortality ascertainment in particular subcohorts, rather than assume uncritically that the low SMRs are the result of the healthy worker effect.

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TABLE 1

Vital Status Through 1977
by Gender and Race

| | Individual Follow-up + SSA[1] | | | SSA | | |
|---|---|---|---|---|---|---|
| | Dead | Alive | Total | Dead | Alive | Total |
| Men | | | | | | |
| White | 37 | 450 | 487 | 39 | 449 | 488 |
| Non-white | 6 | 58 | 64 | 6 | 58 | 64 |
| Women | | | | | | |
| White | 11 | 604 | 615 | 9 | 605 | 614 |
| Non-white | 0 | 105 | 105 | 0 | 105 | 105 |
| TOTAL | 54 | 1217 | 1271 | 54 | 1217 | 1271 |

[1] Ott MG, Skory LK, Holder BB et al. Health evaluation of employees occupationally exposed to methylene chloride. Scand J Work Environ Health 1983;9(suppl 1):1-16.

TABLE 2

Number of Subjects, Deaths, and Person-Years
in the Original Cohort and the Expanded Cohort

| | No. Subjects | Deaths | Person-years |
|---|---|---|---|
| Original Cohort | 1,271 | 122 | 29,960 |
| Expanded Cohort | 5,220 | 312 | 98,967 |
| Additional Exposed | 486 | 18 | 6,623 |
| Not Exposed | 4,694 | 293 | 91,500 |
| Unknown Exposure | 40 | 1 | 844 |

**TABLE 3**

Discrepancies between Follow-ups of the Original Cellulose Fiber Workers Cohort Through June 1977

| | Ind. Follow-Up + SSA | SSA | |
|---|---|---|---|
| Sex/Race | Primary Cause (ICD8) | Primary Cause (ICD9) | Secondary Cause (ICD9) |
| 1. Female/White | Accident (890) | (Alive) | NA |
| 2. Male/White | Suicide (953) | (Alive) | NA |
| 3. Female/White | Acute MI (410) | (Alive) | NA |
| 4. Male/White | (Alive) | Motor Neuron Dis.(335) | (486) |
| 5. Female/White | (Alive) | Brain Cancer (191) | Malignant Neoplasm Site Unspec.(199) |
| 6. Male/White | (Alive) | Acute MI (410) | --- |
| 7. Male/White | Intestinal Obstruction (560) | Acute MI (410) | Intestinal Obstr. (557) |
| 8. Male/White | Unknown Cause (999) | Acute MI (410) | --- |

**TABLE 3 (cont.)**

Discrepancies between Follow-ups of the Original Cellulose Fiber Workers Cohort
Through June 1977

| | Ind. Follow-Up + SSA | SSA | |
|---|---|---|---|
| ID/Sex/Race | Primary Cause (ICD8) | Primary Cause (ICD9) | Secondary Cause (ICD9) |
| 9. Female/White | Pneumonia (486) | Unknown Cause (999) | --- |
| 10. Male/Black | Hypertensive Heart Disease (402) | Unknown Cause (999) | --- |
| 11. Female/White | Malignant Neoplasm Site Unspec. (199) | Ovarian Cancer (183) | Malignant Neoplasm Site Unspec. (199) |
| 12. Female/White | Chronic Ischemic Heart Disease (412) | Cystic Kidney Disease (753) | Chronic Ischemic Heart Disease (414) |
| 13. Male/Black | Chronic Ischemic Heart Disease (412) | Hypertensive Heart Disease (402) | --- |

**TABLE 4**

Comparison of the Results of Follow-Ups Through June 1977
for Major Causes of Mortality

| Cause | White Males | | Black Males | | White Females | | Total | |
|---|---|---|---|---|---|---|---|---|
| | Ind. F.U. + SSA | SSA | Ind. F.U. + SSA | SSA | Ind. F.U. + SSA | SSA | Ind. F.U. + SSA | SSA |
| All Causes | 37 | 39 | 6 | 6 | 11 | 9 | 54 | 54 |
| Malignant Neoplasms | 5 | 5 | 0 | 0 | 2 | 3 | 7 | 8 |
| Ischemic Heart Dis. | 10 | 12 | 2 | 1 | 2 | 0 | 14 | 13 |
| External Causes | 12 | 11 | 2 | 2 | 4 | 3 | 18 | 16 |
| Unknown Causes | 3 | 3 | 0 | 1 | 1 | 1 | 4 | 5 |

TABLE 5

Observed and Expected Numbers of Deaths
in the Unexposed Through 9/1/86[1]

| Cause of Death | Observed | Expected[2] | SMR[2] |
|---|---|---|---|
| All Causes of Death | 293 | 518.04 | 0.57 |
| Tuberculosis | 0 | 2.18 | --- |
| All Malignant Neoplasms | 72 | 107.36 | 0.67 |
| Neoplasms: | | | |
| Buccal Cavity & Pharynx | 0 | 3.36 | --- |
| Digestive Organs & Peritoneum | 16 | 24.56 | 0.65 |
| Esophagus | 1 | 3.51 | 0.29 |
| Stomach | 2 | 2.96 | 0.68 |
| Large Intestine | 3 | 7.73 | 0.39 |
| Rectum | 1 | 1.15 | 0.87 |
| Biliary Passages & Liver | 2 | 2.41 | 0.83 |
| Pancreas | 6 | 6.15 | 0.98 |
| All Other Digestive Organs | 1 | 0.36 | 2.81 |
| Respiratory System | 24 | 31.84 | 0.75 |
| Larynx | 1 | .92 | 1.08 |
| Bronchus, Trachea, Lung | 23 | 30.42 | 0.76 |
| All Other Respiratory | 0 | 0.48 | --- |
| Breast | 7 | 10.17 | 0.69 |
| All Uterine Cancers | 0 | 4.60 | --- |
| Cervix Uteri | 0 | 3.60 | --- |
| Other Female Genital Organs | 3 | 3.22 | 0.93 |
| Prostate | 1 | 3.18 | 0.31 |
| Testes & Other Male Genital | 0 | 0.37 | --- |
| Kidney | 1 | 1.51 | 0.66 |
| Bladder & Other Urinary Tract | 2 | 1.16 | 1.73 |
| Malignant Melanoma of the Skin | 0 | 1.77 | --- |
| Eye | 0 | 0.09 | --- |
| Central Nervous System | 5 | 4.54 | 1.10 |
| Thyroid Gland & Other Endocrine | 0 | 0.29 | --- |
| Bone | 0 | 0.25 | --- |
| All Lymphatic & Hematologic | 10 | 9.17 | 1.09 |
| Lymphosarcoma & Reticulosarcoma | 3 | 1.69 | 1.78 |
| Hodgkins Disease | 0 | .69 | --- |
| Leukemia & Aleukemia | 4 | 3.28 | 1.23 |
| All Other Lymphopoietic System | 3 | 3.52 | 0.85 |
| All Other Malignant Neoplasms | 3 | 7.62 | 0.39 |
| Benign Neoplasms | 1 | 2.04 | 0.49 |
| Diabetes Mellitus | 5 | 10.54 | 0.47 |
| Cerebrovascular Disease | 7 | 40.49 | 0.17 |
| All Heart Disease | 95 | 166.59 | 0.57 |
| Rheumatic Heart Disease | 4 | 3.84 | 1.04 |
| Ischemic Heart Disease | 77 | 115.37 | 0.67 |
| Chronic Disease of Endocardium | 0 | 2.60 | --- |
| Hypertension with Heart Disease | 2 | 6.39 | 0.31 |
| All Other Heart Disease | 12 | 25.48 | 0.47 |
| Hypertension w/o Heart Disease | 0 | 4.54 | --- |
| Non-Malignant Respiratory Disease | 14 | 22.79 | 0.61 |
| Influenza & Pneumonia | 5 | 9.15 | 0.55 |
| Bronchitis, Emphysema, Asthma | 2 | 5.92 | 0.34 |
| Bronchitis | 0 | 0.47 | --- |
| Emphysema | 2 | 4.27 | 0.47 |
| Asthma | 0 | 1.21 | --- |
| Other Non-Malignant Resp. Disease | 7 | 7.39 | 0.95 |

**(Table continues on next page)**

TABLE 5 continued

Observed and Expected Numbers of Deaths
in the Unexposed Through 9/1/86[1]

| Cause of Death | Observed | Expected[2] | SMR[2] |
|---|---|---|---|
| Ulcer of Stomach & Duodenum | 0 | 3.01 | --- |
| Cirrhosis of Liver | 11 | 13.18 | 0.84 |
| Nephritis & Nephrosis | 1 | 7.58 | 0.13 |
| All External Causes of Death | 41 | 80.57 | 0.51 |
| Accidents | 21 | 48.05 | 0.44 |
| Motor Vehicle Accidents | 10 | 24.56 | 0.41 |
| All Other Accidents | 11 | 23.38 | 0.47 |
| Suicides | 10 | 12.86 | 0.78 |
| Homicides & Other External | 10 | 18.30 | 0.55 |
| All Other Causes of Death | 25 | 64.06 | 0.39 |

[1] Total = 4694 persons, 91,500.2 person-years.

[2] Expected deaths calculated from York County, S.C. rates for whites.

TABLE 6

Observed and Expected Numbers of Deaths
in the Additional Exposed Through 9/1/86[1]

| Cause of Death | Observed | Expected[2] | SMR[2] | Expected[3] | SMR[3] |
|---|---|---|---|---|---|
| All Causes of Death | 18 | 31.5 | 0.57 | 44.5 | 0.41 |
| Tuberculosis | 0 | 0.14 | ---- | 0.26 | ---- |
| All Malignant Neoplasms | 4 | 6.62 | 0.61 | 7.84 | 0.51 |
| Neoplasms: | | | | | |
| Buccal Cavity & Pharynx | 0 | 0.19 | ---- | 0.26 | ---- |
| Digestive Organs & Peritoneum | 1 | 1.46 | 0.69 | 1.89 | 0.53 |
| Esophagus | 0 | 0.23 | ---- | 0.37 | ---- |
| Stomach | 0 | 0.20 | ---- | 0.30 | ---- |
| Large Intestine | 1 | 0.45 | 2.23 | 0.43 | 2.31 |
| Rectum | 0 | 0.06 | ---- | 0.07 | ---- |
| Biliary Passages & Liver | 0 | 0.14 | ---- | 0.17 | ---- |
| Pancreas | 0 | 0.35 | ---- | 0.49 | ---- |
| All Other Digestive Organs | 0 | 0.02 | ---- | 0.04 | ---- |
| Respiratory System | 2 | 1.93 | 1.03 | 1.91 | 1.05 |
| Larynx | 0 | 0.06 | ---- | 0.09 | ---- |
| Bronchus, Trachea, Lung | 2 | 1.84 | 1.09 | 1.77 | 1.13 |
| All Other Respiratory | 0 | 0.03 | ---- | 0.05 | ---- |
| Breast | 0 | 0.70 | ---- | 0.89 | ---- |
| All Uterine Cancers | 0 | 0.31 | ---- | 0.67 | ---- |
| Cervix Uteri | 0 | 0.25 | ---- | 0.53 | ---- |
| Other Female Genital Organs | 0 | 0.24 | ---- | 0.31 | ---- |
| Prostate | 0 | 0.17 | ---- | 0.25 | ---- |
| Testes & Other Male Genital | 0 | 0.02 | ---- | 0.02 | ---- |
| Kidney | 0 | 0.08 | ---- | 0.10 | ---- |
| Bladder & Other Urinary Tract | 0 | 0.06 | ---- | 0.07 | ---- |
| Malignant Melanoma of the Skin | 0 | 0.11 | ---- | 0.04 | ---- |
| Eye | 0 | 0.00 | ---- | 0.00 | ---- |
| Central Nervous System | 0 | 0.29 | ---- | 0.24 | ---- |
| Thyroid Gland & Other Endocrine | 0 | 0.02 | ---- | 0.00 | ---- |
| Bone | 0 | 0.02 | ---- | 0.00 | ---- |
| All Lymphatic & Hematologic | 1 | 0.58 | 1.73 | 0.56 | 1.79 |
| Lymphosarcoma & Reticulosarcoma | 0 | 0.10 | ---- | 0.05 | ---- |
| Hodgkins Disease | 0 | 0.05 | ---- | 0.02 | ---- |
| Leukemia & Aleukemia | 0 | 0.21 | ---- | 0.21 | ---- |
| All Other Lymphopoietic System | 1 | 0.21 | 4.70 | 0.28 | 3.59 |
| All Other Malignant Neoplasms | 0 | 0.44 | ---- | 0.65 | ---- |
| Benign Neoplasms | 0 | 0.12 | ---- | 0.23 | ---- |
| Diabetes Mellitus | 1 | 0.61 | 1.64 | 1.16 | 0.86 |
| Cerebrovascular Disease | 1 | 2.49 | 0.40 | 4.56 | 0.22 |
| All Heart Disease | 6 | 9.98 | 0.60 | 13.73 | 0.44 |
| Rheumatic Heart Disease | 0 | 0.27 | ---- | 0.34 | ---- |
| Ischemic Heart Disease | 6 | 6.78 | 0.89 | 8.84 | 0.68 |
| Chronic Disease of Endocardium | 0 | 0.13 | ---- | 0.17 | ---- |
| Hypertension with Heart Disease | 0 | 0.41 | ---- | 1.03 | ---- |
| All Other Heart Disease | 0 | 1.55 | ---- | 2.02 | ---- |
| Hypertension w/o Heart Disease | 0 | 0.29 | ---- | 0.82 | ---- |
| Non-Malignant Respiratory Disease | 2 | 1.34 | 1.49 | 1.76 | 1.14 |
| Influenza & Pneumonia | 0 | 0.59 | ---- | 0.85 | ---- |
| Bronchitis, Emphysema, Asthma | 2 | 0.31 | 6.43 | 0.38 | 5.26 |
| Bronchitis | 0 | 0.03 | ---- | 0.04 | ---- |
| Emphysema | 2 | 0.21 | 9.52 | 0.17 | 11.75 |
| Asthma | 0 | 0.07 | ---- | 0.18 | ---- |
| Other Non-Malignant Resp. Disease | 0 | 0.42 | ---- | 0.50 | ---- |

(Table continues on next page)

TABLE 6 continued

Observed and Expected Numbers of Deaths
in the Additional Exposed Through 9/1/86[1]

| Cause of Death | Observed | Expected[2] | SMR[2] | Expected[3] | SMR[3] |
|---|---|---|---|---|---|
| Ulcer of Stomach & Duodenum | 0 | 0.18 | --- | 0.26 | --- |
| Cirrhosis of Liver | 0 | 0.79 | --- | 0.94 | --- |
| Nephritis & Nephrosis | 0 | 0.47 | --- | 0.72 | --- |
| All External Causes of Death | 3 | 5.03 | 0.60 | 6.21 | 0.48 |
| Accidents | 2 | 2.99 | 0.67 | 3.38 | 0.59 |
| Motor Vehicle Accidents | 2 | 1.54 | 1.30 | 1.64 | 1.22 |
| All Other Accidents | 0 | 1.44 | --- | 1.73 | --- |
| Suicides | 0 | 0.80 | --- | 0.52 | --- |
| Homicides & Other External | 1 | 1.16 | 0.86 | 2.22 | 0.45 |
| All Other Causes of Death | 1 | 3.88 | 0.26 | 6.60 | 0.15 |

[1] Total = 486 persons, 6622.5 person-years.

[2] Expected deaths calculated from York County, S.C. rates; unknown race coded as white.

[3] Expected deaths calculated from York County, S.C. rates; unknown race coded as non-white.

TABLE 7

Observed and Expected[1] Deaths for Terminees of Known Race by Exposure Status

| | | Original Cohort | Additional Exposed | Unexposed |
|---|---|---|---|---|
| All Causes | Observed | 96 | 10 | 73 |
| | Expected | 81.35 | 12.55 | 191.34 |
| | SMR | 1.2 | 0.80 | 0.38 |
| All Neoplasms | Observed | 20 | 2 | 15 |
| | Expected | 20.10 | 2.02 | 30.98 |
| | SMR | 1.0 | 0.99 | 0.48 |
| All Heart Disease | Observed | 38 | 5 | 26 |
| | Expected | 27.98 | 4.21 | 59.97 |
| | SMR | 1.4 | 1.2 | 0.43 |
| All External Causes | Observed | 20 | 2 | 9 |
| | Expected | 10.74 | 1.52 | 28.84 |
| | SMR | 1.9 | 1.3 | 0.31 |
| Unknown Causes | Observed | 5 | 0 | 7 |

[1] Expected deaths calculated from York County, S.C. rates.

TABLE 8

Distribution of Persons and Person-Years by Race
in the Original Cohort and the Expanded Cohort

| Race | Measure | Original Cohort | | Expanded Cohort[1] | |
|---|---|---|---|---|---|
| Whites | Persons | 1,097 | (86%) | 1,233 | (24%) |
| | Person-years | 26,556 | (91%) | 18,133 | (18%) |
| Non-whites | Persons | 174 | (14%) | 1,353 | (26%) |
| | Person-years | 2,798 | (9.5%) | 26,741 | (27%) |
| Unknown | Persons | 0 | (0%) | 2,634 | (51%) |
| | Person-years | 0 | (0%) | 54,093 | (55%) |
| TOTAL | Persons | 1,271 | (100%) | 5,220 | (100%) |
| | Person-years | 29,354 | (100%) | 98,967 | (100%) |

[1] Expanded cohort = additional exposed plus unexposed.

TABLE 9

Distribution of Duration of Employment in the Original Cohort and Expanded Cohort

| Duration of Employment | Original Cohort | | Expanded Cohort[1] | |
|---|---|---|---|---|
| ≤ 6 months | 47 | (3.7%) | 839 | (16%) |
| > 6 - 12 months | 74 | (5.8%) | 552 | (10.6%) |
| > 12 months | 1,150 | (90.5%) | 3,829 | (73.4%) |
| TOTAL | 1,271 | (100%) | 5,220 | (100%) |

[1] Expanded cohort = additional exposed plus unexposed.

**Conclusion**

This thesis examined the mortality of cellulose fiber production workers who were exposed to methylene chloride, a chemical known to increase carboxyhemoglobin levels and to produce neurobehavioral effects in those exposed. The carcinogenicity of methylene chloride is less well understood. The carcinogenicity of methylene chloride is also the subject of public health and regulatory interest due to its widespread use in industrial and consumer applications. The research presented here provides new information about methylene chloride's carcinogenicity, mainly by identifying an association of methylene chloride with cancer of the biliary tract.

In the first paper, *The Mortality of Cellulose Fiber Production Workers*, the largest relative effect of methylene chloride exposure on mortality was observed for cancer of the biliary tract. This association is based on three histologically confirmed cases of cholangiocarcinoma. The association could not be explained by the effects of age, sex, or calendar period. Review of the medical records of the three biliary cancer deaths showed no evidence of gallbladder disease or chronic ulcerative colitis, the major factors considered to cause cancer of the bile ducts. I was unable to evaluate the effect of oral contraceptive use, a potential risk factor for the two female cases. Cellulose fiber production workers were also exposed to acetone and methanol, but I was unable to measure the independent effects of exposure to these solvents. Neither acetone nor methanol are considered to be human carcinogens, however, adequate epidemiologic

studies of the possible carcinogenic effects of acetone and methanol have not been conducted (1,2). The biliary cancer deaths occurred at least 20 years since beginning employment in cellulose fiber production, and two of the decedents worked for over 20 years in jobs that entailed substantial exposure to methylene chloride. While the possibility cannot be ruled out that the excess of biliary cancer was due to either oral contraceptive use or exposure to methanol or acetone, the absence of known risk factors for biliary cancer among the cases, the rarity of the tumor, and the high levels of methylene chloride to which the cellulose fiber workers were exposed suggest that the excess is due to methylene chloride exposure.

An attempt to relate more closely the mortality findings described in the first paper to methylene chloride exposure were largely unsuccessful. Analyses based upon the semi-quantitative exposure scale described in the second paper, *A Reassessment of Methylene Chloride Exposure in a Cohort of Cellulose Fiber Production Workers: Construction of an Exposure Scale and Analyses of Mortality*, failed to reveal meaningful differences in biliary cancer mortality between those classified as greatest exposed and those who experienced a lesser level of exposure. However, these findings do not provide strong evidence against a causal effect of methylene chloride. First, the mortality rates are based on small numbers of deaths at each exposure level: one death among those who worked in jobs with at most intermediate level exposure and two deaths among those who worked at jobs that entailed the greatest levels of exposure. Second, the exposure scale distinguishes only between jobs that were observed to entail exposures greater than 500

ppm (8 hr. TWA) and those that did not. It is possible that if methylene chloride causes biliary cancer the ambient levels required to do so are below 500 ppm (8 hr. TWA).

The fact that the relative excess of biliary cancer, though large, is based on three deaths and that this association has not been observed previously, means that further research is needed. First, it is important that the cellulose fiber production workers cohort continue to be followed. The cohort is still young and much remains to be learned about its mortality. In particular, it is important to determine whether additional deaths from biliary cancer have occurred and whether, with increasing time since initial exposure, an excess of pancreatic cancer has emerged, a finding predicted by Hearne's study of photographic film workers (5). While there is no firm rule that mandates the intervals at which follow-up should be conducted, almost five years have now elapsed since the most recent follow-up, and an extension of the follow-up should be planned. If additional follow-up reveals that more deaths from biliary cancer have occurred among women then a nested case-control study should be planned to assess the possible confounding by oral contraceptive use. Past oral contraceptive use among the biliary cancer decedents and controls could be ascertained via record review or interview with the spouse. The question of whether methanol or acetone, rather than methylene chloride, are responsible for the excess of biliary cancer cannot be addressed directly in this cohort. However, when Ott, *et al.* (4) first studied this cohort they also assembled a cohort of cellulose fiber production workers at another plant where the only solvent used was acetone; otherwise the production processes were virtually the same. This cohort could

be followed to learn whether it shows evidence of excess biliary cancer. A negative finding would argue against acetone exposure having produced the excess biliary cancer in the current study. Finally, it is important to assemble and study other cohorts exposed to methylene chloride to determine whether there is excess mortality from biliary, pancreatic, or other malignancies. These cohorts should include women workers if at all possible.

While it is the biliary cancer results that will most likely attract the attention of the scientific community, it is also important to point out what was **not** observed in this study. Little evidence of excess lung cancer was found, corroborating the negative findings of Hearne, *et al.* in the photographic film workers cohort (5). The negative results in the current study are of particular importance because the cellulose fiber workers were exposed to levels of methylene chloride almost an order of magnitude greater, on average, than the photographic film workers. Unfortunately, the absence of excess pancreatic cancer in the cellulose fiber workers cohort does not carry the same evidential weight. The excess pancreatic cancer observed by Hearne, *et al.* among the photographic film workers required 30 years since exposure to become fully apparent, and the cellulose fiber workers have little experience in this category of induction time. As noted above, further observation of the cellulose fiber workers cohort is needed to address the issue of methylene chloride and pancreatic cancer. If the heavily exposed cellulose fiber workers show no evidence of excess pancreatic cancer mortality even when long induction periods have elapsed, that finding will argue strongly against an

independent causal role for methylene chloride in the pancreatic cancer mortality excess among the less exposed photographic film workers.

It is conceivable that the results of this study could affect the carcinogenicity rating assigned to methylene chloride by the International Agency for Research on Cancer (IARC). Currently, methylene chloride is assigned to the category of "possible human carcinogens" (Group 2B). This decision was based on IARC's determination that while the animal evidence was "sufficient" to conclude that methylene chloride is a carcinogen, the epidemiologic data was "inadequate" (6). The epidemiologic studies considered by IARC were Ott's original study of the cellulose fiber workers cohort (4) and Hearne's retrospective cohort study of photographic film workers (3). At the time of IARC's review neither study had shown excess mortality for any cancer site. The IARC Working Group noted that "... in the available studies, only limited numbers of persons had had long-term exposure and adequate follow-up time for identification of increased cancer rates." (6) Since IARC's review the results of the cellulose fiber workers study have appeared (7) and Hearne, *et al.* have observed excess pancreatic cancer (8 observed, 3.2 expected, SMR=2.6) among those who began employment at least 30 years before death and had experienced the greatest cumulative exposure (5). The epidemiologic data would now appear to be "limited", or perhaps even "sufficient" rather than "inadequate" according to the criteria used by IARC to assign these designations (6, Preamble).

If methylene chloride does cause biliary cancer the rarity of this tumor indicates that the public health impact would be small. Also, general population exposures to methylene chloride through air, water, and food are generally considered to be orders of magnitude less than the exposures experienced by the cellulose fiber workers, though there are other occupational groups, e.g., plastic film industry workers and those employed in paint stripping and furniture refinishing, whose exposure to methylene chloride may equal or exceed that of the cellulose fiber workers (6). These industries and occupations appear to be suitable populations for future epidemiologic studies.

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