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AN EPIDEMIOLOGIC INVESTIGATION OF AN EXCESS LUNG CANCER RISK IN A SYNTHETIC CHEMICALS PLANT

Dubrovnik

Vinyl Chloride PVC Plant

0000331

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AN EPIDEMIOLOGIC INVESTIGATION OF AN EXCESS LUNG CANCER RISK IN A SYNTHETIC CHEMICALS PLANT

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An excess lung cancer risk (39 observed and 27 expected) was observed among a cohort of 4984 males employed at a synthetic chemical plant since it opened in 1942. Upon review of the pathologic material, the excess was found to be limited to adenocarcinoma and large cell undifferentiated lung cancer. Many of the workers were exposed to vinyl chloride, but other exposures including chlorinated solvents, polyvinylchloride (PVC) dust, acrylates, and acrylonitrile existed. Thus, detailed work histories of each cohort member along with exposure ratings of each job for each calendar year since 1942 for each of nineteen different chemicals (or chemical groups) were obtained. A serially additive expected dose model was constructed which compared the doses of the chemicals observed for the lung cancer cases to the doses expected based on subcohorts individually matched to the cases. PVC dust appeared to be the most likely etiologic agent. Observed and expected doses were then analyzed by year before death to uncover the relevant latent period. This technique may prove very useful in other occupational studies where multiple potential carcinogens exist simultaneously in a chemical plant.

INTRODUCTION

Recent epidemiologic investigations of cancer in persons occupationally exposed to vinyl chloride monomer (VCM) gas showed excess deaths due to liver, brain, and lung cancer. Animal bioassays also found a relationship between VCM exposure and one or more of these site specific malignancies. However, the excess lung tumors found in these experiments had unclear dose response gradients. Furthermore, only three of the six retrospective cohort studies (Byren, 1976; Tabershaw, 1974; Waxweiler, 1976) found an excess of lung cancers, and the relative risks were much lower than for angiosarcoma of the liver (e.g., respiratory system cancer standardized mortality ratios were 168, 138, and 156). Additionally, the synthetic plastics plants studied used numerous chemicals other than VCM, yet none of these other exposures were assessed in spite of the fact that some of these chemicals have demonstrated or are being tested for carcinogenicity and mutagenicity. Thus while the weight of the evidence fell heavily on VCM as being the lung carcinogen at these synthetic plastics plants, the need to study the relationship of other chemicals to the lung cancer risk was significant.

One plant in Louisville, Kentucky, made synthetic plastics and rubbers consisting mainly of combinations of styrene, butadiene, and acrylonitrile; and additionally polymerized VCM gas into polyvinyl chloride (PVC) plastic. The employees who were exposed to VCM in this plant were included in a previously published mortality study (Waxweiler, 1976). After learning of the association between VCM and angiosarcoma of the liver in 1974, the plant personnel rated each job in each year since 1942 on a zero to five scale of exposure for each of nineteen different chemicals or groups.

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The work histories, vital statistics information, death certificates, and, in the case of deaths due to cancer, pathology reports and tissue specimens had all previously been collected by the National Institute for Occupational Safety and Health on every one of the approximately 5100 persons who had ever worked at the plant since it opened in 1942. These latter data, not including the 19 chemicals exposure information, were used as part of the aforementioned retrospective cohort analysis of the mortality experience of VCM exposed workers.

The lung cancer excess found among VCM exposed workers in this plant was intriguing for two reasons. First of all, the histologic distribution based on a preliminary review indicated that adenocarcinomas and large cell undifferentiated cancers accounted for a much greater proportion of the lung cancers than usual. Secondly, a number of cases of these histologic types occurred in men who had worked in areas of the plant associated with much lower exposures of VCM than the PVC polymerization area. Hence, there was a strong incentive to search for occupational lung carcinogens other than VCM. Thus the following research had three objectives: 1) to determine if the excess lung cancer risk among employees exposed to vinyl chloride monomer at a synthetic plastics and rubber plant also existed for the total plant population, including those persons not exposed to VCM, 2) to determine whether an excess lung cancer risk of a particular histologic type was in force at the plant, and 3) to test whether one or more particular chemicals used at the plant were responsible for either the excess risk of all, or of a specific histologic type (adenocarcinoma and large cell undifferentiated) of lung cancer. Non-occupational etiologies were also considered and investigated to the extent possible, but the emphasis lay on occupational risk factors.

II. METHODS

A. Retrospective Cohort Study

The first objective, that of determining whether an overall excess risk of lung cancer existed at the plant, could only be accomplished by the use of an external referrent population. Thus a retrospective cohort study design and standardized mortality ratios (SMR's), using the United States death rates as a referrent, were chosen to answer the question.

The population at risk (PAR), 5,093 employees, consisted of all persons ever employed at this plant since it opened in 1942 until May 1974. Of these, the 4,806 males, 98% of whom were white according to the company, who began work at the plant by December 31, 1973, were selected for study (Figure 1). Date of birth and detailed work history at this plant in the form of, "department number, job number, date in, date out," for all jobs held by each individual were collected. Follow-up of all study members was undertaken from the first date hired at the plant through December 31, 1973, the termination date of the ensuing mortality analysis. Death certificates were obtained for those individuals known to have died. The underlying cause of death was coded according to the "Seventh Revision of the International Lists of Diseases and Causes of Death" by a qualified nosologist. A life table analysis based on the Cutler-Ederer (1958) technique was used to obtain person-months at risk of dying by five year age, calendar, and time since work onset (latency) groups. So as not to overestimate the risk of mortality in the plant cohort, persons lost to follow-up were considered alive throughout the analyses. United States white male death rates specific for five year age and calendar intervals were used to calculate the expected deaths.

B. Worker Case - Community Compared Case Study

Because no histologic specific lung cancer incidence or mortality rates exist, and because histologic classification is somewhat variable between pathologists and over time, a synthetic-plant worker lung cancer case versus community comparand case design was chosen to accomplish the second objective.

Medical records and pathology reports were obtained on all deceased members of the cohort whose death certificates mentioned cancer or respiratory disease. If a primary or unspecified lung cancer was reported on any of these three records, then histologic material was obtained, if available, and reread by a panel of three pathologists unaware of the employment histories of the cases.

Forty-five cases were so identified. A few cases found to have died after December 31, 1973, the cohort ending date, were included in the worker case-community comparand case study.

As a comparison group, the lung cancer cases most closely preceding and succeeding the chemical plant worker case in the chronologically ordered hospital pathology logs were selected that matched on age diagnosis (+ or -2 years) sex, race, and county of residence. Although only 67% of the controls met the strict criteria of ±2 years, 94% of the controls were within ±6 years of age. For four cases, only one matched control could be found.

The histologic type distributions were then compared between the worker cases and the community comparand cases after review of the microscopic material by the pathology panel using the Veterans Administration classification scheme.

C. Serially Additive Expected Dose Model

The third objective required testing hypotheses on a number of chemicals with regard to their possible role in causing lung cancer. Thus, it was decided to analyze the previously mentioned cohort data in a Serially Additive Expected Dose (SAED) Model, obtaining observed and expected doses of each chemical conditional on certain characteristics.

The basis of the serially additive expected dose (SAED) method in descriptive terms is to compare the observed exposure of each case in a study with the exposures of fellow workers close to the case in year of birth, and in age at commencement of work for the company in the study. If the total work force in the plant being studied is referred to as the cohort, then each case can be thought of as belonging to a sub-cohort of workers with approximately the same year of birth and age at commencement of work in the plant. In each year that a case worked at the plant, his exposure can be compared with the other members of his sub-cohort who were working in that year. If the exposure being studied is causally related to the disease of interest, then the cases should, on average, be exposed for longer periods and/or to higher levels of the causative agent than other workers in their sub-cohorts who did not get the disease, and who did not get some other disease attributable to the same exposure. If the exposure is not causally related to the disease then we would expect case exposures to average out to be the same as for their sub-cohorts. Thus for each case, we want to use members of his sub-cohort to calculate an expected exposure for him, and compare this with his observed exposure, taking into account both exposure level and exposure duration.

The exposure data required for the analysis consist of some measures of exposure to a given chemical for each job in a plant, for each calendar year involved in the study. The exposure measures should ideally be interval measures, but can also consist of ranked exposure data. Ranked data were compiled by company personnel with a 0 to 5 scale of exposure for each of 12 chemicals examined (Table 1). Each job was assigned an exposure rank for each calendar year of the study (Table 2). These exposure data were then linked with work histories identifying the jobs each worker had in the plant and the calendar time involved. The analytical method used is based on estimating exposure

2X1 dose by multiplying the exposure level and the duration worked at that level. These "doses" are accumulated over each calendar year to yield the observed dose for each year that a case works. If a worker is exposed at level 1 for all of a calendar year then he has accumulated 365 dose units. If he spends 200 days at level 2, and the remainder of the year at level 1 then he has accumulated 565 dose units,

The calculation of the expected dose for each year a case works is obtained from the cohort dose matrix (Figure 1). This is a three dimensional matrix defined by age of first employment, year of first employment and calendar year. During employment in the industry, each non-case contributes to the relevant cells of this matrix the number of days spent in the given calendar year at each of the possible exposure levels. For example, an employee aged 22 when first employed in 1944 who spent 200 days of 1944 at level 2 and 165 days at level 1 would contribute to the corresponding cell shown in Figure 1, the respective number of days at the two levels. Subsequent employees of the same age when first employed in 1944 would add to the values in this cell in a similar manner. For computational simplicity this matrix is defined by age at first employment rather than year of birth which was suggested

above to define the sub-cohorts. Each cell is uniquely defined whichever approach is used.

Once data from each non-case have been entered into the cohort dose matrix, the case exposure dose can be compared with the matrix values for each year the case works. However this comparison is somewhat restrictive as only non-cases with exactly the same year of birth and age at first employment are involved. It was indicated earlier that comparisons might be made with sub-cohorts with approximately the same year of birth and age at first employment. This is put into effect in the SAED model by using a moving sum accumulation of data in the cohort dose matrix. In the application to be presented we define a sub-cohort for comparison with a case as consisting of all non-cases whose year of first employment and age at first employment are within two years of those of the case. However in the first year of employment of a case there are obviously no non-cases working who were first employed in the two subsequent years. For this reason the expected values for the first year of employment are calculated only from non-cases who started work in the same year as the case. In the second year of work the non-cases first employed in the year before and the year after the year of hire of the case are included. In subsequent years the estimation is from the whole sub-cohort within two years of first employment and within two years of birth of the case. When the cohort being studied is small in number the moving sum accumulation may need to span more years than this.

The cohort dose matrix is then used to calculate the expected dos for each year that a case works. Table 3 presents the first two years of work for a case who was aged 22 when first employed, and who was first employed in 1944. In his first year he worked 115 days, 50 of them at level 0, followed by 65 at level 5. He thus accumulates a dose of 50x0 + 65x5 = 325 dose units. The non-case members of his sub-cohort

accumulated 600 days at level 0, 1350 days at level 1, etc. The total number of sub-cohort days of work in 1944 was 3165 days, and the total sub-cohort dose units was 4830. The dose units per work day for the sub-cohort equal 4830/3165 = 1.53. Now the case worked for 115 days in that year, so his expected dose units (ie. the expectation for his dose units under the null hypothesis that the exposure does not cause the disease) is 115x1.53 = 176 dose units. The actual exposure was 325 dose units so it can be seen that this particular case was exposed to roughly twice the dose units for the chemical as would be expected for that year if he were an average member of his sub-cohort.

The calculations so far relate to one year of work history at the plant. As indicated previously, an individual's doses can be summed over his entire work history to give his observed total dose. His expected dose for each year of work can also be summed to give his expected total dose.

In addition to giving this test of the hypothesis that cases have more than expected total doses of an exposure, the SAED analysis facilitates an examination of the relationship between dates of exposure and the dates of death of the cases.

For each case in the study, one can calculate for each year prior to death his observed dose and his expected dose based on his sub-cohort. (If the case does not work in a given year then both observed and expected are set to zero.)

There were three definitions of cases for this SAED study. The first definition consisted of the 45 deceased lung cancer cases identified in the cohort study as determined by best diagnosis after review of all medical data and of available microscopic material as stated in the worker case-community comparand case study. Because previous investigation just of the vinyl chloride monomer exposed sub-cohort (ignoring other exposures) indicated an excess of adenocarcinomas (Type 3) and more so of large cell undifferentiated lung cancers (Type 4), a second definition of cases was further restricted to just Types 3 and 4 and a third definition was limited to only Type 4.

In the SAED model, each of a number of chemicals can be tested separately. However, since it was not known how well the model might discriminate between chemicals, the ability of the SAED Model to identify a carcinogenic agent was tested by first using the liver angiosarcoma cases at this plant and the Cohort Dose Matrix for a number of chemicals including vinyl chloride monomer. The results indicated the model could identify VCM as the liver carcinogen, but it could not distinguish between highly correlated chemical exposures.

RESULTS

A. Retrospective Cohort Study

Ninety-eight percent of the 4,806 male cohort were believed to be white according to communication with the plant personnel office. The distribution of year of birth indicated that by the end of study date, December 31, 1973, over 80% of the cohort, if alive, would have been over 34 years of age, 63% over 44 years of age, and only 30% over 54 years of age.

Most of the employees that have ever worked at the plant were hired before 1954 (Table 4); in fact 63% of the cohort had the opportunity to achieve at least nineteen years latency and 80% had the opportunity to achieve nine years latency. The ages of first employment at this plant are probably fairly typical of a large manufacturing company. Over two thirds of the employees began work before age 30. The other third is more heavily weighted with persons who began work at the plant during the 1940's, ie. during and just after World War II. This trend is probably due to bringing in skilled people and older persons not eligible for the armed forces during the first years the plant was in operation. A number of workers moved through various job titles at the plant but two thirds of the workers had only one or two job titles. This inplant job stability facilitates the investigation of specific chemical etiologies by limiting the number of exposures a typical worker will experience.

By follow-up of the 4806 man cohort until the end of 1973, it was determined that 4174 members of the cohort were alive, 559 deceased, and 73 lost-to-follow-up. The sixteen deceased persons whose death certificates could not be found were treated as deceased, cause of death unknown. Two separate analyses of the cohort were made. Initially all members were considered at risk from their first date of employment at the plant. This analysis yielded 556+ observed and 550 expected deaths (Table 5). Death due to malignant neoplasms of the central nervous system (SMR = 209) and respiratory system (SMR = 149) were both in excess. Additi nally, ten angiosarcomas of the liver observed in this cohort were vastly in excess but an expected number of deaths could not be calculated for this rare (27 angiosarcomas are expected to occur in the entire United States in one year) malignancy.

A second "over ten year latency" analysis was carried out by beginning person years at risk only after an individual had achieved his tenth anniversary since his first date of employment at the plant, regardless of still working there. The ten year period was chosen to coincide with the original published analysis of just the VCM exposed workers at this plant (Waxweiler, 1976). This analysis demonstrated very similar results to those in the first cohort analysis but with slightly higher SMR's. Respiratory system cancer displayed an SMR of 156 based on 39 observed cases. Because the analysis of just VCM exposed workers at the plant, described in the introduction, also found an SMR of 156 after 10 years latency, it was felt that these plant-wide results implied the existence of an excess lung cancer risk not solely

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+ As shown in Figure 1, three of the 559 deaths were rejected from analysis since they had no work histories.

due to VCM exposure. It must be reiterated here that the earlier VCM exposed cohort was defined on much cruder exposure criteria than were used in the SAED model. In the earlier reported VCM exposed cohort, exposure at this plant was determined on a departmental basis following a walk-through survey by National Institute for Occupational Safety and Health industrial hygienists and review of company process, engineering control, and air sampling data. Those specific departments classified as having VCM exposure included VC Monomer production, VCM polymerization PVC compounding, and maintenance. While that cohort study used a dichotomous definition of exposed departments, the SAED model used a 0-5 ranking developed by company personnel.

B. Worker Case - Community Comparand Study

As previously stated in the methods section, death certificates, medical and pathology records, and re-examinations of histologic specimens were used to make a best diagnosis that resulted in 45 lung cancer deaths. The twenty-seven of these 45 cases for whom histologic specimens were available made up the worker case group. As could be expected, cases with histologic specimens available for reconfirmation occurred slightly more frequently in later years and among younger persons than did cases with no specimens available. There were no differences between the two groups with respect to the first year employed (both medians 1947) or duration of employment (both have 40 percent greater than five years). The results of the majority opinion of the pathology panel are seen in Table 6. The panel found a substantially higher percentage of large cell undifferentiated (Type 4) cancers in the worker cases than in the community comparands (30% vs 10%) which was statistically significant ($p < .05$).

Starting with the SMR for respiratory system cancer of 149 found in the retrospective cohort study, and the observed and expected histologic distribution of lung cancer deaths based on the worker-case community-comparand study, Table 7 calculates histologic specific lung cancer SMR's (column C). It appears the lung cancer excess is limited to types 3 and 4, adenocarcinoma and large cell undifferentiated, with the greatest rate ratio lying in the large cell category. Furthermore, if one assumes that the 27 cases for whom histologic specimens were available are representative of all 45 lung cancer cases, then the 14.8 excess cases that would exist (given an SMR of 149), can be broken down by histologic type (Column E). This theoretical breakdown shows that approximately 13.5 of the 14.8 excess lung cancers among the plant workers would be due to adeno and especially large cell undifferentiated carcinoma. Note the total excess cases of each cell type do not add up to 14.8 because of the 2% of the expected distribution, column B, that is due to other types of lung cancer.

Thus it appears that there is indeed a histologic specific excess lung cancer risk among workers at this plant and that this differential distribution of cell types is not an artifact of the geographic region nor the pathologists' techniques. The fact that this risk occurs for adenocarcinomas and large cell undifferentiated lung cancers makes it very unlikely that it is due to cigarette smoking and is further encouragement to seek an occupational etiologic agent.

C. Serially Additive Expected Dose Model

The 398 department number - job number combinations that were originally identified from the plant personnel records were transformed into 72 job categories the company identified as having some exposure at some time in the past to at least one of the nineteen chemicals. Table 8 gives a general idea of how frequently high exposure job

categories occurred among the 72 possible ones. This does not necessarily imply frequency of person years exposed because some job categories contain many more person years than others, but one can infer from Table 8 that no single exposure dominates the others. This is especially evident from the raw data which are too voluminous to reproduce here. Seven of the chemicals were felt to have so few persons exposed to levels 3, 4 and 5 that they were excluded from consideration in the analysis. These were acrylic acid, acrylamides, bisphenol A, chloroethyl vinyl ether, diethyl maleate, phenol, and toluene.

The distribution of first year employed by age first employed is shown for all lung cancers in Table 9, and for Type 3 and 4 lung cancers in Table 10. The distributions in these tables are very similar, the only noticeable differences being that the Type 3 and 4 lung cancers started work at earlier ages. The distribution of the eight Type 4 lung cancer cases resembled that of the 15 cases of Type 3 and 4 combined.

None of the six lung cancer deaths occurring before 1960 were adenocarcinoma or large cell undifferentiated. This is partially due to the fact that only one of these six cases had available specimens for histologic re-examination. Types 3 and 4 lung cancer deaths were more heavily represented (39% vs 27%) than all lung cancers at ages of death below fifty.

The duration of employment distribution of the lung cancer cases (Table 4) is delimited by the corresponding distribution for all employees. Thus, it is not unexpected that 28% - 38% of the cases worked at least ten years because only 21% of the cohort worked that long.

The SAED Model Analysis resulted in the observed minus expected cumulative dose differences per case found in Table 12. Surprisingly, only two chemicals had a positive dose difference for all 27 histologically reviewed cases and no chemical had a positive dose difference for the 18 cases without histologic reconfirmation. The differences for PVC Dust doses stand out strikingly compared with the other exposures. For the Type 3 and 4 cancers and Type 4 alone, the PVC Dust differences are three to four times as large as the next most evident chemical, vinylidene chloride. The significance levels of the larger of these differences are found in Table 13 . They are listed for the total cumulative doses shown in Table 12 and also for cumulative doses up until ten years before death. The p-values of these t-tests signal a significant excess dose only for PVC dust. P-values below .05 exist only for all pathologically reviewed cases and for adenocarcinomas and large cell undifferentiated cancers combined. The p-value for large cell undifferentiated by itself is just above .05. Regardless of the definition of cases, the p-values become larger when the exposures occurring only 10 or more years before death are considered. The reason for this is illustrated in the latency analysis in Figure 2 which shows a peak positive PVC-Dust dose difference in the five to sixteen years before death range that would contribute more to the cumulative dose difference over all years than to just the ten years before death sum. As the diagnosis of the disease of interest becomes more narrowly defined the dose difference per case increases, yet the relevant latent period stays constant. The p-values associated with the paired t-tests are shown for call types 3 and 4 (adenocarcinoma and large cell undifferentiated) in Figure 3.

No more than seven of the 15 Type 3 and 4 lung cancer cases worked in any single year before death. Despite this consistency, a sharply defined cluster of p-values below .01 occurs in the interval seven to thirteen years before death.

V. DISCUSSION

The first objective of this study was to determine if the excess lung cancer risk among employees exposed to vinyl chloride monomer (VCM) also existed for the total plant population including those persons not exposed to VCM. The retrospective cohort mortality study showed that respiratory system malignant neoplasms occurred approximately 50% more frequently among the employees of the entire plant than would have been expected based on age, sex, race, and calendar year, United States death rates. A similar excess had been previously shown to exist among the subcohort of employees exposed to VCM (Waxweiler, 1976). Thus the excess lung cancer risk at the plant appeared to be independent of VCM exposure unless one hypothesized that it was due to extremely low levels of VCM that could have permeated almost all buildings.

Potentially confounding variables in the study of lung cancer are age, sex, calendar year, race-ethnicity, migration, urban residence, cigarette smoking and socioeconomic status. In the retrospective cohort study age and calendar year are standardized. Furthermore, all persons in the study are males and 98% are white, thus white male specific rates were used for comparison and these variables are controlled by subject category restriction. Ethnicity and migration (both inter and intra country) effects are considered minimal for all three study designs because of the clustering of birthplaces of the cases in and around the state of Kentucky.

While an urban effect could have accounted for some of the 50% excess in the cohort it probably played a very insignificant role because Haenszel (1962) found it to exist mainly for epidermoid and small cell lung cancers and the worker case community comparand study showed these cell types not responsible for the excess rate at the plant. Socioeconomic status could potentially effect lung cancer relative risks of the following magnitudes: 1) 1.2 if everyone at the plant had received no more than eight years of education (Kitagawa, 1973) or 2) 1.3 if everyone was classified as a laborer (Guralnick, 1963). Recent information indicates these gradients may be partially due to smoking patterns (Sterling, 1976; Winklestein, 1975). Since many of the employees in most of the departments would be classified at a higher socioeconomic status, there is probably insignificant confounding at the plant considered as a whole. However, it is possible that some exposure areas consisted of extremely homogeneous SES groups that were different from the plant as a whole. Even if this were true, SES could only have accounted for a 20-30% excess in lung cancer, much less than was found for cell types 3 and 4 in the histopathology study. Unfortunately education data on current employees were not available. Cigarette smoking with its tenfold relative risk is a more threatening confounder when first considered. Its relationship can best be elucidated in the worker case community comparand study discussion.

The second objective was to determine whether an excess lung cancer risk of a particular histologic type was in force at the plant. The worker case versus community comparand study showed that regardless of whose pathologic diagnosis one accepts, there was clearly an excess

representation of Type 3 and 4 lung cancers within the cases occurring among plant employees compared to other community lung cancer cases.

By having the same pathologists review both sets of slides without knowing which were of plant employees, one can feel fairly certain that no diagnostic biases occurred.

One could argue that the twenty-seven cases for whom histologic specimens were available were not representative of the entire 45 lung cancer cases at the plant. The major differences between those cases with and without specimens were date and age of death. Histologic specimens were plainly more difficult to find the earlier the date of death and the older the age of death. However, community comparand cases were matched on date of diagnosis and had to have available specimens themselves. One could also argue that less common types of lung cancer, such as large cell undifferentiated, would more often tend to have specimens taken or saved for research of diagnostic interests. For such bias to have an effect on the results, one would have to conceive of a selection that caused different types of lung cancers to be biopsied or autopsied among community members than among plant employees. Such a bias is difficult to imagine, particularly after the age matching procedure. The choice of community comparand cases makes it unlikely that a community wide pollutant was responsible for the excess risk at the plant specifically for Types 3 and 4 lung cancer.

Under the assumption that the 27 lung cancer cases with histologic

specimens available were representative of all 45 lung cancer cases among plant employees, it can then be inferred from Table 7 that the excess lung cancer risk in the cohort was limited to adenocarcinoma and large cell undifferentiated cancer. Adenocarcinomas, accounting for a minor proportion of this excess risk, have been shown at most to be only weakly related to cigarette smoking (Doll, 1964; Weiss, 1972) and some studies show no association at all (Yesner, 1973; Auerbach, 1973).

Large cell undifferentiated carcinoma of the lung, accounting for the vast majority of the excess lung cancer risk, is the only major histologic type that has always appeared in epidemiologic studies not to be related to cigarette smoking. Thus it is felt that cigarette smoking was not a major confounding variable in any of the three study designs in this dissertation. However, the role of smoking as a promoter or co-carcinogen cannot be ruled out. Such an effect appeared among uranium miners and asbestos workers. Interestingly enough such an effect did not appear to alter the characteristic histologic specificity of the lung cancer risk for oat cell carcinomas among the uranium miners (Archer, 1974). Furthermore in this study of chemical plant workers 71% of the histologically reviewed cases and 75% of the large cell undifferentiated cases were smokers, while all the rest had no smoking history data available. If fewer cases than comparands had smoked it would reflect an independent effect due to occupation, otherwise an interactive effect could be inferred. With such a large proportion of smoking histories missing for the lung cancer cases it is difficult to discern what role, if any, smoking played in the excess lung cancer risk at the plant. Nevertheless, the conclusion of this phase of the investigation was that an excess risk occurred among plant

employees for Types 3 and 4 lung cancer, especially Type 4.

The third objective was to test whether one or more particular chemicals used at the plant were responsible for either the excess risk of all lung cancer or of the Types 3 and 4 or just Type 4 lung cancer. The SAED model was specifically developed for this objective. It proved to be very useful in confirming the relationship between angiosarcoma of the liver and VCM and was subsequently used in the lung cancer investigation.

The major hypothesis was tested for each chemical in the SAED model by using the one sided t-test of the observed minus expected cumulative doses over 1) all years before death and 2) just ten or more years before death (Table 13). PVC-dust was the only chemical that was or even came near being statistically significant. It was not near statistical significance for all 45 lung cancer cases but attained p-values of .026 and .047 for the 27 cases with histologic specimens available. More importantly for Types 3 and 4 cases in the p-values were .037 and .061 and for Type 4 were .068 and .177.

In epidemiology one must look beyond straightforward statistical significance at times to other criteria such as strength of the association, consistency of results, and biological plausibility. The strength of the association was four-fold for the large cell undifferentiated SMR for the entire plant (Table 7), and a 1.7 dose ratio existed for PVC-dust. Consistency of results was evident in that for all sets of lung cancer cases PVC-dust, out of all nineteen chemicals, showed; 1) the largest positive cumulative dose difference and the largest positive dose ratio (1.2-1.7), and 2) a generally unimodal

yearly dose difference distribution over a conceivably biologically relevant latent period. These results lead me to believe that this research suggests that an excess of Type 3 and 4 lung cancer cases exists at this plant and is related to PVC-dust exposure. More extensive exposure and smoking data are currently being collected by researchers at the University of Louisville and will allow them to retest this hypothesis. These results differ from the earlier reported study at this plant (Waxweiler, 1976) which implicated VCM as the likely lung carcinogen because other chemicals and workers exposed to those chemicals were not considered at that time. The more detailed exposure data developed by the company also contributed to the differing results. Biologically the suggestion of PVC dust being a lung carcinogen is very plausible. PVC-dust particles are often in the respirable range. Almost all PVC particles produced by the emulsion system, one of the systems at this plant, are in the respirable range (Jones, 1978). These particles could easily settle in the lungs and conceivably by themselves cause lung cancer. In fact one case of supposedly PVC-dust induced pneumoconiosis has been found in a worker (Szende, 1970), and pulmonary granulomas (Frongia, 1974; Agarwal, 1978) have been induced in animals exposed to PVC-dust. Additionally, a large proportional mortality study of 4341 deaths that occurred among PVC fabricators, persons expected to be exposed to VCM and PVC dust was reported (Chiazze, 1977) to find no angiosarcomas of the liver but a slight (PMR=117) excess lung cancer risk.

Vinyl chloride monomer gas is easily inhaled and possibly only a short duration of tissue contact time would occur before the gas is either exhaled or absorbed into the bloodstream. However, it is known that VCM becomes entrapped in the PVC-dust and can be released slowly over time. Thus there exists the possibility that PVC-dust particles in the lung slowly release VCM to small adjacent areas of the tissue, prolonging the contact time of that chemical to tissue. If this latter hypothesis is true then it begs the question of why almost all the angiosarcoma cases occurred among polymer reactor cleaners who received extremely high VCM doses, but the lung cancer cases occurred quite often among the less heavily exposed workers. In fact VCM showed no relationship with lung cancer in the analysis. One would expect the lung to be the major route of entry for VCM regardless of the cancer site. However, the etiologic mechanism is a problem to be answered in laboratories and is only speculated upon here in the context of biologic relevancy and as a lead to further investigation.

Finally, it is hoped that this SAED Model could be refined to sort out confounding or interactive chemical carcinogens perhaps in a multiple regression adaptation and used in both an industrial health surveillance system to test its utility in a prospective basis and also in a case-control research situation.

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TABLE 1

Exposure ratings

0 -------- No exposure

1 -------- Minimal exposure to low levels (Chemical in building--not handled, low vapor pressure and dust level, probably works on different floor)

2 -------- Moderate exposure (Works around the chemical, but exposure is minimal)

3 -------- Works in area subject to occasional high excursions (Normally exposure is mimimal but occasional spills, leaks, or dust exposure may occur)

4 -------- Works in areas where level is high (Exposure levels in the area are frequently high. Might consider that some risk is involved if chemical is very toxic)

5 -------- Intimate contact -- skin or high inhalation (Such as poly cleaners in the old days -- handling slurry)

TABLE 2

Chemical Exposure Ratings Specific For Job Identification Number And Calendar Year For A Given Chemical

CHEMICAL #1 Job Identification Number	Calendar Year 1942	1943	1944	1945	1946	1973
1	0	0	0	2	2	2
2	5	5	5	5	5	5
3	2	2	1	1	0	0
.	.	.	.	.	.	.
.	.	.	.	.	.	.
84	4	4	4	1	1	1

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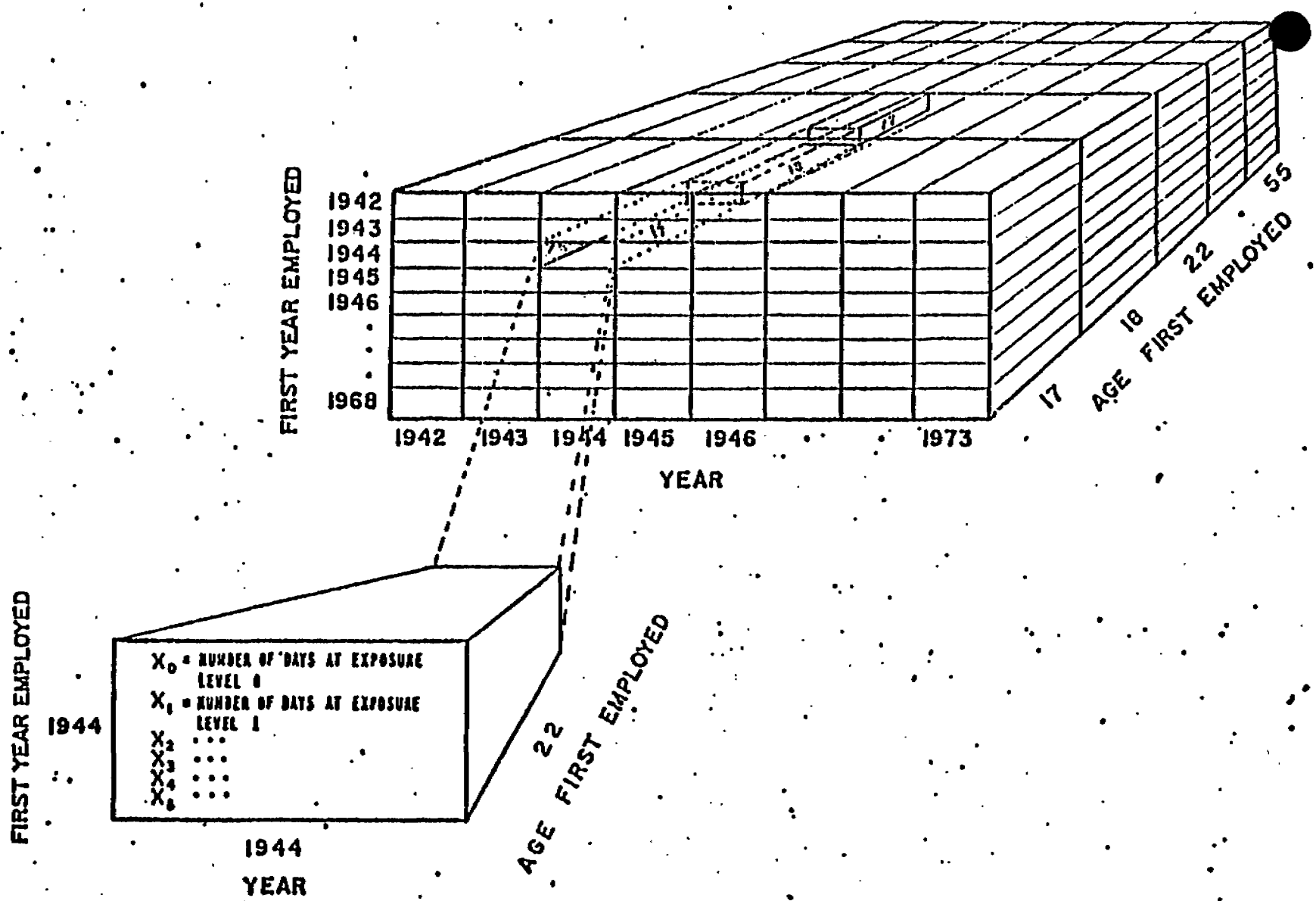

Fig. 1 Cohort dose matrix

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TABLE 3

Example of Data Used to Calculate the Observed and Expected Dose Units for a Case in One Calendar Year

Year	Exposures level	Case days	Case dose units	Sub-cohort days	Sub-cohort dose units
1944	0	50	0	600	0
	1	0	0	1350	1350
	2	0	0	540	1080
	3	0	0	400	1200
	4	0	0	175	700
	5	65	325	100	500
TOTAL		115	325	3165	4830

TABLE 4

First Year Employed by Age First Employed Distribution
of Male Cohort of Workers Ever Employed Before 1974

First Year Employed	Age First Employed				
	16-29	30-39	40-49	50-66	Total
1941-1949	1103	528	192	73	1896 (40%)
1950-1959	1120	325	97	10	1552 (33%)
1960-1973	1049	230	53	7	1339 (28%)
Total	3272 (68%)	1083 (22%)	342 (7%)	90 (2%)	4787* (100%)

* Of the 4806 males, 19 were missing either date of birth or detailed work hx, leaving 4787 in the above table.

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TABLE 5

LOUISVILLE PLANT COHORT MORTALITY

Cause (ICD Code)	All			Over Ten Years Latency		
	Observed	Expected	SMR	Observed	Expected	SMR
All Causes	556*	550.2	101	450	421.7	107
All Malignant Neoplasms (140-205)	109	92.5	118	94	76.4	123
i) Central Nervous System (193)	9	4.3	209†	8	3.1	256†
ii) Respiratory* System (160-164)	42	28.2	149††	39	24.9	156††
iii) Digestive System (150-159 excl. 156B)	24	25.6	94	21	21.0	100
iv) Lymphatic & Hemat. (200-205)	9	11.4	79	7	8.5	82
v) Other Cancers	25	23.0	109	19	18.8	101

* Includes 3 non lung cancer deaths with ICD 161.

† one tailed Poisson p value <.05

†† one tailed Poisson p value <.01

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TABLE 6

Worker Case and Matched Community Comparand Histologic Distributions

Histologic Type	Veterans Administration Classification Code	Frequency Worker Cases	Frequency Community Comparand Cases
Epidermoid	1	6(22%)	15 (30%)
Small Cell Undifferentiated	2	6(22%)	15 (30%)
Adenocarcinoma	3	7(26%)	14 (28%)
Large Cell Undifferentiated	4	8(30%)	5 (10%)
Other	-	0	1 (2%)
Total		27(100%)	50 (100%)

TABLE 7

Histologic Specific Lung Cancer Risk Among Plant Personnel

	Histologic Distribution		Histologic Specific SMR	Excess Cases Among Those Pathologically Reviewed	Total Excess Cases
	Observed (A)	Expected (B)	(C)=149x$\frac{A}{B}$	(D)†	(E)††
Total	100%	98%	149	8.9	14.8
Epi-dermoid	22.2%	30%	110	.6	.9
Small Cell	22.2%	30%	110	.6	.9
Adeno-carcinoma	25.9%	28%	138	1.9	3.2
Large Cell	29.6%	10%	441	6.2	10.3

†D = $(A \times 27) - (B \times 27 \times \frac{100}{149})$

††E = $(A \times 45) - (B \times 45 \times \frac{100}{149})$

TABLE 10

First Year Employed by Age First Employed Distribution
of Adenocarcinoma and Large Cell Undifferentiated Lung Cancers (Type 3 and 4)

First Year Employed	Age First Employed				
	20-29	30-39	40-49	≥50	Total
1941-1949	2	5	1	1	9 (60%)
1950-1959	2	2	1	0	5 (33%)
1960-1964	1	0	0	0	1 (7%)
Total	5 (33%)	7 (47%)	2 (14%)	1 (7%)	15 (100%)

TABLE 11

Duration of Employment Distribution
of Lung Cancer Deaths

Years	All Lung Cancer Deaths	Adenocarcinoma and Cell Cell Undifferentiated (Type 3 and Type 4)	Large Cell Undifferentiated (Type 4)
0 - .9	21(46%)	6(40%)	3(38%)
1 - 4.9	7(16%)	2(13%)	0(0%)
5 - 9.9	4(9%)	2(13%)	2(25%)
≥10	13(28%)	5(33%)	3(38%)
TOTAL	45(100%)	15(100%)	8(100%)

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TABLE 12

Observed - Expected Cumulative Dose Differences
Per Lung Cancer Case

Chemical	All Lung Cancers	Pathologically Reviewed Cases	Adenocarcinoma & Large Cell	Large Cell
Acrylonitrile	-652	-402	-446	-128
Acetylene	-353	-289	291	-167
Acrylates	-322	-251	-83	-339
Butadiene	-330	-207	-406	-622
Caprylyl Chloride	-547	-258	-270	-1139
Clorinated Solvents	-868	-672	-150	749
Mercuric Chloride	-507	-425	-211	-62
Methanol	-430	-618	-456	-1078
Vinyl Chloride Monomer	-1428	-795	26	907
Vinylidene Chloride	-341	210	804	1525
Vinyl Acetate	-707	-480	-217	328
PVC-Dust	763	2448	3225	4526

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TABLE 13

Probability Value of Paired T-Tests of Cumulative Differences Between Lung Cancer Cases' Observed and Expected Doses

	Total† (All Years)	10 Years Before Death
All Cell Types		
PVC-Dust	.185	.253
All Pathologically Reviewed		
PVC-Dust	.026*	.047*
Adenocarcinoma & Large Cell (Types 3 and 4)		
Vinylidene Chloride	.267	.333
PVC-Dust	.037*	.061
Large Cell (Type 4)		
Chlorinated Solvents	.360	.435
Vinylidene Chloride	.201	.322
PVC-Dust	.068	.177

* $p<.05$

† Twelve chemicals were tested for each lung cancer group thus under an assumption of independence of tests one would expect one test to be significant at the .08 level.

FIGURE 2

Observed Minus Expected Dose Differences Per Case Among Lung Cancer Cases for PVC Dust

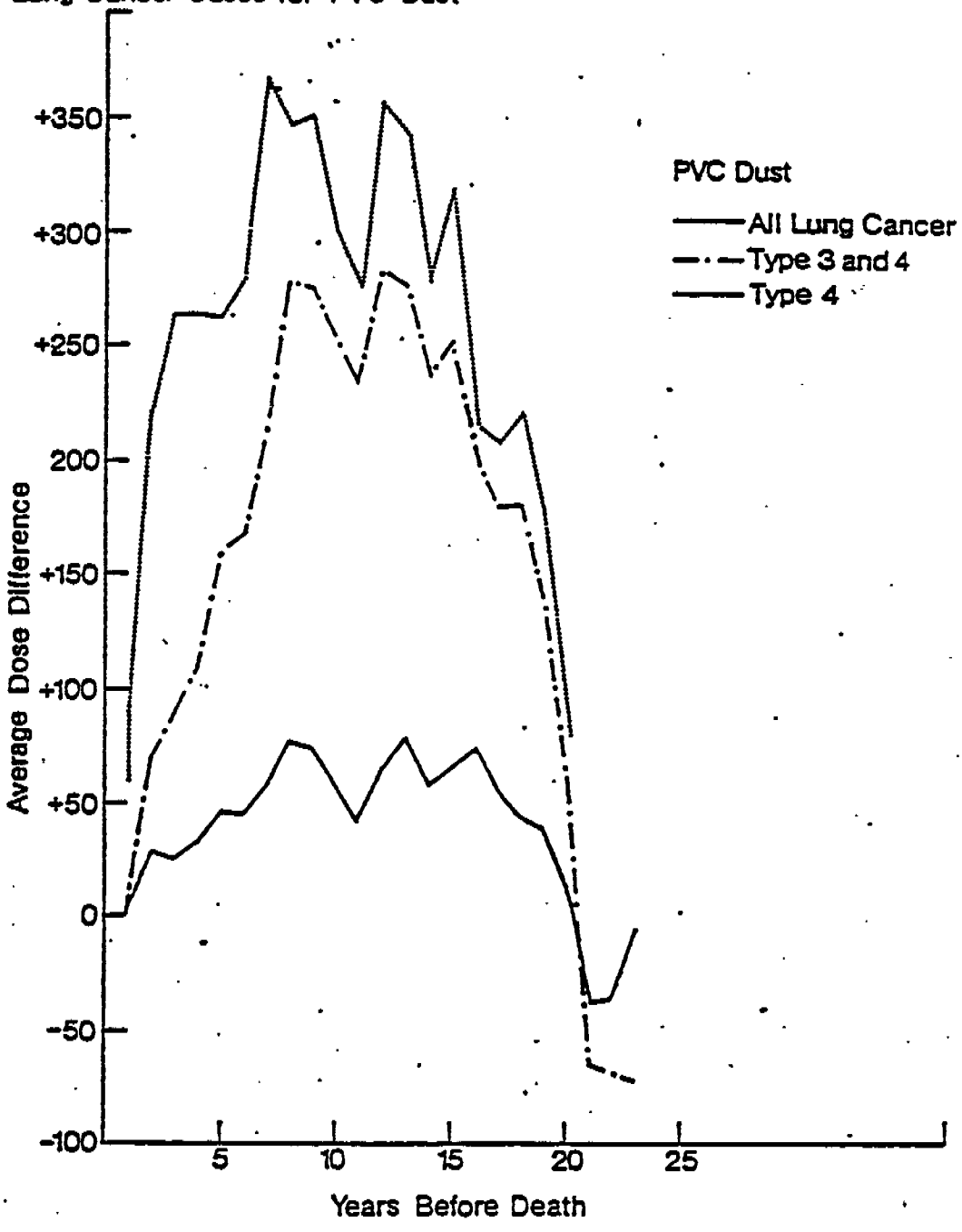

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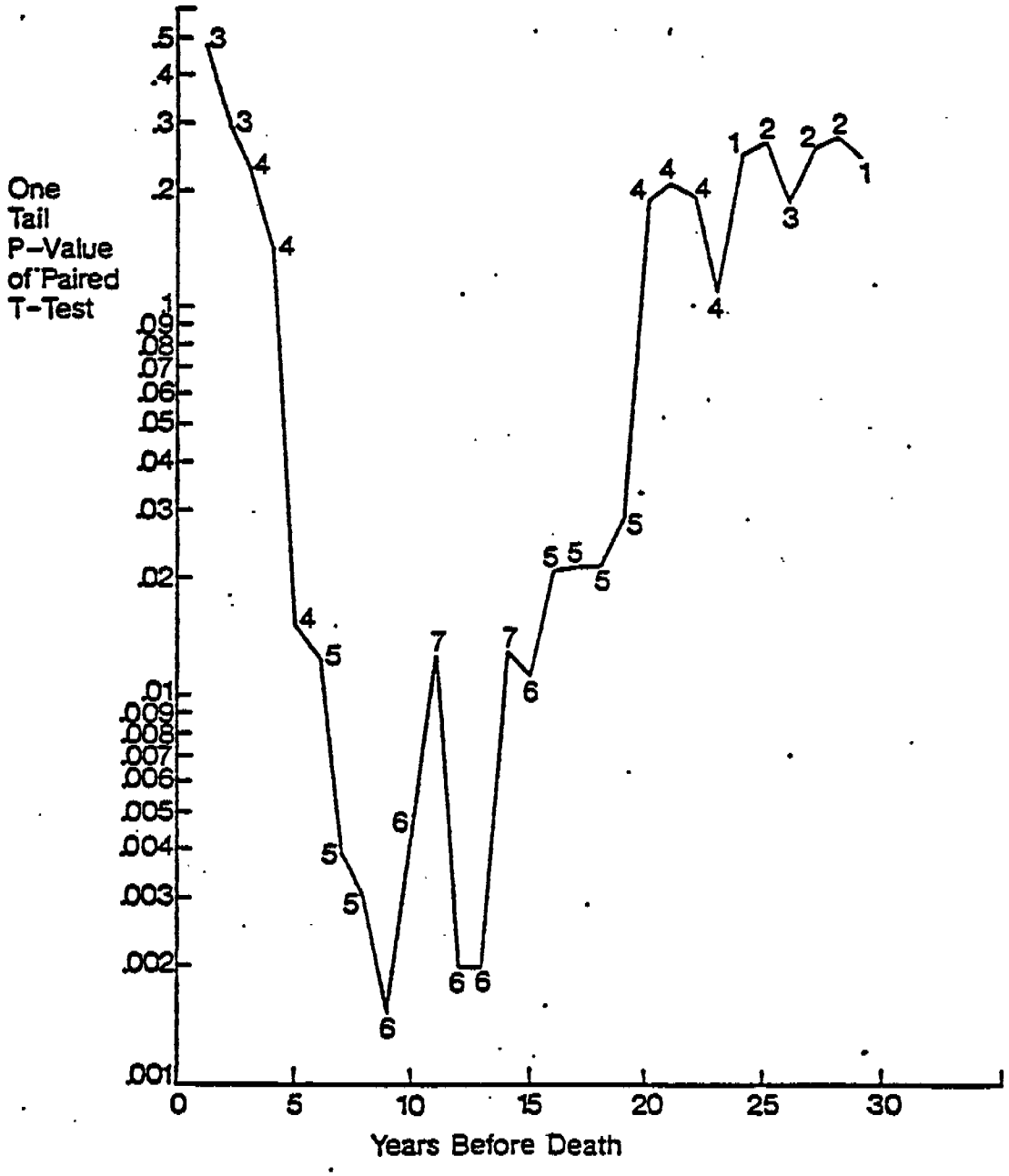
FIGURE 3

P-Values of Paired T-Tests of Observed Versus Expected Annual Doses of PVC Dust Among Type 3 and 4 Lung Cancer Cases
(Number of Cases Working Each Year is Noted at Each Point)



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R&S 111724

Your ref	Our ref	Tel ext	Date
VC Dust	IFHP:SMS	116	9 Oct 78

Dear Dr Waxweiler

Thank you for letting me have a copy of your paper, "An epidemiologic investigation of an excess lung cancer risk in a synthetic chemicals plant". Unfortunately, but not unexpectedly(!), I was unable to find you again at the Congress and so I thought it best to write to you to give you some of my preliminary impressions of your paper.

Firstly, may I say that I found it an extremely thought-provoking paper and you seem to have developed a powerful new tool in the SAED model. I will be most interested to see it used in other situations.

As you may know, I am a biologist not a statistician, and any comments I make are from that point of view. The statistics you use are far too complex for me to comment on! There are two main comments which stem from a biological appreciation of the chemical induction of cancer which I believe have a direct bearing on the conclusions of your paper.

The first depends on the relationship between dose and time on the one hand, and incidence of cancer on the other. Druckery has studied the induction of cancer in rats with a whole series of nitrosamines and has produced quantitative data on the dose/time/cancer incidence relationship. The best publication of this data is: H Druckery, "Quantitative aspects in chemical carcinogenesis" p.60, in "Potential carcinogenic hazards from drugs" R Truhaut ed. UICC Monograph Series, vol 7. Basically he finds that incidence is proportional to daily dose x time^n. In most cases the value of n is about 3. Coroboration of this relationship comes from a study by Jones and Grendon (Food Cosmet Toxicol 13 251-268 1975) using partly Druckery's data but also data from other studies, and again the relationship between time and incidence is a 3rd-power relationship. There are other examples in the literature which support this observation. In your study the time of exposure is treated as if it had a constant influence on cancer incidence over the whole life of the plant. This is contrary to the way in which the relationship is known to operate, where earlier exposure should have a weighting which acknowledges its much greater contribution to cancer incidence. In your study the only way that this problem is tackled is via latency, where your analysis is carried out on

all the exposure data and also on the exposure data minus the last ten years. It seems to me that this overlooks one of the basic and important characteristics of the biology of cancer.

The second problem I have relates to the estimation of dose in the SAED technique. I understand that the only technique available is to grade it from 0 - 5 using the opinion of the plant personnel, and clearly this is a good technique with which I do not have any quarrel. The problem is in regard to the biological significance of the doses and the best way I can explain it is by an hypothetical example. Let us assume that there are two chemicals, exposure to which is estimated by the SAED technique. The chemicals have the following properties:-

A : (1) relatively non-toxic in the acute sense;
(2) exposure undetected by human senses, ie odourless, non-irritant, allowing a relatively high TLV (say 1,000 ppm);
(3) carcinogenic to man at a high dose.

B : (1) same physical properties as A;
(2) acutely toxic;
(3) irritant and with pungent odour, requiring a very low TLV (say 1 ppm);
(4) carcinogenic to man at the same dose as A.

In this example, the estimation of exposure of A and B, in the absence of knowledge of carcinogenicity, could well be very different. Thus, figures might be:-

Category of exposure	Exposure in ppm	
	Chemical A	Chemical B
0	0	0
1	?	?
2	?	?
3	?	?
4	1,000 ppm	1 ppm
5	>>>>1,000 ppm	>1 ppm not acceptable because of smell etc

Remembering that our assumption is that the chemicals are of equal carcinogenicity, but that the TLV is not based on knowledge of carcinogenicity (as would be the case with PVC dust if your deductions are right), you can see that a grade 4 exposure might be allocated by the company personnel to doses (in ppm) of chemicals which are 1,000-fold different, and this would also be reflected in terms of carcinogenicity. The reason for this is that the company personnel are grading exposure on criteria which are definitely different from those assumed in the further statistical treatment of the grades.

Expressing the concept outlined above has proved to be very difficult, and I hope that it is well enough laid out for you to understand. There are other ways of expressing it and possibly you might like to compare, in ppm terms, the grading which would be given to ethylene and vinyl chloride or ethylene and sulphur dioxide. All are gases, vinyl chloride and ethylene being controlled in the old days because of flammability hazards and SO_2 being very irritant. A grade 5 exposure for ethylene and SO_2 might easily be 1,000-fold different with vinyl chloride more like ethylene, but in addition being a carcinogen. How does the SAED technique take account of these different biological properties?

In conclusion there are possible flaws in both of the parameters used in computing the serially additive dose which, I believe, will not be corrected by the sophisticated statistics which are later applied to the data. I am also forced to conclude that the arguments which connect tumour incidence specifically to exposure to <u>any</u> of the chemicals on this plant are not particularly persuasive, but I would be pleased to hear from you that I have overlooked something.

These issues are so complex, that writing a letter is a poor substitute for personal discussion - something I hope we will be able to arrange in the not too distant future.

Yours sincerely

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Your ref	Our ref	Tel ext	Date
JS/MJE/DSO-107	GMP/CMC	5354	11 October 1978

Dear John

PVC DUST

26.9.78

Thank you for sending me Waxweiler's thesis; it is a fascinating piece of work. As an item of research I think it is excellent. Indeed, had I sufficient staff available, it is precisely the sort of approach I would like to have investigated myself. It also manages to throw in several reminders to budding epidemiologists which are well worth recording for future reference. For instance, the misguided linking of vinyl chloride with lung cancer without checking for alternative causes, and the sensible division of lung cancers into those which show an exces and those which do not, expose flaws in my own simplistic approach to problems.

But you ask for an expert view on the hypothesis that PVC dust causes lung cancers. You will have noticed that the calculations are rather complicated and that they have to be performed by a computer program. A sound assessment f the validity of the calculations requires some intermediate data which are not provided. Lacking these data, one is forced to say that there are flaws in the technique, and that it is impossible to assess the importance of these flaws. The significance level at which the hypothesis 'PVC dust exposure is unrelated to lung cancer' is rejected is certainly far from the 1% or 5% figures which are to be found in the report. It is possible that it approaches the 50%, or toss of a coin, level. Some of the flaws are subtle, some less so, while others are improvements on greater flaws in other techniques. It is all rather complicated.

As this paper is likely to be widely quoted, and as this technique is now available as a computer program and is a novel way of creating hypotheses, I feel an attempt should be made to put the technique on a firmer footing. Is there any satisfactory way of going about such a task?

Yours sincerely

Geoff

G M Paddle (Dr)

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