*British Journal of Industrial Medicine* 1988;45:766–776

# Incidence of laryngeal cancer and exposure to acid mists

K STEENLAND,[1] TERESA SCHNORR,[1] J BEAUMONT,[2] W HALPERIN,[1] T BLOOM[1]

*From the National Institute for Occupational Safety and Health,[1] Cincinnati, Ohio 45226, and University of California at Davis,[2] Davis, California, USA*

ABSTRACT To determine the relation between exposure to acid mist and laryngeal cancer, the smoking habits, drinking habits, and incidence of laryngeal cancer of 879 male steelworkers exposed to acid mists during pickling operations was ascertained. Sulphuric acid mist was the primary exposure for most men in this cohort. These men had all worked in a pickling operation for a minimum of six months before 1965, with an average duration of exposure of 9·5 years. Exposures to sulphuric acid in the 1970s averaged about 0·2 mg/m$^3$, and earlier exposures were probably similar. Interviews were conducted with all cohort members or their next of kin in 1986 and medical records of decedents were reviewed. Nine workers were identified who had been diagnosed as having laryngeal cancer, using a conservative case definition that required medical record confirmation for any case among decedents and confirmation by a physician for any case among live individuals. Using data from national surveys of cancer incidence as referent rates, 3·44 laryngeal cancers would have been expected. Excess smoking by the exposed cohort compared with the United States population resulted in an upward adjustment of the expected number of cases of laryngeal cancer to 3·92. The standardised incidence rate ratio for laryngeal cancer was 2·30 (9/3·92), with a one sided p value of 0·01 (assuming a Poisson distribution). The finding of excess laryngeal cancer in this cohort is consistent with four other studies published since 1981.

Three recent reports have indicated an association between exposure to sulphuric acid and an increase in the incidence of laryngeal cancer. Ahlborg *et al* studied 110 men exposed for at least one year to various acids in a pickling operation and observed three incident cases of laryngeal cancer compared with 0·6 expected.[1] No data on smoking were available. Soskolne *et al* conducted a nested case-control study of 34 cases of laryngeal cancer among men who worked in a refinery and chemical plant.[2] A 13-fold excess risk of laryngeal cancer was found for those exposed to the highest levels of sulphuric acid compared with those least exposed, and a fourfold risk for the moderately exposed versus the least exposed, after controlling for alcohol and tobacco consumption. Cookfair *et al* (reported at Society for Epidemiological Research Conference, Chapel Hill, 1985) conducted a population based case-control study of 352 white men with laryngeal cancer at a cancer research hospital in New York. After coding lifetime work histories for exposure to sulphuric acid and controlling for smoking and drinking, they found that the risk of laryngeal cancer increased for those with longer exposure to sulphuric acid. Finally, Forastiere *et al* studied 361 soap workers in Italy who had been exposed to sulphuric acid for a minimum of one year and observed five cases of laryngeal cancer over the study period compared with approximately one expected[3]; there was no control for smoking in this study.

Beaumont *et al* at the National Institute for Occupational Safety and Health had previously studied the mortality of a cohort of 1156 men exposed to sulphuric and other acids in pickling operations at three midwestern steel mills.[4] In this study two deaths from laryngeal cancer were observed versus 1·03 expected (not significant). Mortality studies for laryngeal cancer are relatively insensitive, however, because the five year survival rate for laryngeal cancer is greater than 50%,[4] and many patients with laryngeal cancer die of other diseases. Given the evidence that sulphuric acid might be associated with an increased risk of developing laryngeal cancer, and the relative insensitivity of the mortality study, we conducted a study of the incidence of laryngeal cancer in the cohort assembled by Beaumont.[4]

Accepted 21 September 1987

## Materials and methods

### ORIGINAL COHORT DESCRIPTION

The original cohort consisted of 1156 men, all of whom had worked for at least six months before 1965 in a pickling department at one of three midwestern steel mills. Demographic and work history data from company records for these men were collected in 1980–1. Most of these men began work in 1940 or later, although a few began in the 1930s.

Of the entire cohort, 373 (32%) had died by the end of 1985. The average duration of employment in an exposed job (in the pickling area) was 8·8 years. Twelve per cent of these men were non-white (black and hispanic). Details of this study have been reported elsewhere.[4]

### PROCESS DESCRIPTION AND EXPOSURE LEVELS

Acids are used to remove impurities (oxides) from newly manufactured steel. Sulphuric acid was the predominant acid used for steel pickling until the mid-1960s when it began to be replaced by other acids (hydrochloric, nitric, hydrofluoric, and hydrocyanic, with hydrochloric being the most common). By 1980, sulphuric acid was no longer being used at any of the three plants studied. Historical exposure data from 1975, 1977, and 1979 at two of the three plants in the original study indicated that exposure levels for sulphuric acid averaged 0·2 mg/m$^3$ (time weighted average), less than the current OSHA standard of 1·00 mg/m$^3$[6,7] (table 1). Based on our observations, we estimated that exposures at the third plant were similar to the two from which exposure data were available. Furthermore, given that processes had not changed substantially over time, exposure in earlier years probably did not differ greatly from the measured levels, although this possibility cannot be excluded.

Sampling data also indicated that the pickling process did not generate appreciable levels of metal particulate.[7] Twenty samples taken for chromium were all non-detectable or found only trace amounts (less than 0·01 mg/m$^3$) whereas ten samples taken for nickel were all non-detectable. Lead, copper, and manganese levels were similarly negligible. The only metal found in appreciable quantities was iron oxide, which averaged 0·67 mg/m$^3$ over 20 samples (range 0·2–2·7).

Based on personnel records and knowledge of process changes at the three plants, all men in the cohort were classified by NIOSH industrial hygienists into categories according to type of acid exposure.[4] Sixty two per cent of the original cohort was exposed to only sulphuric acid, 22% to sulphuric and other acids, and 16% only to acids other than sulphuric.

### INCIDENCE COHORT DEFINITION AND CASE CONFIRMATION PROCEDURES

The incidence cohort was a subset (77%) of the study population included in the mortality study by Beaumont *et al*[4] and was composed of all men for whom we could determine whether or not they had ever had laryngeal cancer. Such a determination was made for all live men for whom we obtained an interview and for all deceased men for whom next of kin were able to answer whether they had had laryngeal cancer. Any decedents for whom we had no interview with next of kin but for whom we were able to obtain medical records with a complete medical history were also included. Medical records (admissions, pathology reports, necropsy reports, discharges) were sought from all hospitals and physicians listed on the death certificate.

Table 1 *Exposure data in pickling departments. Area and personal samples of sulphuric acid air concentrations measured at two study plants during NIOSH and company industrial hygiene surveys**

| *Plant* | *Batch (B) or continuous (C) pickling* | *Area or job sampled* | *No of samples* | *Concentration (mg/m$^3$)* | |
|---|---|---|---|---|---|
| | | | | *Mean* | *Range* |
| | | *Personal samples* | | | |
| 3 | B | Pickle hooker | 7 | 0·15 | 0·07–0·25 |
| 3 | B | Asst pickle hooker | 4 | 0·20 | 0·03–0·48 |
| 3 | B | Craneman | 4 | 0·22 | 0·15–0·29 |
| | | Average | | 0·19 | |
| | | *Area samples* | | | |
| 2 | B | Cold finishing | 2 | 0·09 | 0·04–0·14 |
| 2 | C | Cold strip mill | 3 | 0·92 | 0·35–1·20 |
| 3 | B | Pickle tanks helper | 2 | 0·15 | 0·12–0·27 |
| 3 | B | Crane operator | 10 | 0·25 | 0·01–0·50 |
| 3 | B | Lunch table | 2 | 0·21 | 0·18–0·24 |
| 3 | B | Crane stairs | 15 | 0·15 | 0·00–0·61 |
| | | Average | | 0·29 | |

*Table taken from Beaumont *et al*.[4] Data for plant 2 from Young,[6] data for plant 3 from Price,[7] and from 1975 company data.

All reported cases of laryngeal cancer had to be confirmed by a physician or by medical records to be considered cases in the study. For decedents, neither a report by next of kin nor a death certificate was considered sufficient to define a case. Such reports had to be confirmed by medical records. Similarly, for any live men reporting cancer of the larynx, physician or medical record confirmation was required.

### METHODS OF OBTAINING INTERVIEWS

We attempted to contact all the members of the original cohort used in the mortality study, or their next of kin, to determine incidence of cancer, smoking habits, and alcohol consumption. Live cohort members were also asked whether they had had vocal chord polyps, and whether they had been exposed to asbestos, nickel, or wood dust, since these exposures have been identified as potentially associated with laryngeal cancer.[8]

Original addresses for all cohort members were available from personnel records, but in many cases these addresses dated back many years. Current addresses for live members of the cohort were obtained through the Internal Revenue Service (IRS) and the Health Care Financing Administration (HCFA) for those aged over 65. Addresses were also sought for live individuals from the Motor Vehicle Bureaus in the presumed state of residence. For decedents, addresses of next of kin were obtained primarily from death certificates and through HCFA.

When addresses could not be obtained, living individuals and next of kin were also sought through telephone directory assistance checks in cities where cohort members were last known to live.

Mailed questionnaires were sent in 1986 to all cohort members or their next of kin by certified mail. If the first mailing was unsuccessful a follow up mailing was done. If no response was obtained through the mailings then interviews were conducted by telephone.

### ANALYTICAL DESIGN

We analysed the data by a comparison of the exposed cohort with a non-exposed referent group, comparing observed laryngeal cancers with expected laryngeal cancers, based on conventional person-years analysis. The resulting measure was a standardised incidence ratio (SIR).

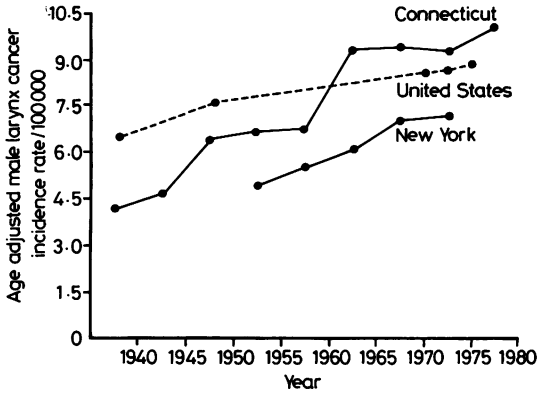
The NIOSH life table program was used to calculate person-years at risk for the cohort.[9] The appropriate referent rates (see below), stratified by sex, age, and calendar time, were applied to the person-years derived from the program to determine expected numbers of laryngeal cancer. Observed versus expected cases were tested using a modified one sided exact test, assuming a Poisson distribution, as discussed by Rothman and Boice.[10] A one sided test was used because this study was undertaken to test the a priori hypothesis of an excess incidence of laryngeal cancer.

Further analyses were conducted after dichotomising the cohort by duration of exposure and time since first exposure. Cut off points for the categories were determined a priori, after the person-years distribution of the cohort was known but without knowledge of the duration of exposure and time since first exposure of the observed cases. The cut off point for duration of exposure (five years) was chosen to distribute approximately the expected laryngeal cancers evenly between the two strata, whereas that for time since first exposure (20 years) was chosen because it is a conventional cut off point chosen to reflect the fact that most occupational agents require at least a 20 years latency period before resulting in solid tumours.

### REFERENCE RATES FOR INCIDENCE OF LARYNGEAL CANCER

We calculated the expected number of laryngeal cancers using three sources of incidence data. There is no ideal referent population for which there exist complete incidence rates of laryngeal cancer for the entire study period, stratified by age, sex, and calendar time. Partial data over time, however, exist from the Connecticut Cancer Registry (1935–79) and the New York Cancer Registry (1950–72). These data were kindly provided by Dr William Burnett (New York State Health Department) and John Flannery (Connecticut Department of Health Services). Rates reported from the New York Registry did not include New York City before 1973, and rates subsequent to 1973 cannot be compared with earlier rates. Neither Connecticut nor New York rates are stratified by race. In addition, rates corresponding to a sample of all United States geographical areas exist for 1938 and 1948 (1st and 2nd National Cancer Surveys[11]), for 1970 (3rd National Cancer Survey),[12] and for 1973–7 and 1978–81 (1st and 2nd surveillance, epidemiology, and end results (SEER) surveys).[13] The United States rates are based on cancer registry data in several large cities and some entire states. Although United States rates are stratified by race, there is little difference in rates between whites and non-whites and the numbers for non-whites are quite small and unstable. We have used rates for all races combined in calculating expected laryngeal cancers in our cohort.

We have calculated the slope of the increase in rates over time for each source of rates (Connecticut, New York, United States, using linear regression. These regressions were used to estimate rates during five year calendar periods when actual rates were missing. For each of the three sources of rates 15 regression lines were calculated, corresponding to five year age intervals beginning with 15–19 and ending with all




*Age adjusted incidence rates of male laryngeal cancer per 100 000 (adjusted to 1970 United States population except for first two United States data points which were adjusted to the 1950 United States population).*

ages over 85. Five year age and calendar time intervals were used because person-years at risk in the NIOSH life table system are broken down into these same intervals.[9] Referent rates were derived for the period 1940–85. As may be seen from the figure in which the available age adjusted referent rates have been plotted over calendar time, the number of rates that needed to be estimated varied.

For Connecticut, rates for only one time point (out of 10) needed to be estimated. For New York, and the United States, data needed to be estimated for five out of 10 time points. As the figure illustrates, the similarity of the plots of the rates from the three data sources, as well as the apparent linearity of trend with time, gave us some confidence that our regression estimates were reasonable.

## ADJUSTMENT FOR CONFOUNDING BY TOBACCO AND ALCOHOL CONSUMPTION

### *Smoking data*

The strongest known risk factor for laryngeal cancer is smoking, with a relative risk on the order of 15 for smokers versus non-smokers.[14] In our reference rates laryngeal cancer incidence data are not available separately for smokers and non-smokers. Therefore, we were unable to calculate the expected number of laryngeal cancers for different smoking categories in our cohort. Instead, we used a technique first described by Axelson, which adjusts the expected laryngeal cancers upward or downward depending on the prevalence of smoking in our incidence cohort compared with the prevalence of smoking in the United States. This adjustment assumes that there are known relative risks for the different smoking categories considered, and calculates the incidence rates of laryngeal cancer, as a weighted average of rates for different smoking categories. We obtained the known relative risks from a large case-control study by Wynder *et al.*[15]

Smoking prevalence in the United States was estimated using data from the 1965 Health Interview Survey (HIS) conducted by the National Center for Health Statistics.[16] The 1965 United States data were chosen because such data were situated at about the midpoint of our study period and because smoking habits of earlier periods were more relevant than current data when considering the subsequent development of laryngeal cancer. Furthermore, dead cohort members, who might be expected to have smoked more,[17] would be less well represented in a more recent comparison. We did, however, also make a second Axelson adjustment using 1976 United States smoking prevalence data, by way of checking how much effect such a change in calendar time would make.

The 1965 HIS survey included data from about 35 000 men stratified into five age groups (20–24, 25–34, 35–44, 45–64, $\geqslant$65). In the published HIS data this sample population was weighted to obtain estimates for the entire United States. The HIS data refer to cigarette smoking only, without reference to pipes or cigars. We have made comparisons between our cohort and the HIS data for cigarette smoking status (current, former, and never). We further stratified current smokers by amount smoked a day (a pack or less, or more than one pack). Former smokers were those who had smoked regularly but were not currently smoking.

Lifetime smoking histories of the cohort were obtained in early 1986. We used these data to determine the cohort's smoking habits as of 1965, the same year as the HIS survey. All 46 men who died before 1965 were excluded from the comparison for the smoking adjustment.

Expected cases of laryngeal cancer are derived from rates which are not stratified by race (see above). Thus in our smoking prevalence comparison we have not stratified the data on race.

Expected proportions of the different categories of cigarette smokers, based on the United States data, were calculated using an age adjustment. In 1965 3·3% of our cohort was aged 20–24, 19·1% were 25–34, 30·3% were 35–44, 42·4% were 45–64, and 4·9% were 65 or older. Age adjusted smoking prevalences in the United States were calculated by using the above proportions to weight an average of the age specific United States smoking prevalence rates, for the various smoking categories.

To account for the effect of pipe and cigar smoking, we have also calculated the numbers of men in our cohort who did not smoke cigarettes but did smoke pipes and cigars, and compared this proportion with

the expected number based on data gathered by the American Cancer Society.[18]

*Alcohol data*

Alcohol is a much weaker determinant of laryngeal cancer than smoking. The relative risk for drinkers versus non-drinkers is of the order of 2–3.[15] To adjust for possible confounding by divergent alcohol consumption patterns between the incidence cohort and the United States referent population, we again used an adjustment of the expected laryngeal cancers according to the technique suggested by Axelson[14] and the relative risks for laryngeal cancer were taken from the study by Wynder *et al.*[15]

Alcohol histories of the cohort were obtained in early 1986. Good historical data on United States alcohol consumption, based on a sample of the entire population and stratified by age and sex, have not been available until recently. As a comparison with our cohort we used the drinking habits of the national population obtained in 1983 in the HIS conducted by the National Center for Health Statistics.[19] Because the HIS survey was conducted toward the end of our study period, our comparison was restricted to cohort members who were alive at the time of our interviews. Whereas drinking habits some time ago might be more relevant than current data when considering the subsequent development of laryngeal cancer, these data were not available for the United States. Although this could be considered a disadvantage, the relative importance of alcohol as a potential confounder is much less than the importance of smoking, and only an extreme divergence between drinking habits between our cohort and the United States could cause much of an effect on the expected number of laryngeal cancers.

The 1983 HIS survey obtained data from about 9000 men. We stratified them into three age groups (18–44, 45–64, and $\geqslant 65$). We have made comparisons between our cohort and the HIS data for drinking status (current, former, and never/occasional). Current drinkers were those who drank three to four times a week or more often and were further stratified by amount drunk a day ($\leqslant 3$ drinks, 3–6 drinks, $\geqslant 7$ drinks). Former drinkers were those who had drunk alcohol regularly but were not current drinkers. Men who had never drunk or who did currently drink occasionally ($<3$–4 times a week) were defined as never/occasional drinkers. An exception to this classification were those current drinkers who drank only occasionally but who consumed more than seven drinks on a given day (binge drinkers). These binge drinkers were added to the heavy drinker category. This categorisation corresponded to the drinking categories for which relative risks for laryngeal cancer were estimated by Wynder *et al*[15] and could also be derived both from our cohort's data and the HIS data.

To compare our cohort with the national population, we considered their age and their drinking habits as of 1983, about the same time as the HIS survey. As in the adjustment for smoking, no attempt was made to stratify our cohort or the United States by race in considering drinking habits. We have age adjusted the HIS data to our cohort's age distribution. In 1985 6·6% of our cohort were 18–44, 59·5% were 45–64, and 33·9% were 65 or older. The age adjusted United States data were calculated by assuming that the men in the United States had this same age distribution, and calculating a weighted average of the proportions of various drinking categories.

## Results

### RESPONSE RATE FOR FOLLOW UP OF ORIGINAL COHORT

Using the mailed questionnaire followed by telephone interviews for non-respondents, responses were obtained from 841 (73%) of the original cohort. Table 2 indicates the percentage of telephone and self administered (mailed) questionnaires completed among each group.

In addition to the interviews with next of kin, for all decedents in the cohort we sought medical records from the hospitals and doctors listed on the death certificate. Some medical record was obtained for 72%. Nevertheless, a medical history sufficient to determine the incidence of cancer was obtained for only 42%. Those for whom we had no next of kin interview were included in the cohort if an adequate medical history was available. This led to the inclusion of an additional 45 for whom we had no interview with next of kin.

### DESCRIPTION OF INCIDENCE COHORT

We were able to determine the incidence of cancer for

Table 2 *Cohort interview response rate, by vital status**

| | Live | Next of kin |
|---|---|---|
| Total sought | 783 | 373 |
| Completed interview: | 621 (79·3% of live) | 220 (59·0% of dead) |
| Mailed interview | 480 | 146 |
| Telephone interview | 141 | 74 |
| Non-response: | 162 (20·7% of live) | 153 (41·0% of dead) |
| No address found | 106 | 122 |
| Some address found | 56 | 31 |

*For seven decedents the interview with next of kin was insufficient to determine the incidence of laryngeal cancer, and these men were subsequently excluded from the incidence study. On the other hand, medical record information sufficient to determine the incidence of laryngeal cancer was available for 45 men for whom we had obtained no interview with next of kin and these men were added to the incidence study.

77% of the original cohort and these men were included in the "incidence" cohort for further analysis. The incidence cohort consisted of 879 men, of whom 621 were alive and 258 were dead. We had received an interview from all live men. Interviews were available from next of kin for 220 decedents; however, for seven the next of kin were unable to provide a history of cancer and these were excluded. In addition, 45 decedents for whom we did not receive any interview with next of kin, but for whom we obtained an adequate medical history from medical records, were included. The 879 men in the incidence cohort represented 76·9% of the original cohort (79·2% of the live cohort members and 69·4% of dead cohort members).

The average duration of exposure of the incidence cohort was 9·5 years. Fifteen per cent of these men were non-white (black and hispanic). Sixty per cent were exposed only to sulphuric acid, 17% to only other acids, and the remainder were exposed to sulphuric and other acids. Fourteen per cent of the men had worked at plant 1, 31% at plant 2, and 55% at plant 3. By comparison with the original mortality cohort (see sections 1 and 2 of the materials and methods section), the men in the incidence cohort had been exposed slightly longer (9·5 versus 8·8 years). Distributions by race, type of acid exposure, and plant were similar in the incidence cohort and the original mortality cohort.

## DETERMINATION OF EXPECTED LARYNGEAL CANCERS

The incidence of laryngeal cancer has increased over time, possibly due to the effects of increasing prevalence of smoking, a strong risk factor. The figure shows the age adjusted summary rates for the different time points for all three sources of rates. There is some distortion because the two early United States data points (1938 and 1948) are age adjusted to the United States population in 1950, whereas the other data points are all adjusted to the United States population in 1970.

It is apparent that the United States data fit roughly between the lower rates of New York (without New York City) and the higher rates of Connecticut for most of the study period. Although we have calculated the expected laryngeal cancers using all three sets of rates, we believe the expected cancers based on United States rates are the most appropriate, for two reasons. Firstly, our study population is from the midwestern United States, and the general United States rates probably provide a better comparison than either New York or Connecticut. Secondly, United States rates are based on larger numbers and are somewhat more stable. Disadvantages to the United States rates come primarily from a lack of confidence in the early data points (1938 and 1948), at which time the surveys suffered from several methodological problems and covered somewhat different geographical areas than later surveys (J Horm, NCI, personal communication, 1986).

The life table analysis yielded 27 476 person-years at risk for the total cohort, almost all of which were accumulated after 1940 (97·0%). Twenty one per cent were accumulated between 1950 and 1959, 28% between 1960 and 1969, 27% between 1970 and 1979, and 12% between 1980 and 1986. Thirty four per cent of the person-years were accumulated by men aged 20–39, 50% by men aged 40–59, and 16% by men aged 60 and older.

We calculated that 3·44 cases of laryngeal cancer were expected after applying the United States rates specific to five year calendar time and age intervals to

Table 3 *Cases of laryngeal cancer*

| *No* | *Source** | *Vital status (date of death)* | *Age (date) of diagnosis* | *Year first exposed* | *Years from first exposure to cancer* | *Years exposed†* | *Acid type (plant)* | *Smoking status†* | *Drinking status†* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | MR, DC | Dead 1980 | 52 (1977) | 1947 | 30 | 7·2 | Sulphuric (2) | Current | Unknown |
| 2 | MR, DC | Dead 1979 | 45 (1978) | 1962 | 16 | 7·6 | Mixed (3) | Former | Occ |
| 3 | NOK, MR | Dead 1975 | 63 (1972) | 1933 | 39 | 38·5 | Sulphuric (3) | Current | Never |
| 4 | NOK, MR | Dead 1977 | 44 (1952) | 1940 | 12 | 5·3 | Other (2) | Unknown | Unknown |
| 5 | NOK, MR | Dead 1983 | 57 (1970) | 1945 | 25 | 0·9 | Other (2) | Former | Heavy |
| 6 | INT, PHY | Live | 59 (1981) | 1947 | 34 | 28·9 | Mixed (3) | Current | Occ |
| 7 | INT, PHY | Live | 56 (1979) | 1951 | 28 | 2·2 | Sulphuric (3) | Current | Mod |
| 8 | INT, PHY | Live | 61 (1971) | 1939 | 32 | 2·0 | Sulphuric (3) | Current | Never |
| 9 | INT, PHY | Live | 46 (1976) | 1958 | 18 | 17·3 | Mixed (3) | Current | Mod |

*Source of information about laryngeal cancer. For a dead person to be confirmed as a case, medical record confirmation was required. For a live person to be confirmed, his own interview and confirmation by a physician were required. MR: medical record; DC: death certificate; NOK: next of kin; INT: interview; PHY: physician.

†Years exposed are calculated before diagnosis. Smoking and drinking status are self reported or reported by next of kin. Smoking status is determined as of the date of diagnosis. For drinkers: occ, occasional/less than three to four times a week, consumes six or fewer drinks when drinking; mod: moderate/current drinker (at least three to four times a week or more) consuming three to six drinks when drinking; heavy: current drinker consuming seven or more drinks when drinking.

these person-years. The expected cases using New York and Connecticut rates were 2·94 and 3·89 respectively.

### LARYNGEAL CANCER INCIDENCE, BENIGN GROWTHS, AND POLYPS

Nine men in our cohort were found to have had laryngeal cancer, five of whom had died. Table 3 provides details on the source of information about laryngeal cancer, dates of diagnosis, employment history, smoking history, drinking habits, and type of acid exposure. Three of the five decedents with laryngeal cancer had no indication of the disease on their death certificate. Conversely, one individual who was listed as having died of laryngeal cancer was subsequently found, through medical records, to have actually had pharyngeal cancer and was not considered a case in this study.

The average age at diagnosis for these men was 53·2 years and the average number of years between first exposure and diagnosis was 26·0. The proportion of these nine men exposed to each of the three acid types (only sulphuric, only other types, and mixed) did not differ appreciably from the proportion in the entire cohort (see table 3). Similarly, the proportion of cases working at the three plants was similar to the entire cohort. Although no cases occurred at plant 1, only 14% of the incidence cohort worked there.

The average duration of exposure for the cases was 12·2 years (compared with 9·5 years for the entire incidence cohort), with a range of 0·9 to 38·5 years. All of the cases were either current or former smokers (laryngeal cancer is extremely rare among non-smokers). Drinking habits varied. All four live laryngeal cases were asked about past exposure to asbestos, wood dust, and nickel, and all denied any past exposure.

In addition to the cases of laryngeal cancer other men in the incidence cohort had benign laryngeal growths (table 4). There were two reported benign growths on the vocal cords and seven cases of polyps. One of the men with polyps subsequently developed laryngeal cancer (he is one of the nine cases). Table 4 probably underestimates the incidence of benign growths and polyps. With the exception of one benign laryngeal tumour found through medical records, table 4 reflects incidence only among the live members of the incidence cohort. Next of kin were not asked about benign growths and polyps for cohort decedents.

### ADJUSTMENT FOR SMOKING

As explained above, we sought to compare the smoking habits of our incidence cohort with the smoking habits of the United States population as of 1965. In 1986 we had obtained 841 interviews with men (or their next of kin) in our incidence cohort. These interviews included a smoking history from which we could determine smoking habits as of 1965. Nevertheless, 46 men had to be excluded because they had died before 1965, leaving 795 men to be considered in our comparison of smoking habits (22% of these men were dead by 1985). The average age of these 795 men in 1965 was 44·1. Of these 795, smoking information sufficient to categorise them by smoking status was available for 752, 86% of the incident cohort. Results for cigarette smoking prevalence, comparing the incidence cohort with the United States as of 1965, are shown in table 5. Clearly in our cohort there was a similar overall prevalence of smoking compared with all United States men but cohort members who did smoke smoked more than the United States average. These results are not surprising, reflecting well known national trends that blue collar workers smoke more than the United States average.[20] It is also apparent that whereas men who subsequently died and men who survived were virtually the same regarding the proportions of never smokers, current smokers, and former smokers, the current smokers who subsequently died smoked more than the current smokers who survived.

Relative risks (by cigarette smoking status), based on the data in the study by Wynder *et al*[15] were

Table 4 *Benign growths and polyps on vocal cords**

| *Outcome* | *Age at diagnosis* | *Date of diagnosis* | *Year first exposed* | *Years from first exposure* | *Acid type* | *Surgery?* |
|---|---|---|---|---|---|---|
| Benign tumour | 76 | 1962 | 1926 | 36 | Other | Yes |
| Leukoplakia | 33 | 1950 | 1937 | 13 | Mixed | No |
| Polyps† | 31 | 1952 | 1950 | 2 | Sulphuric | Yes |
| Polyps | 48 | 1972 | 1955 | 17 | Sulphuric | Yes |
| Polyps | 38 | 1969 | 1948 | 21 | Sulphuric | No |
| Polyps | 48 | 1972 | 1950 | 22 | Sulphuric | Yes |
| Polyps | 41 | 1960 | 1948 | 12 | Sulphuric | No |
| Polyps | 45 | 1970 | 1948 | 22 | Sulphuric | Yes |
| Polyps | 51 | 1972 | 1939 | 33 | Sulphuric | Yes |

*As reported on interview with live incidence cohort members (n = 621) with the exception of first individual in the table who had died and whose benign tumour was discovered through medical records. There are nine distinct men in this table.
†This individual developed laryngeal cancer in 1979.

Table 5 *Comparison of smoking habits, United States population versus sulphuric acid cohort, as of 1965*

| | *US age adjusted** | *Cohort (all)*† | *Cohort (live)*‡ | *Cohort (dead)* |
|---|---|---|---|---|
| Per cent never smoked regularly | 24·5 | 24·1 (n = 185) | 24·2 (n = 148) | 23·7 (n = 37) |
| Per cent current smoking one pack or less | 39·9 | 34·3 (n = 255) | 35·6 (n = 215) | 28·9 (n = 40) |
| Per cent current, smoking more than one pack | 14·8 | 27·0 (n = 200) | 25·5 (n = 154) | 33·7 (n = 46) |
| Per cent former | 20·9 | 14·6 (n = 112) | 14·7 (n = 90) | 14·1 (n = 22) |
| Total | 100·0 | 100 (n = 752) | 100 (n = 607) | 100 (n = 145) |

*United States proportions weighted according to the age distribution of our cohort.
†Subjects for whom sufficient information for smoking categorisation was available.
‡Vital status determined as of end of study.

assumed to be one for non-smokers, about 11 for smokers of one pack or less, about 21 for smokers of more than one pack, and about eight for former smokers. The risks for current cigarette smokers are available directly from the data by Wynder *et al.*[15] The eightfold risk for former smokers, however, is an estimate based on the stratified data presented by Wynder *et al* for former smokers.[15]

Applying these relative risks to the smoking categories for both our cohort and the United States, according to the method of Axelson,[14] the following results are obtained. In these equations $I_0$ represents the background laryngeal cancer incidence rate for non-exposed, non-smokers. The numbers in parentheses (see table 5) are the percentages of men in different smoking categories. $I_{exp}$ represents the incidence rate of laryngeal cancer for the exposed (the incidence cohort), based on their smoking habits and known relative risks, assuming no effect of exposures. $I_{non\text{-}exp}$ represents the incidence rate of laryngeal cancer for the non-exposed (in this case the United States population), again based on their known smoking habits and known relative risks.

$$I_{non\text{-}exp} = 1(0{\cdot}245)I_0 + 11(0{\cdot}399)I_0 + 21(0{\cdot}148)I_0 + 8(0{\cdot}209)I_0 = 9{\cdot}41I_0$$

$$I_{exp} = 1(0{\cdot}241)I_0 + 11(0{\cdot}343)I_0 + 21(0{\cdot}270)I_0 + 8(0{\cdot}146)I_0 = 10{\cdot}85I_0$$

Hence, the non-exposed group would be expected to experience an incidence of laryngeal cancer 9·41 times greater than background due to smoking, whereas the exposed group would be expected to show an incidence 10·85 times greater than background. The divergence in smoking habits between exposed and non-exposed, then, would lead us to expect an approximately 15% (10·85/9·41) increase in laryngeal cancers among the exposed compared with the non-exposed due to cigarette smoking.

We also conducted this same adjustment using a comparison between the prevalence of cigarette smoking of our cohort versus the United States in 1976 to determine how much a change calendar time would effect the adjustment. Results using 1976 smoking data indicated an upward adjustment of the expected laryngeal cancers of 13%, which compared well with the 15% based on 1965 smoking data. For the reasons outlined above in the Methods section (more relevance to later disease, more of the dead included), we chose to use the adjustment based on 1965 data.

Pipe and cigar smoking also involve an excess risk of lung cancer, although such risk is considerably less than that of cigarettes, and could confound our results correspondingly less. The study of Wynder *et al* indicated that cigarette smokers who also smoke cigars or pipes have *less* risk of laryngeal cancer than those who smoke cigarettes alone, possibly because of a decreased amount of cigarettes smoked.[15] Among non-smokers of cigarettes, however, Wynder *et al* found that men who smoked pipes or cigars had a fourfold excess risk of laryngeal cancer. Hence, potentially, if in our cohort a large percentage of men who did not smoke cigarettes did smoke pipes or cigars this could possibly confound our results.

While we did collect information on whether our cohort members had ever regularly smoked pipes or cigars, the HIS surveys do not collect such information and hence provide no comparison group. We have compared our data with a more recent American Cancer Society survey of 521 000 United States men conducted in 1982.[18] In this population, which had a similar age distribution to our cohort in 1982 (mean ages of 58 and 59, respectively), 25% of non-smokers of cigarettes smoked pipes or cigars. In our cohort the corresponding figure was a similar 22%. Given these data, no substantial confounding by pipe or cigar smoking appears likely.

### ADJUSTMENT FOR ALCOHOL CONSUMPTION

Of the 621 men who were alive in 1985 and for whom we had an interview, information on alcohol consumption sufficient to categorise them by drinking status was available for 593. Table 6 shows the results comparing the alcohol consumption of our cohort and the United States population. Clearly in our cohort

Table 6 *Comparison of alcohol consumption, United States population versus sulphuric acid cohort, as of 1985*

| *Drinking status (%)* | *US age adjusted* | *Cohort (live)* |
|---|---|---|
| Never/occasional drinkers, fewer than 3 days a week | 62·1 | 60·5 (n = 359) |
| Current drinkers, 3 or fewer a day | 10·6 | 6·7 (n = 40) |
| Current drinkers, 3–6 a day | 7·9 | 8·6 (n = 51) |
| Current drinkers, ⩾7 a day | 9·3 | 4·4 (n = 26) |
| Former drinkers | 9·8 | 19·7 (n = 117) |
| Total | 100·0 | 100·0 (n = 593) |

there was a lower prevalence of current drinkers compared with all United States men. The prevalence of both heavy drinkers and light drinkers among the cohort was less than the United States average. The cohort had a higher prevalence of former drinkers than did the United States population.

Relative risks (by alcohol consumption status), based on the data in the study of Wynder *et al*,[15] were assumed to be 1 for never/occasional drinkers (less than three days a week), 1·25 for light drinkers (one to three drinks a day), 1·75 for moderate drinkers (four to six drinks a day), 2·8 for heavy/binge drinkers (seven or more drinks a day), and 1·75 for former drinkers. The risks for current drinkers are calculable from the data in the study by Wynder *et al*. Relative risks for former drinkers were not estimated by them. Hence, the 1·75-fold risk for former drinkers is an estimate. Since the relative risk for moderate drinkers was midway between the highest relative risk (2·8) and 1, we selected 1·75 as an appropriate risk for former drinkers.

Applying these relative risks to the drinking categories for both our cohort and the United States, according to the method of Axelson,[14] we obtained the following results. In these equations $I_0$ represents the background incidence rate of laryngeal cancer for non-exposed, non-drinkers. The numbers in parentheses (see table 6) represent the percentages of men in the various drinking categories. $I_{exp}$ represents the incidence rate of laryngeal cancer for the exposed, based on their drinking habits and known relative risks, assuming no effect of exposures. $I_{non\text{-}exp}$ represents the incidence rate of laryngeal cancer for the non-exposed, again based on their known drinking habits and known relative risks.

$$I_{non\text{-}exp} = (1)(0{\cdot}621)I_0 + 1{\cdot}25(0{\cdot}106)I_0 + 1{\cdot}75(0{\cdot}079)I_0 + 2{\cdot}8(0{\cdot}093)I_0 + 1{\cdot}75(0{\cdot}098)I_0 = 1{\cdot}32I_0$$

$$I_{exp} = (1)(0{\cdot}605)I_0 + 1{\cdot}25(0{\cdot}067)I_0 + 1{\cdot}75(0{\cdot}086)I_0 + 2{\cdot}8)(0{\cdot}044)I_0 + 1{\cdot}75(0{\cdot}197)I_0 = 1{\cdot}311_0$$

Hence, the non-exposed group would be expected to experience an incidence of laryngeal cancer 1·32 times greater than background due to drinking, whereas the exposed group would be expected to show an incidence 1·31 times greater than background. The divergence in drinking habits between exposed and non-exposed, then, would lead us to expect an approximately 1% (1·31/1·32) decrease in laryngeal cancers among the exposed compared with the non-exposed due to alcohol consumption.

### OBSERVED VERSUS EXPECTED LARYNGEAL CANCERS

The expected number of laryngeal cancers, based on United States rates, was 3·44. The data on smoking would indicate that this figure should be adjusted upward by 15%, whereas the data on drinking would indicate a downward adjustment of 1%. A net upward adjustment of 14% yields an adjusted expected number of laryngeal cancers of 3·92 (the corresponding figures using Connecticut and New York rates are 4·43 and 3·35). The observed number of cancers is nine, and hence the ratio of observed to expected (SIR) is 2·30. If a Poisson distribution is assumed the one sided p value for this ratio is 0·013. The SIRs using Connecticut and New York rates are 2·04 and 2·70 respectively, with corresponding one sided p values of 0·025 and 0·005.

We also analysed the cohort according to duration of exposure (⩽5 years, > 5 years). The SIRs (observed versus expected, after a 14% upward adjustment of the expected) were 1·70 (3/1·77) and 2·76 (6/2·17), respectively. Analysis by time since first exposure (⩽20 years, > 20 years) resulted in incidence ratios of 3·27 (3/0·92) and 2·03 (6/2·95), respectively. Neither of these trends (increasing with duration of employment and decreasing with latency) is statistically significant, given the small numbers concerned. It should also be noted that these findings are highly dependent on the cut off points. For example, two cases developed at 16–18 years from first exposure, so that had the cut off point for time since first exposure been 15 instead of 20 years, a significant positive trend would have been observed.

## Discussion

The data from this study indicate that the exposed (incidence) cohort has experienced an approximately 2·3-fold excess of laryngeal cancer compared with the United States referent population. The use of Connecticut or New York state rates as referent rates change this result only slightly and, assuming a Poisson distribution, the results are statistically significant regardless of which referent rates are used. We have used a one sided test given our a priori hypothesis, but all results would have still been significant with a two sided test.

Some uncertainty in these results arises due to the adjustment for confounding by alcohol and tobacco

consumption. Given the lack of a referent population with known smoking specific (or alcohol specific) laryngeal incidence rates, it was not possible to calculate expected cancers among the exposed by different strata of smokers and drinkers. Furthermore, a case-control approach was not appropriate because of (1) the lack of any non-exposed group within the cohort permitting an internal analysis comparing exposed with non-exposed and (2) the lack of any quantitative exposure data permitting an internal analysis comparing the high exposed and low exposed. Hence, we have used the technique suggested by Axelson[14] to account for known differences between the exposed and referent groups for smoking and drinking habits. Whereas this adjustment is necessarily somewhat imprecise, it probably provides a reasonable estimate of the expected number of laryngeal cancers. Given that the observed number of cancers is more than double the expected, slight changes in the expected will not change the overall result. If one can assume a Poisson distribution for the observed cancers, with the expected taken as the population mean, a one sided test would find significance even if the expected number of cancers was 5·0, instead of the 3·92 we have used. An expected number of five could result only from a much more extreme disparity in smoking habits between our cohort and the United States than was actually observed. For example, in our cohort we observed 24% non-smokers, 34% light smokers, 27% heavy smokers, and 15% former smokers (as of 1965). Even had we observed 20% non-smokers, 35% light smokers, 45% heavy smokers, and no former smokers, our result would still have been statistically significant.

Various methods could have been used to perform the Axelson type adjustment. For example, in theory it might have been possible to combine alcohol and tobacco consumption categories and do one adjustment instead of two. There are several justifications for separate adjustments, however. Firstly, in the light of the fact that the overall drinking habits of the cohort differed scarcely at all from that of the referent population, it is unlikely that such a combined approach would differ substantially from the separate one we have presented. Secondly, while doing a single combined adjustment might have a theoretical advantage of using known relative risks appropriate to combined categories of both smoking and drinking (using information on synergism or interaction), in practice the categories of smoking and drinking used in the few large case-control studies available did not correspond to our own or to the available HIS categories for the United States population, making it difficult to know what relative risks to use. For example, in the study by Wynder *et al*, which we have used to estimate risks, the relative risks presented for combined smokers and drinkers reflect only current smoking and drinking, excluding former smokers and drinkers from consideration.[15] Finally, combined categories would have required using smoking prevalence in 1983 in order to conform to the alcohol comparison which of necessity relied on 1983 data (HIS). As we have argued earlier, it was preferable to compare smoking habits as of 1965, when they were more important for subsequent cancer incidence, and when (subsequent) decedents in the cohort were better represented. Smoking is a far stronger risk factor than alcohol, and we wanted the adjustment for smoking to be as accurate as possible.

We have used fairly strict criteria for case definition in this study; the decedents had to have had case confirmation by medical record and live cohort members were required to have the case confirmed by a physician or medical record. As a result, it is unlikely that we have overestimated the number of incident cases of laryngeal cancer. On the other hand, we may have underestimated the number of cases. Decedents for whom their next of kin said they had not had laryngeal cancer were included in the cohort as non-cases and contributed to the person-years at risk, even if no medical records were available to confirm that they did not have laryngeal cancer. Some of these men may have had laryngeal cancer despite the assertions of next of kin.

The finding of polyps preceding the laryngeal cancer of one of the cases is noteworthy given published hypotheses that irritation to the vocal cord may result in the formation of non-malignant nodules, which may then progress to malignancies under the influence of other carcinogens (such as tobacco smoke).[21] In our cohort seven live men (out of 621) reported vocal cord nodules. Unfortunately, we know of no referent population with which to compare this incidence.

The particle size of acid mist in an industrial setting averages about five microns,[22] and particles of this size are primarily deposited in the upper airways, where they have an irritating effect.[23] Possibly such irritation may damage the epithelium, making subsequent carcinogenic effects of other substances such as cigarette smoke more potent. Soskolne *et al* found a significant positive association between laryngeal cancer and prior history of ear, eye, or nose conditions in the medical record.[2] Such an argument would implicate not just sulphuric acid but any acid mist. In our study men were exposed not only to sulphuric acid but also to other acids, and the observed cases of laryngeal cancer were not uniquely exposed to any particular acid.

It is possible but unlikely that other occupational carcinogens in the work environment, rather than acid mists, caused the observed excess in cancer of the larynx. There is some evidence that exposure to nickel

is associated with laryngeal cancer,[8] but industrial hygiene sampling data indicated no detectable levels of nickel in the pickling area. It remains possible that the pickling workers worked in other areas of the steel mills where they were exposed to nickel or other unknown occupational carcinogens. The 11 pickling workers who had also worked on coke ovens were excluded from our cohort.

The findings of this study parallel those of four studies in the past few years indicating that exposure to sulphuric acid, or to acid mist in general, is significantly associated with laryngeal cancer. Three of these studies have been based on occupational cohorts.[1-3] Observed numbers of cases in two of these studies were quite small,[1 3] however, and only two of these studies have been able to control for cigarette smoking[2] (and D Cookfair *et al*, Chapel Hill, 1985).

Our data did not show strong evidence of a relation between excess risk of laryngeal cancer and either duration of exposure or time since first employment, two relations often present for occupational carcinogens. Given the small numbers of observed and expected cases in this study, however, such analyses have low power to detect trends. Furthermore, duration of exposure may be a poor surrogate for dose if men with higher exposures worked less time.

Most of the other published studies have also failed to show any type of dose response, again possibly because of insufficient power. The two cohort studies were based on five and three observed cases respectively.[1 3] The case-control study by Soskolne *et al* was nested in a cohort in a refinery and had greater power but cases and controls were matched on duration of employment, and the authors did not conduct an analysis by duration of exposure.[2] They did observe, however, an increased risk in those who had worked in jobs with higher exposure to sulphuric acid compared with those with lower exposures. Finally, the hospital based case-control study by Cookfair *et al* (Chapel Hill, 1985) found a slight trend with duration of potential exposure, but this finding was limited because duration of exposure to sulphuric acid was estimated based on job titles.

## References


1 Ahlborg G, Hogstedt C, Sundell L, *et al.* Laryngeal cancer and pickling house vapors. *Scand J Work Environ Health* 1981;7:239–40.

2 Soskolne C, Zeighami E, Hanis N, *et al.* Laryngeal cancer and occupational exposure to sulfuric acid. *Am J Epidemiol* 1984;**120**:358–69.

3 Forastiere F, Valesnin S, Salimei E, *et al.* Respiratory cancer among soap production workers. *Scand J Work Environ Health* (in press).

4 Beaumont J, Leveton J, Knox K, *et al.* Lung cancer mortality in workers exposed to sulfuric acid mist and other acid mists in steel pickling operations. *J Natl Cancer Inst* 1987;**79**:911–21.

5 Robbins S, Angell M. *Basic pathology.* Philadelphia: Saunders, 1976.

6 Young M. *Sulfuric acid exposure.* Cincinnati: IH, IWSB, DSHEFS, NIOSH, 1979. (Walk-through survey report 62.17.)

7 Price JH. *Health hazard evaluation No 77-31-432.* Cincinnati: HHS, NIOSH, 1977.

8 Rothman K, Cann C, Flander D, *et al.* Epidemiology of larynx cancer. *American Journal of Epidemiologic Reviews* 1980;**2**: 195–209.

9 Waxweiler R, Beaumont J, Henry J, *et al.* A modified life-table analysis for cohort studies. *J Occup Med* 1983;**25**:115–24.

10 Rothman K, Boice J. *Epidemiologic analysis with a programmable calculator.* Washington: Government Printing Office, 1979. (NIH publ No 79–1649.)

11 Dorn H, Cutler S. *Morbidity from cancer in the United States.* Washington: Government Printing Office, 1959. (Public Health monograph 56.)

12 Cutler S, Young J, eds. *Third national cancer survey: incidence data.* Washington: Government Printing Office, 1975. (NIH publ 75-787, 1975.)

13 Horm J, Asire A, Young J, *et al*, eds. *SEER program: cancer incidence and mortality in the US, 1973–1981.* Washington: Government Printing Office, 1985. (NIH publ 85-1837, 1985.)

14 Axelson O. Aspects on confounding in occupational health. *Scand J Work Environ Health* 1978;**4**:85–9.

15 Wynder E, Covey L, Mabuchi K, *et al.* Environmental factors in the cancer of the larynx. *Cancer* 1976;**38**:1591–1601.

16 National Center for Health Statistics. *Health—United States 1981.* Rockville, Maryland: NCHS, 1982. (DHHS publ 82-11232.)

17 McLaughlin J, Blot W, Mehl E, *et al.* Problems in the use of dead controls in case-control studies I. *Am J Epidemiol* 1985;**121**: 131–9.

18 Stellman S, Garfinkel L. Smoking habits and tar levels in a new American Cancer Society prospective study of 1·2 million men and women. *INCI* 1986;**76**:1057–63.

19 National Center for Health Statistics. *An inventory of alcohol, drug, and mental health data.* Rockville, Maryland: NCHS, 1985. (NCHS, DHSS publ (PHS) 85–1319.)

20 Sterling T, Weinkam J. Smoking characteristics by type of employment. *J Occup Med* 1976;**18**:743–54.

21 Chovil A. Laryngeal cancer: an explanation for the apparent occupational association. *Medical Hypotheses* 1981;7:951–6.

22 Jones W, Gamble J. Environmental study of lead acid battery workers. *Environ Res* 1984;**35**:1–10.

23 Schlesinger R. Effects of inhaled acids on respiratory tract defense mechanisms. *Environ Health Perspect* 1985;**63**:25–38.