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LARYNGEAL CANCER AND OCCUPATIONAL EXPOSURE TO SULFURIC ACID

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Workers on an ethanol unit which used sulfuric acid in strong concentrations at a large refinery and chemical plant in Baton Rouge, Louisiana were reported, in 1979, at excess risk for upper respiratory cancer. The carcinogen implicated by indirect evidence was diethyl sulfate. However, with the continued use of sulfuric acid in the same plant, and with additional cases not attributable to the ethanol process, the hypothesis of an association between sulfuric acid exposure and upper respiratory cancer was tested. Each of 50 confirmed cases of upper respiratory cancer diagnosed between 1944 and 1980, was matched to at least three controls on sex, race, age, date of initial employment, and duration of employment. Thirty-four of the 50 cases were laryngeal cancers. Data were obtained from existing plant records. Retrospective estimates of exposure were made without regard to case or control status. Findings from conditional logistic regression techniques were supported by other statistical methods. Among workers classified as potentially highly exposed, four-fold relative risks for all upper respiratory cancer sites combined were exceeded by the relative risk for laryngeal cancer specifically. Exposure-response and consistency across various comparisons after controlling statistically for tobacco-use, alcoholism and other previously implicated risk factors, suggest increased cancer risk with higher exposure.

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Laryngeal cancer incidence rates in industrialized nations are increasing annually by some 3 per cent, with the mean age of occurrence becoming increasingly

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younger in successive cohorts (1). The single most significant risk factor for laryngeal cancer is cigarette smoking (1).

Sulfuric acid, the most irritating of the particulate sulfur-species, is an atmospheric pollutant that has been regarded primarily as causing acute health effects in humans (2). To date, no chronic health effects related to the upper respiratory tract in humans have been directly associated with sulfuric acid exposures (3). Animal studies (4), however, have indicated chronic health effects, including changes to the epithelium of the respiratory tract.

Sulfuric acid is used for a variety of purposes in many industries, including the production of storage batteries, detergents, pharmaceuticals, petrochemicals, steel, and textiles. Examples of occupational groups commonly exposed to sulfuric acid are electroplaters, jewellers, metal cleaners, and picklers. Historically, in refinery and chemical plant operations, sulfuric acid has been used either as a reactant or a catalyst depending on its concentration. It is one of the most commonly manufactured chemicals sold in the United States (2). Results from toxicologic studies (2–5) together with some epidemiologic findings (6, 7) raise concern about the potential health effects of sulfuric acid on various upper respiratory sites that line the route of inhalation from the nasal cavities through the larynx.

In 1977, an excess incidence of upper respiratory cancer was found in association with work on the ethanol unit (6) of a petrochemical plant, which used sulfuric acid in excess of 90 per cent concentration in water ("strong" acid). From toxicologic, industrial hygiene, and engineering data, the inference was drawn that diethyl sulfate, known to be carcinogenic in laboratory animals (5) and present in the ethanol process (6), could have been the active carcinogen. The entire refinery and chemical plant population from which the original ethanol study population was derived (6) formed the study population in the present investigation (8) because sulfuric acid is used in processes other than ethanol production, and because additional cases of upper respiratory cancer were noted that could not be associated with work on the formerly investigated ethanol unit. This represents the first epidemiologic study that we know of that is designed to test the hypothesis of an association between upper respiratory cancer and exposure to sulfuric acid.

Materials and Methods

Fifty histologically-confirmed male cases of primary upper respiratory cancer, diagnosed between July, 1944, and August, 1980, were identified through the various tracing procedures shown in table 1. Case ascertainment included an extensive canvass of the population at risk, comprising all persons who had ever worked for at least 12 continuous months at the industrial complex studied, a large refinery and chemical plant in Baton Rouge, Louisiana. The 50 cases of malignancy were distributed over the major organ sites that constitute the upper respiratory tract as follows: 34 (68 per cent) were laryngeal, six (12 per cent) were oropharyngeal, five (10 per cent) were nose, nasal cavities, middle ear and accessory sinuses, two (4 per cent) were nasopharyngeal, two (4 per cent) were hypopharyngeal, and one (2 per cent) was pharyngeal (unspecified).

Each case was matched with a minimum of three controls randomly selected from the pool of eligible controls, comprising any employee without upper respiratory cancer from the study population. Cases and controls were matched on duration of employment (within four years) and on the year of first employment (within three years), in order to ensure that differences in these factors did not create differences in opportunity for sulfuric acid exposure. Age (within three

TABLE 1

Distribution of cases of upper respiratory cancer among company employees (past/present) by ascertainment source, Baton Rouge, Louisiana, July, 1944–August, 1980

Source of initial ascertainment	No.	%
Company medical department		
While an active employee	14	28
As a deceased annuitant†	12	24
Living annuitant notified medical department independently of any follow-up efforts	2	4
Ethanol unit follow-up of exposed workers	3*	6
Living annuitant follow-up	8	16
Non-company tumor registry‡	11	22
Social Security Administration§	0	0
Total	50	100

* These three cases also were ascertained independently through other listed sources.

† Annuitants are those retirees who have worked a minimum period to satisfy company pension plan requirements (i.e., workers usually with at least 10–15 years of company service).

‡ The non-company tumor registry was an ascertainment source of particular value for terminees (i.e., workers with <10 years of company service).

§ The Social Security Administration was able to provide vital status on 34 terminees who were lost to follow-up. No case of upper respiratory cancer existed among eight decedents established through this source.

years), sex (all male), and race (white, black) were also used as matching variables. For each of the 50 cases, the matched controls from the same industrial complex were randomly drawn from all possible matches based on the availability of a roster of persons ever examined by the plant's medical department (9) resulting in a variable matching ratio providing a total of 175 controls distributed over 50 cases for study purposes.

The inclusion of an additional 25 controls, based on a minimum, fixed case:control matching ratio of 1:3, was designed to facilitate analyses based on alternative, *a priori*, control selection criteria. If any control selected under the 1:3 matching ratio was found to have had a history of any cancer or was found, through the nature of his employment, to have had no opportunity for sulfuric acid exposure, an additional control was matched as a potential substitute control. A variety of comparisons thus was made possible to assist in explaining any possible associations found. The distribution of the 175 controls over the 50 cases (comprising matched sets) was as follows: 28 sets had a case:control ratio of 1:3; 19 sets had a case:control ratio of 1:4; three sets had a case:control ratio of 1:5.

Data collection was entirely record-based, with the date of diagnosis for the case considered as the end of the observation period for each matched set. Medical history data, including information on tobacco use, alcoholism, and a history of ear, nose, or throat disease, were collected from plant medical records, which had been updated annually or biannually at examination. In order to minimize any possible information bias attributable to differential record keeping, we excluded any information that had been collected in a record because of special surveillance programs. Medical records were unavailable for seven matched sets, resulting in the exclusion of 31 individuals from certain analyses controlling for confounders available only in the medical record. The reason all seven cases and almost all of their matched controls had missing medical records was that each set had terminated employment with the company prior to 1955 and their medical records had been lost.

Because of the significance of cigarette smoking as a risk factor for laryngeal cancer (1), all tobacco-related data were abstracted from the medical records. In 1959, the plant's medical department had conducted a census of current and historic tobacco-use profiles for each current employee, including cigarette, cigar, pipe, and chewing tobacco use. At periodical medical examinations thereafter, the tobacco-use data were updated. A cigarette-smoking pack-year equivalence index was derived in order to utilize all tobacco data, based on the equivalence criteria shown in table 2. The equivalence categories adopted for grades 0 through 5 were the same as those used by the medical department for the recording of tobacco-use data. Of the 79 per cent of the 225 persons in the study with a history of tobacco-use, two per cent only chewed tobacco. In general, final grade assignments are most heavily influenced by a history of cigarette use.

History of alcoholism was based on physician impressions and is likely to be incomplete or inaccurate.

Ear, nose, or throat disease was scored on a scale of 0 through 5, weighting more heavily any anatomical defects or changes recorded in the medical record. In regard to this anatomical region, other factors contributing to the overall score included any chronic inflammatory conditions, and episodes of allergic responses and general illness (8).

Environmental monitoring of sulfuric acid is a recent endeavor, and has been carried out only in selected areas of the industrial complex; thus, retrospective qualitative estimates of exposure were necessary. The plant industrial hygienist (employed since 1951), with the help of senior employees and documented plant history, assigned an ordinal grade (0 through 5) of likely sulfuric acid exposure to a dictionary of 3,995 unique job-location-era entries. The dictionary was compiled from the detailed work history records of the 225 persons studied. A grade of zero meant "unlikely to have been exposed", while a grade of 5 meant "frequent or intense contact to high levels resulting in intense irritation." The grade assignments were made without any knowledge of the health status of the worker to whom the specific entries applied.

The plant population is composed of two major categories of workers, namely process workers and mechanical craftsmen. Process workers are usually confined to specific processes involving the operation of units producing special products. Mechanical craftsmen (such as pipefitters, welders and electricians) perform functions towards maintaining the variety of plant processes. The utility of work history records for these two groups differ, in that retrospective exposure estimates for process workers can be deduced directly from the work history record; exposures for mechanical craftsmen can be esti-

TABLE 2

*Grading system adopted for combining the various modes of tobacco use among company employees (past/present), Baton Rouge, Louisiana, 1959–1980**

Grade	Cigarettes	Cigars	Pipes	Chewing tobacco
0	Never	Never	Never	Never
1	Once in a while	Once in a while	Once in a while	Once in a while
2	<½ pack/day	1–2/day	<5 pipefuls/day	<¼ pack/day
3	½ – <1 pack/day	3–4/day	5–9 pipefuls/day	>¼ but <½ pack/day
4	1–2 packs/day	5–8/day	10–19 pipefuls/day	½–¾ pack/day
5	>2 packs/day	≥9/day	≥20 pipefuls/day	¾+ pack/day
6	Known tobacco user, but quantity *unknown;* assumed grade 3 throughout			

* The grading system is based on the same criteria used by the Baton Rouge company for recording tobacco use data from a census of employees conducted in 1959.

mated only indirectly through the information recorded in the work history. Therefore, exposure estimates for mechanical craftsmen can not be as reliable as those for process workers. Since matching was not carried out on the major category of the worker (i.e., process or mechanical), subsequent analysis within either category was made difficult owing to limitations on sample size. In fact, an examination of process-specific workers rendered only 17 matched pairs for subsequent data analysis where attempts were made to examine exposure-disease associations within worker groups having equally comparable exposure estimates.

The same grading technique applied to sulfuric acid exposure was applied also to other agents which were potential confounders of the sulfuric acid-upper respiratory cancer relationship under study (1). The eight agents that made up the exposure dictionary were: strong (≥90 per cent strength), intermediate (75–89 per cent strength), and weak (≤74 per cent strength) sulfuric acid; ethanol; isopropanol; asbestos; nickel; and wood dust. The effects of the three sulfuric acid strengths could not be separated in this study because most individuals exposed to one acid strength were found to have also been exposed to both of the other two acid strengths during the period of observation. Therefore, no dose-response relationship could be measured in this study. However, exposure-response could be examined in terms of odds ratios at different levels of the exposure variable. Exposure to strong sulfuric acid has been chosen for reporting purposes since results for all three levels of acid strength are similar (8).

The individual exposure grade assignments over appropriate periods of the work histories were combined to form summary measures of worklife exposure for the eight agents studied. In table 3, the six summary worklife exposure measures examined in the course of this investigation are presented together with their dimensions (10). Measures containing time in their dimensions were suspected of introducing an overmatching bias into the analysis owing to the several time-related matching variables established at the design stage. "Mean grade", calculated by summing the

TABLE 3

Summary worklife exposure measures examined in a Baton Rouge, Louisiana study of refinery and chemical plant workers whose work histories spanned the period 1911–1980*

Exposure measure	Formula	Dimensions
A. Mean grade†	Σ(grade * time exposed)/ total time exposed	Grade
B. Highest grade ever	The highest grade to which exposed for ≥7 days	Grade
C. Grade-years (dose)	Σ(grade * time exposed)	Grade and time
D. Time-weighted-average grade	Σ(grade * time exposed)/ total time employed	Grade
E. Grade-years (dose) weighted by time since last exposed	Σ(grade * exposed * time elapsed)	Grade and time^2
F. Total time exposed	Σ time exposed	Time

* Exposure to the agents of interest was considered only to the date of diagnosis of the case in each matched set.

† Mean grade: >0 if time exposed >0; = 0 if never exposed.

products of all time and grade combinations over a working lifetime in the observation period, and then dividing by the sum of all time spent at jobs with grades greater than zero, was selected as the measure least likely to be influenced by the matching criteria (8). Where no exposure was recorded in the observation period, a mean grade value of zero was assigned. For analysis, the mean grade was divided into three categories as the lower 20 per cent, middle 60 per cent, and upper 20 per cent of its frequency distribution. Values in the lower 20 per cent of the distribution were placed in the "no/low" exposure category, the middle 60 per cent in the "moderate" exposure category, and the upper 20 per cent in the "high" exposure category. Respectively, the "mean grade" ranges for these categories were: 0.00–1.09, 1.10–2.09, and 2.10–4.88.

The data were analyzed with the summary worklife exposure measures categorized on an ordinal scale as opposed to treating the summary measures as continuous variables. The philosophy behind the categorization was motivated by the crudeness acknowledged as being inherent in the retrospectively assigned exposure grades. The primary intention through the categorical approach was to separate those workers having had likely higher exposures from those most likely to have had significantly lower exposures for comparative purposes.

Statistical analysis of the data involved both standard stratification techniques and multivariable logistic regression, employing conditional maximum likelihood estimation (11). Risk was modelled as a function of the exposure variable, potential confounders, and interaction terms involving the exposure variable, and various combinations of the potential confounders. Exposure was included in the modelling as two dummy binary variables, coded as 0 or 1 based on the three categories into which exposure had been divided. Alcoholism was treated as a single binary variable coded as 0 or 1; a history of ear, nose, or throat disease was included as an ordinal variable coded 0, 1, . . . , 5; and, tobacco use was treated as two dummy binary variables coded as 0 or 1 based on three categories with divisions at 4 and 45 cigarette-smoking pack-year equivalents, respectively. In practice, 0 indicated "not exposed" and 1 indicated "exposed".

RESULTS

Table 4 shows the distribution of cases and controls ignoring the matching over the three categories of the sulfuric acid exposure variable. Cases were more commonly exposed at higher mean grade levels than controls. The estimated odds ratio comparing "high" with "no/low" sulfuric acid exposure between cases and controls, based on the unmatched data in table 4, is 3.33 ($p < 0.025$); the comparison of "moderate" with "no/low" exposure gives an estimated odds ratio of 1.84, not statistically significant ($p > 0.10$). These results parallel, in both magnitude and direction of association, those results found subsequently when retaining the matching in the analysis.

TABLE 4

*Distribution of cases of upper respiratory cancer and their controls over three categories of sulfuric acid exposure disregarding the matching, Baton Rouge, Louisiana, 1944–1980**

Disease status	Mean grade categorization			
	No/low	Moderate	High	Total
	No. (%)	No. (%)	No. (%)	No. (%)
Cases	6 (12)	29 (58)	15 (30)	50 (100)
Controls	40 (23)	105 (60)	30 (17)	175 (100)
Total	46 (20)	134 (60)	45 (20)	225 (100)

* See results for a description of these data which are included to provide only a general perspective on the origins of the associations found in the succeeding tables 5 and 6. The latter tables, which show results consistent with table 4, represent the more appropriate analyses since they are based on analyses retaining the matching.

A rigorous strategy was implemented to test for the presence of interaction. All possible combinations of pairwise interactions among the three concomitant risk factors confirmed as significant in this study (alcoholism; ear, nose, or throat disease history; and tobacco use) were considered. Although a tobacco-sulfuric acid interaction term approached statistical significance, no interaction terms were found at $p \leq 0.05$.

A number of main effects models were examined. In table 5, model fitting statistics are presented for two of the main effects models examined; one controls for no confounders and another controls for three significant confounders and established risk factors: tobacco use ($p < 0.10$), alcoholism history ($p < 0.10$), and ear, nose, or throat disease history ($p < 0.05$). The log likelihood ratio statistic comparing the confounder model with the model containing no confounders was statistically significant ($p < 0.02$), indicating that the confounder model was a significantly better model for the data. Further selected summary odds ratio estimates representing typical associations confirmed by a variety of models examined in the study are presented in table 6.

The first row of table 6 presents an analysis of all 50 matched sets; since seven of the 50 matched sets contained no data on tobacco use, alcoholism, or a history of ear, nose, or throat disease, this analysis is unadjusted for these confounders and is included for the sake of completeness only. In each succeeding row of table 6, simultaneous adjustment on all three confounders was achieved. The positive association reported for all upper respiratory cancer sites is seen to be even stronger for laryngeal cancer specifically. No other single site had sufficient cases for evaluation. The odds ratio estimates for the moderately exposed workers were consistently above unity, but were lower than those for the highly exposed, and were not statistically significantly elevated in any of the comparisons. This provides some evidence for an exposure-response relationship, despite the general lack of statistical significance at the 0.05 level for the moderately exposed workers.

None of the other industrial agents examined—ethanol, isopropanol, asbestos, nickel, and wood dust—was found to be related to upper respiratory cancer in the population studied; nor was there evidence of any confounding of the sulfuric

TABLE 5

*Model fitting statistics: the association between sulfuric acid exposure and upper respiratory cancer, Baton Rouge refinery and chemical plant population, Louisiana, 1944–1980**

Terms	Coefficients	Standard error	Test statistic (Z)	Exposure-disease odds ratio	95% confidence interval
A. No confounder model					
Sulfuric acid "high"	1.712	0.679	2.52	5.5	1.46–20.99
Sulfuric acid "moderate"	0.972	0.634	1.53	2.6	0.76–24.23
B. Confounder model					
Sulfuric acid "high"	1.650	0.736	2.23	5.2	1.23–22.09
Sulfuric acid "moderate"	1.060	0.694	1.52	2.9	0.74–11.26
Alcoholism history	1.109	0.661	1.67	3.0	
Ear, nose, or throat history	0.343	0.160	2.13	1.4	
Tobacco "high"	1.124	0.639	1.75	3.1	
Tobacco "moderate"	0.498	0.620	0.80	1.7	

* The data presented are based on all cases and their matched controls having a medical record from which risk factor information could be abstracted (i.e., 43 matched sets; 194 observations).

TABLE 6

Exposure-response relationships shown by odds ratio estimates for selected comparisons of matched upper respiratory cancer (URC) case-control sets (main effects models only), Baton Rouge refinery and chemical plant population, Louisiana, 1944–1980*

Comparison	No. of sets	Estimated odds ratio: High vs. no/low exposure	Estimated odds ratio: Moderate vs. no/low exposure
All URC sets†	50	4.0¶ 1.26–12.70‡	2.2 0.78–6.36
All URC sets with medical records§	43	5.2¶ 1.23–22.09	2.9 0.74–11.26
URC sets with medical records excluding oropharyngeal sets§	37	4.9‖ 0.99–23.74	2.6 0.59–11.79
URC sets with medical records excluding the eight ethanol study cases§	35	5.4¶ 1.18–24.30	3.4‖ 0.82–13.97
Laryngeal sets with medical records§	30	13.4¶ 2.08–85.99	4.6‖ 0.83–25.35

* A set is a case and a minimum of three matched controls.

† The unadjusted odds ratio estimates are based on all 225 observations.

‡ 95 per cent confidence interval.

§ Odds ratio estimates are adjusted for tobacco use ($p < 0.10$), alcoholism ($p < 0.10$), and a history of ear, nose, or throat disease ($p < 0.05$).

‖ $p < 0.10$.

¶ $p < 0.05$.

acid-upper respiratory cancer relationship resulting from these other exposure variables.

DISCUSSION

Some workers in petrochemical facilities have been exposed to a variety of substances, including certain by-products of processes, whose presence and potential for effect are not fully characterized. Questions of altered cancer risk for various organ sites have been raised for workers in the petrochemical industry (12, 13).

The results of this study provide evidence for a positive association between the development of upper respiratory cancer and exposure to sulfuric acid in the workplace studied, particularly in comparisons of workers in the "high" versus "no/low" sulfuric acid exposure categories. The results are especially elevated for laryngeal cancer. Odds ratios range from 3.33 to 13.4 (tables 4–6). Moderately exposed workers also show elevated odds ratios compared to the "no/low" exposure category, consistent with a dose-response effect, although the latter results are not always statistically significant.

The present study was initiated because cases of upper respiratory cancer, which had appeared to be confined to individuals on a strong acid ethanol process, subsequently were observed in workers with no history of ethanol unit exposure. The results are consistent with the findings of that study which associated excess risk with work on the strong acid ethanol unit (6); however, they do suggest a further interpretation that sulfuric acid exposure itself, notwithstanding the role of other possible carcinogenic agents, may be a major risk factor in the development of upper respiratory cancer in the industrial population studied.

Because low concentrations of dialkyl sulfates may be present in weaker acid strengths as well (5, 6), the present investigation was undertaken to test the hypothesis of an association between sulfuric acid used in numerous refinery and chemical plant processes and the development of upper respiratory cancer. The acid concentration in the mixture used in a given process (generally labelled "weak", "intermediate", or "strong") was thought to be important because by-products of the processes (for example, diethyl sulfate) in which the different concentrations are used may be different. Unfortunately, exposure to one concentration generally implied a similar exposure to other concentrations during any given period of time, explaining why similar results were found when the data were analyzed for "strong", "intermediate", and "weak" sulfuric acid concentrations. Because of the multiple exposures of the study population to all acid strengths, it has not been possible to isolate the separate effects of sulfuric acid exposure at different concentrations. The inability to discriminate between the three sulfuric acid concentrations eliminates any possibility of demonstrating a dose-response relationship based on acid concentration itself. This imposes a limitation on the ability of this study to implicate any specific acid concentration in relation to the development of upper respiratory cancer.

The hypothesis of an association between dialkyl sulfate exposure and the development of upper respiratory cancer was not examined in this study, since industrial hygiene knowledge about the presence of dialkyl sulfates across all units and processes in the industrial complex studied was unavailable. Besides, the focus of this study was on sulfuric acid *per se*, a chemical employed in numerous processes in the workplace studied.

The present study was not designed to test an association between sulfuric acid and a specific process, but rather to examine sulfuric acid-related effects across all refinery and chemical plant processes. While the present study was limited in its ability to examine risk among workers from different processes owing to the existence of only 17 pairs for which both members were process workers, work histories of cases appeared to indicate exposure to sulfuric acid in a variety of refinery and chemical plant processes. One difficulty encountered in estimating exposure levels was that exposures for maintenance workers who could have worked in the variety of refinery and chemical plant processes were exceedingly difficult to estimate. It was possible to establish, however, that the associations found in the present study were not due to any misclassification of exposure among the maintenance workers (8).

The inability of this study to confirm the association of both nickel and wood dust with upper respiratory cancer possibly can be ascribed to a lack of statistical power; both nickel and wood dust are more specifically associated with carcinoma of the nasal cavities (14) comprising a target-site-specific sample of only two matched sets in the present study. It should be noted, however, that asbestos, nickel, and wood dust have also been associated with laryngeal cancer (1), but the site-specific evidence for such an association is less well supported (1, 8); the mechanism by which sulfuric acid operates may overwhelm any possible effects associated with exposure to asbestos, nickel, or wood dust in the studied plant.

Damage to the respiratory tract of

guinea pigs by nonfatal exposure to sulfuric acid is repaired very slowly (15). Lesions resulting from such exposure have included degenerative changes to the epithelium of the respiratory tract (4). Chronic exposure might cause a series of irritations manifesting as a history of ear, nose, or throat conditions (8), which have been associated in the literature with the development of upper respiratory cancer despite the lack of hard data (16, 17). In the present investigation, cases were more likely than controls to have had a history of ear, nose, or throat conditions recorded in the medical record; these conditions may have resulted from chronic tissue irritation. An inference which could be made from this is that sulfuric acid may be a promoter of carcinoma through the mechanism of chronic tissue irritation. However, it must be recognized that the ear, nose, or throat conditions observed in the industrial complex studied indeed may be unrelated to sulfuric acid exposure *per se*.

A potential bias in case-control studies of disease etiology is differential case ascertainment by exposure status. The extensive case finding efforts used in this study were implemented to minimize such potential bias. Case ascertainment for the study is probably reasonably complete for the diagnostic period post-1969, when a regional tumor registry was operational. The association reported here is even stronger when the data are only analyzed for this more recent time period. While differential ascertainment is difficult to rule out completely, there is no reason to believe that differential ascertainment of cases relative to sulfuric acid exposure prevailed. Furthermore, an analysis of the data specifically excluding all eight upper respiratory cancer cases from the formerly studied ethanol unit (6) has shown consistently similar results (see table 6). An interpretation indeed may be that the effect is attributable to sulfuric acid alone or in combination with the ethanol process or processes other than ethanol.

At the design stage, the wisdom of matching on "duration of employment" had been considered. The decision was taken to obtain two referent groups: one including "duration of employment" as a matching variable; the other excluding this matching variable. In the field, however, it was observed that controls selected without "duration of employment" as a matching variable were found to have had short-term service relative to cases. The reason for the preponderance of short-term employees as controls stems from the nature of the frequency distribution of employment duration in the plant studied. Because such controls would have introduced implicit differences on potential for sulfuric acid exposure in any matched set, duration of employment was included as essential to ensuring equal opportunity for exposure. Matching on "duration of employment" thus provides comparable observation intervals, assuring comparable data quality and opportunity for exposure. As a consequence, it was not possible to examine the effect of this matching variable in the analysis.

The use of a summary worklife exposure measure of some type is mandatory in a situation of multiple job and engineering changes over time. Any summary measure utilized has some weaknesses. Considering limitations thereby imposed, it is noteworthy that both the "highest grade ever" and "grade-years (dose)" (measures B and C, respectively, in table 3) showed consistently elevated risk, even though statistical significance was not always achieved. For "highest grade ever", odds ratios ranged from 2.6 to 5.5, while for the "dose" measure, odds ratios were in the range 1.1 to 1.8, lending support to the results obtained using "mean grade". Although preference may exist for one summary measure over any other, the *a priori* choice in this study was that of "mean grade". Other summary measures were examined as a methodologic component to this research and will be fully described in a manuscript currently in preparation (18).

The subjective nature of the retrospective exposure assessments may raise questions about the reliability of the exposures. However, since exposure grades were assigned without regard to case or control status, it is unlikely that any exposure suspicion bias was introduced. Although the "high" versus "no/low" comparisons yielded significant differences, small sample size was a limiting factor in the multivariable modelling. The crude level of detail available for tobacco use and, particularly, for alcohol consumption, may impose limitations on the interpretability of these results in so far as the control for major confounders is concerned. However, the availability of such data, however crude, has provided the opportunity for some degree of control over major confounders. Despite these limitations, the evidence presented in this study indicates a problem that warrants further investigation.

In a recent case-control study (19), which achieved matching on tobacco and alcohol consumption histories, farmers, textile processors who separated, filtered, or dried textile fibers, and all laborers and maintenance personnel studied in Richmond County, Georgia were found to be at increased risk for laryngeal cancer. The authors in that study were unable to identify a carcinogenic agent common to all of these occupational/industrial groupings. The possibility that sulfuric acid may be involved deserves investigation based on the results of the current study. Certainly, sulfuric acid is known to be used in the processing of textiles, and as a solvent in some maintenance, labor, and farming-related operations.

The overall results of the different models examining site-specific case groups and homogeneously restructured control groups by various methods of analysis and modelling are consistent (8), providing additional support for the finding of increased upper respiratory cancer risk associated with sulfuric acid exposure. The magnitude of the observed risk estimates, particularly those for laryngeal cancer, argues for the existence of an exposure-disease association. It may be that sulfuric acid, instead of acting as a direct carcinogen or as a promoter itself, is a surrogate for or a synergist with other exposures in the workplace studied. Further research is indicated to determine the precise role of sulfuric acid and associated carcinogens such as dialkyl sulfate in the etiology of upper respiratory cancer. The widespread use and presence of sulfuric acid make this imperative.

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