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CASE-CONTROL STUDY OF BRAIN TUMOR
DEATHS AMONG EMPLOYEES AT A
CHEMICAL MANUFACTURING PLANT

R&S 113220

G. G. BOND, R. R. COOK, R. J. SHELLENBERGER,
R. L. DANIEL, AND W. A. FISHBECK

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ON BRAIN TUMORS
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RECENTLY, AN UNPUBLISHED NIOSH/OSHA COMMUNITY-BASED CASE-CONTROL STUDY OF BRAIN TUMOR DEATHS AMONG RESIDENTS OF BRAZORIA COUNTY, TEXAS SUGGESTED A TWO-FOLD RISK FOR HAVING EVER BEEN EMPLOYED BY THE LARGEST LOCAL INDUSTRY, DOW CHEMICAL U.S.A., TEXAS DIVISION, FREEPORT. WHILE COOPERATING WITH NIOSH AND OSHA IN A VALIDITY CHECK OF THEIR INITIAL RISK ESTIMATE, WE CONDUCTED A PLANT-BASED CASE-CONTROL STUDY IN AN ATTEMPT TO LOCALIZE THE PRESUMPTIVE RISK TO A PARTICULAR PROCESS, CHEMICAL, OR OTHER PUTATIVE AGENT. THIS PAPER SUMMARIZES OUR INVESTIGATION.

(SLIDE 1: CASE-CONTROL PLANT)

THERE ARE FEW KNOWN RISK FACTORS FOR BRAIN NEOPLASMS IN HUMANS. THE INCIDENCE AND MORTALITY RISE STEEPLY AFTER AGE 30 TO A PEAK BETWEEN 55 AND 64, AND ARE RELATIVELY HIGHER AMONG WHITES AND MALES. WITHIN THE PAST FEW YEARS, A SERIES OF TOXICOLOGIC AND EPIDEMIOLOGIC REPORTS HAVE FOCUSED ATTENTION ON THE POSSIBLE ETIOLOGIC ROLE OF CHEMICALS AND, TO A LESSER EXTENT, VIRUSES.

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EXPERIMENTAL SYSTEMS FOR INDUCING GLIOMAS BY DIRECT INJECTION OF CARCINOGENS AND VIRUSES HAVE BEEN SUMMARIZED. ANIMAL STUDIES HAVE SUGGESTED THAT ACRYLONITRILE CAN INDUCE CENTRAL NERVOUS SYSTEM TUMORS, AND CONTROLLED EXPOSURES TO EXTREMELY HIGH LEVELS OF VINYL CHLORIDE (2,500 - 10,000 PPM) HAVE PRODUCED BRAIN TUMORS IN RATS.

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THE EPIDEMIOLOGIC REPORTS HAVE BEEN LESS DEFINITIVE. A STUDY OF RECORDS MAINTAINED BY THE OIL, CHEMICAL AND ATOMIC WORKERS UNION NOTED A PROPORTIONATE EXCESS OF BRAIN TUMORS AMONG UNION MEMBERS, BUT WAS UNABLE TO LINK THE OBSERVATION TO SPECIFIC EXPOSURES. EXCESS MORTALITY DUE TO BRAIN NEOPLASMS HAS BEEN REPORTED AMONG OTHER U.S. PETROCHEMICAL EMPLOYEES AND AMONG SWEDISH CHEMISTS. WHILE SUGGESTING AN INCREASED RISK ASSOCIATED WITH EMPLOYMENT, NEITHER STUDY WAS ABLE TO IDENTIFY A SPECIFIC CAUSATIVE AGENT. IN A LARGE, INTER-COMPANY STUDY OF VINYL CHLORIDE WORKERS, AN EXCESS OF BRAIN CANCER DEATHS WAS OBSERVED. BUT THERE WAS NO APPARENT DOSE RESPONSE RELATIONSHIP WITH VINYL CHLORIDE AND THUS THE FINDINGS WERE PROBABLY COINCIDENTAL TO EXPOSURE.

(SLIDE 3: OBJECTIVE: FOCUS AGENT)

IT WAS THE PURPOSE OF THIS STUDY TO ATTEMPT TO IDENTIFY A COMMON OR UNIQUE HISTORY OF EXPOSURE AMONG DOW TEXAS EMPLOYEES KNOWN DECEASED WITH A DIAGNOSIS OF PRIMARY INTRACRANIAL NEOPLASM, BENIGN OR MALIGNANT. BECAUSE WE HAD NO A PRIORI HYPOTHESIS REGARDING A SPECIFIC EXPOSURE AGENT, WE CONSIDERED THIS A HYPOTHESIS GENERATING INVESTIGATION, I.E., IT WAS INTENDED TO SUGGEST AREAS FOR MORE RIGOROUS STUDY.

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MATERIALS AND METHODS

CASE-CONTROL METHODOLOGY WAS CHOSEN AS THE MOST APPROPRIATE TOOL FOR INVESTIGATING THE PROBLEM. WHILE PRONE TO A NUMBER OF INADVERTENT BIASES AND INCAPABLE OF YIELDING DIRECT ESTIMATES OF RISK, THE CASE-CONTROL APPROACH HAS A NUMBER OF ADVANTAGES. IT IS RAPID; IT IS EFFICIENT WHEN, AS IS THE CASE WITH BRAIN TUMOR, THE DISEASE OF INTEREST IS RELATIVELY RARE; AND IT CAN EVALUATE A MULTITUDE OF POSSIBLE EXPOSURE VARIABLES IN RELATION TO A DEFINED DISEASE ENTITY.

CASE AND CONTROL SELECTION

(SLIDE 5: CASES (ICD 8))

THE CASE POPULATION WAS COMPRISED OF DOW, TEXAS DIVISION EMPLOYEES KNOWN DECEASED WITH A DEATH CERTIFICATE DIAGNOSIS OF PRIMARY INTRACRANIAL NEOPLASM (ICD 8TH REVISION CODES 191, MALIGNANT NEOPLASM OF BRAIN; 192.9, MALIGNANT NEOPLASM OF OTHER PARTS OF NERVOUS SYSTEM, SITE UNSPECIFIED; 225.0, BENIGN NEOPLASM OF BRAIN; AND 238.1, NEOPLASM OF UNSPECIFIED NATURE OF BRAIN). ALL CASES WERE WHITE MALES. THE ONLY FEMALE WAS EXCLUDED FROM STUDY BECAUSE OF A LACK OF SUITABLE CONTROLS; HER CHEMICAL COMPANY EMPLOYMENT WAS LIMITED TO HAVING BEEN A TELEPHONE OPERATOR AT THE LOCAL COMMUNITY HOSPITAL.

(SLIDE 6: BRAIN TUMOR CASE ASCERTAINMENT)

THE CASES WERE IDENTIFIED VIA TWO SEPARATE MECHANISMS. ALL DEATH CERTIFICATES ON FILE IN THE INDUSTRIAL MEDICINE DEPARTMENT (IMD) OF THE COMPANY WERE SURVEYED FOR MENTION OF BRAIN TUMOR. CASES AMONG FORMER EMPLOYEES WHO TERMINATED

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EMPLOYMENT WITHOUT HAVING BEEN VESTED WERE IDENTIFIED IN TWO STAGES. FIRST, ALL DEATHS FROM PRIMARY INTRACRANIAL NEOPLASMS RECORDED BY THE TEXAS BUREAU OF VITAL STATISTICS FOR RESIDENTS OF BRAZORIA COUNTY AND 3 CONTIGUOUS COUNTIES (HARRIS, GALVESTON AND MATAGORDA) FOR THE YEARS 1950-1979 WERE IDENTIFIED BY NIOSH/OSHA. SECONDLY, THESE CASES WERE CHECKED AGAINST DOW, TEXAS DIVISION PERSONNEL FILES TO DETERMINE A PRIOR HISTORY OF EMPLOYMENT.

(SLIDE 7: CONTROL GROUPS SELECTION)

TWO CONTROL GROUPS WERE SELECTED UTILIZING A MULTIPLE-MATCH-PER-CASE DESIGN. THE FIRST CONTROL POPULATION, CONTROL GROUP A, WAS SELECTED FROM THE FILE OF DEATH CERTIFICATES MAINTAINED BY THE IMD. TO BE CONSERVATIVE, ALL DEATHS FROM MALIGNANT NEOPLASMS WERE EXCLUDED. THE CONTROLS WERE RESTRICTED TO WHITE MALES TO REFLECT THE RACE AND SEX DISTRIBUTION OF THE CASES. FOUR CONTROLS WERE THEN MATCHED TO EACH CASE BASED ON YEAR OF BIRTH $\pm$ 5 YEARS AND YEAR OF DEATH. WHEN MORE THAN FOUR MATCHES WERE AVAILABLE FOR ANY GIVEN CASE, FOUR WERE SELECTED RANDOMLY USING A COMPUTER PROGRAM. FOR ONE CASE THERE WERE ONLY THREE AVAILABLE CONTROLS WHO SATISFIED THE MATCHING CRITERIA. IN ADDITION, THREE OTHER CASES COULD NOT BE MATCHED DIRECTLY ON YEAR OF DEATH SO THAT CONTROLS FOR THESE CASES WERE MATCHED ON YEAR OF DEATH $\pm$ 1 YEAR.

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THE SECOND CONTROL POPULATION, CONTROL GROUP B, WAS DERIVED FROM A RANDOMLY SELECTED SAMPLE REPRESENTING EVERYONE WHO HAD EVER WORKED AT DOW, TEXAS DIVISION USING THE WORK HISTORY FILES AS THE SOURCE POPULATION. FOUR CONTROLS WERE MATCHED TO EACH CASE ON YEAR OF BIRTH $\pm$ 5 YEARS AND WERE RESTRICTED TO WHITE MALES. THESE CONTROLS, IN CONTRADISTINCTION TO THOSE ABOVE, WERE MATCHED WITH THE CASES ON WHETHER THEY WERE HOURLY OR SALARIED AT THE TIME OF EMPLOYMENT TERMINATION; HOWEVER, THIS WAS NOT ALWAYS POSSIBLE, THUS SOME RESIDUAL CONFOUNDING DUE TO PAY STATUS COULD BE PRESENT.

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EXPOSURE DETERMINATION

COMPLETE DOW, TEXAS DIVISION WORK HISTORIES, AS AVAILABLE FROM PERSONNEL DEPARTMENT RECORDS, WERE CODED AND COMPUTERIZED FOR BOTH CASES AND CONTROLS. ON-SITE INDUSTRIAL HYGIENISTS EXTRAPOLATED CHEMICAL AGENT SPECIFIC EXPOSURE PROFILES FOR EACH SUBJECT BASED ON WORK HISTORY, PRESENT SURVEY DATA AND KNOWLEDGE OF PROCESS CHANGES. THIS WAS DONE WHILE THE INDUSTRIAL HYGIENIST WAS "BLIND" TO WHETHER THE SUBJECT WAS A CASE OR A CONTROL. DUE TO THE IN-PLANT MOBILITY OF SOME JOBS (E.G., CRAFTSMEN) IT WAS IMPOSSIBLE TO ASSIGN PRESUMPTIVE CHEMICAL EXPOSURES TO JOBS HELD BY 29% OF THE CASES AND 34% OF THE CONTROLS. THE RISK OF BEING A CRAFTSMAN, HOWEVER, WAS INDIRECTLY ASSESSED IN THE ANALYSES OF HAVING HELD A JOB ASSIGNMENT IN A MAINTENANCE

DEPARTMENT OR IN A BOILER, PIPE OR MACHINE SHOP SINCE CRAFTSMEN WERE ASSIGNED TO ONLY THESE DEPARTMENTS.

IN SCREENING FOR VARIABLES, THE POTENTIAL FOR CHEMICAL EXPOSURE WAS TREATED IN TWO DIFFERENT WAYS: FIRST, WORK HISTORIES OF CASES AND CONTROLS WERE SCANNED FOR COMMON EXPERIENCE IN A PARTICULAR DEPARTMENT OR GROUP OF DEPARTMENTS RELATED BY FUNCTION OR CHEMICAL PROCESS; SECONDLY, EXPOSURE PROFILES FOR CASES AND CONTROLS WERE SEARCHED FOR COMMON CHEMICAL EXPOSURES. EACH OF THESE WAS TREATED AS A DICHOTOMOUS VARIABLE: EVER OR NEVER WORKED IN DEPARTMENT OF INTEREST; AND, EVER OR NEVER HAD EXPOSURE TO CHEMICAL OF INTEREST.

WHILE QUANTITATIVELY EXPOSURES WITHIN A DEPARTMENT MOST CERTAINLY VARIED, PERSONNEL ASSIGNED TO THE SAME WORK AREA WOULD HAVE HAD EXPOSURES TO THE SAME GENERAL MATERIALS. TO MAKE THE ANALYSES MORE MEANINGFUL, ONLY DEPARTMENTS IN WHICH A MINIMUM OF FIVE CASES HAD EVER HELD AN ASSIGNMENT WERE CONSIDERED.

(SLIDE 9: WORK ASSIGNMENTS OF CASES)

THERE WERE THREE SUCH DEPARTMENTS: MAGNESIUM, MAINTENANCE, AND THE GROUPED CLASSIFICATION OF BOILER, PIPE OR MACHINE SHOP.

IN ORDER TO PROVIDE FOR A PLAUSIBLE LATENT PERIOD BETWEEN JOB ASSIGNMENT AND TUMOR DEVELOPMENT, SEPARATE ANALYSES WERE PERFORMED WHICH IGNORED ALL JOB ASSIGNMENTS HELD BY CASES AND CONTROLS WITHIN 5, 10, 15 AND 20 YEARS OF THE DEATH OF THE CASE.

SINCE DATE OF TUMOR DEVELOPMENT WAS UNKNOWN, THE DATE OF DEATH OF THE CASE WAS USED TO DEFINE THE LATENCY PERIOD.

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DEFINITION OF OTHER VARIABLES CONSIDERED

TO ENSURE AS COMPLETE AN ASSESSMENT OF THE WORK HISTORY AS POSSIBLE, SEVERAL ADDITIONAL VARIABLES WERE CONSIDERED. WHILE CONTROLS WERE MATCHED TO THE CASES ON YEAR OF BIRTH AND YEAR OF DEATH IT WAS POSSIBLE THE GROUPS MIGHT HAVE DIFFERED WITH RESPECT TO YEAR OF HIRE; THUS, AN ANALYSIS OF THE RISK ASSOCIATED WITH EMPLOYMENT BEFORE 1950 WAS PERFORMED. DURATION OF EMPLOYMENT WAS ALSO OF INTEREST AS IT HAS OFTEN BEEN USED AS A SURROGATE FOR DOSE OF EXPOSURE IN OCCUPATIONAL STUDIES. FOR THIS ANALYSIS, DURATION WAS CATEGORIZED ACCORDING TO THE FOLLOWING: > 1 YEAR BUT $\leq$ 5 YEARS, $\times$ 5 YEARS BUT $\leq$ 10 YEARS, AND > 10 YEARS. IN ADDITION, THE CASES AND CONTROLS WERE ANALYZED FOR PAY STATUS, WHETHER HOURLY OR SALARIED, AT TIME OF TERMINATION OF EMPLOYMENT. THE HOURLY-SALARIED DISTINCTION HAS IMPLICATIONS FOR BOTH EXPOSURE AND SOCIOECONOMIC VARIABLES. FINALLY, MEDICAL RECORDS WERE REVIEWED FOR A HISTORY OF MEDICAL TREATMENT FOR AN ACUTE CHEMICAL OVEREXPOSURE.

IN ADDITION TO THE VARIABLES MENTIONED ABOVE, SOME NON-OCCUPATIONAL VARIABLES WERE ALSO CONSIDERED. MEDICAL RECORDS MAINTAINED BY THE IMD FOR CASES AND CONTROL GROUP A WERE SEARCHED FOR AN ENTRY INDICATING A POSITIVE HISTORY OF SALK POLIO VACCINATION. MEDICAL RECORDS WERE ALSO REVIEWED FOR A HISTORY OF ALCOHOL AND TOBACCO USE.

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ANALYTIC TECHNIQUE

SINCE ONLY THREE MATCHED CONTROLS COULD BE FOUND FOR ONE OF THE CASES IN CONTROL GROUP A, A CASE-CONTROL ANALYSIS FOR A VARIABLE MATCHING RATIO WAS PERFORMED. THE ANALYSIS WITH CONTROL GROUP B WAS THAT PROPOSED FOR A FIXED 4:1 MATCHING RATIO WITH $R > 1$. POINT ESTIMATES OF THE ODDS RATIO WERE CALCULATED AND CONFIDENCE LIMITS FOR THE ODDS RATIO WERE TAKEN AS TEST-BASED LIMITS BASED ON THE POINT ESTIMATES AND THE CHI FROM HYPOTHESIS TESTING. FOR CALCULATING THE CONFIDENCE LIMITS, A z VALUE OF 1.645 WAS USED, CORRESPONDING TO A TWO-TAILED TEST WITH $\alpha = 0.10$. SELECTION OF THIS α VALUE WAS CONSISTENT WITH THE HYPOTHESIS GENERATING NATURE OF THIS STUDY. ALL ANALYSES WERE PERFORMED ON A PROGRAMMABLE CALCULATOR WITH A PACKAGED SET OF PROGRAMS.

RESULTS

CHARACTERIZATION OF CASES AND CONTROLS

A REVIEW OF THE IMD MORTALITY FILE IDENTIFIED 14 CASES WITH A DEATH CERTIFICATE DIAGNOSIS CONSISTENT WITH PRIMARY INTRACRANIAL NEOPLASM. AN ADDITIONAL 10 CASES WERE IDENTIFIED VIA A CHECK OF BRAIN TUMOR DEATHS, AS RECORDED IN FOUR COUNTIES, AGAINST DOW, TEXAS DIVISION PERSONNEL RECORDS. ALL CASES WERE WHITE MALES (AS MENTIONED, A FEMALE WAS EXCLUDED).

AS YET, PATHOLOGIC CONFIRMATION HAS NOT BEEN RECEIVED FOR THE MAJORITY OF THE CASES; HOWEVER, THE NIOSH/OSHA INVESTIGATIVE TEAM IS SEEKING THIS. DISTRIBUTION OF THE CASES BY YEAR OF DEATH AND AGE AT DEATH WAS GENERALLY UNREMARKABLE; BOTH WERE CONSISTENT WITH THE POPULATION DYNAMICS OF THE WORK FORCE AND AGE-SPECIFIC MORTALITY FROM BRAIN TUMOR. AGE AT DEATH RANGED FROM 37 TO 70 YEARS WITH A MEDIAN OF 55 YEARS. THE DEATHS OCCURRED OVER A

26 YEAR PERIOD AND THERE HAVE BEEN NO PRIMARY INTRACRANIAL NEOPLASTIC DEATHS AMONG THE DOW, TEXAS DIVISION POPULATION SINCE 1977.

THE MATCHING TECHNIQUE EMPLOYED RESULTED IN A TOTAL OF 95 DECEASED EMPLOYEES INCLUDED IN CONTROL GROUP A. AFTER EXCLUSION OF DEATHS FROM MALIGNANT NEOPLASMS, A HIGH PROPORTION OF DEATHS FROM DISEASES OF THE CIRCULATORY SYSTEM (69%) WAS NOT UNEXPECTED. THIS DOES NOT SUGGEST A SELECTION BIAS AS THERE ARE FEW CHEMICAL SPECIFIC OCCUPATIONAL EXPOSURES WHICH HAVE BEEN RELATED TO AN INCREASED RISK OF CARDIOVASCULAR DISEASE.

THERE WERE 96 CONTROLS WHO WERE MATCHED SUCCESSFULLY WITH THE CASES USING THE CRITERIA EMPLOYED FOR THE SELECTION OF CONTROL GROUP B. OF THE 24 KNOWN DEATHS IN CONTROL GROUP B, ONLY ONE WAS DUE TO A MALIGNANT NEOPLASM; AGAIN THE HIGH PROPORTION OF DEATHS FROM CIRCULATORY DISEASES (71%) DOES NOT READILY SUGGEST ANY SELECTION BIAS.

EXPOSURE COMPARISONS

NONE OF THE ODDS RATIOS FOR ANALYSES OF DEPARTMENTAL ASSIGNMENT OR CHEMICAL EXPOSURE DEVIATED SIGNIFICANTLY FROM UNITY. THE NEXT TWO SLIDES ARE CONDENSATIONS OF THE MORE COMPLETE TABLES WHICH WILL BE FOUND IN THE PROCEEDINGS

(SLIDE 11: RISK LATENCY)

HERE WE FOCUS ONLY ON THE POINT ESTIMATES OF RISK ASSOCIATED WITH PROCESS AREA BY CONTROL GROUP BY MINIMUM LATENCY.

CONSISTENTLY ELEVATED ODDS RATIOS WERE NOTED FOR EVER HAVING HELD A JOB ASSIGNMENT IN MAGNESIUM PRODUCTION DEPARTMENT (1.84 AND 1.80 VS. CONTROL GROUP A AND B, RESPECTIVELY) AND SOME

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ELEVATIONS WERE FOUND IN SUBCATEGORIES OF THE GROUP: BOILER, PIPE OR MACHINE SHOPS. CONSISTENTLY DEPRESSED ODDS RATIOS WERE IDENTIFIED FOR MAINTENANCE. NONE OF THESE FINDINGS WERE STATISTICALLY SIGNIFICANT AND A DECREASING ODDS RATIO WITH INCREASING LATENT PERIOD WAS NOTED FOR MAGNESIUM PRODUCTION; AN INCREASING ODDS RATIO: BOILER, PIPE AND MACHINE SHOPS.

(SLIDE 12: RISK GROUP)

HERE WE FOCUS ON THE POINT ESTIMATES OF RISK ASSOCIATED WITH A NUMBER OF OCCUPATIONAL AND NON-OCCUPATIONAL VARIABLES: DATE OF HIRE, SALARY STATUS, SALK POLIO VACCINE, DURATION OF EMPLOYMENT, AND POTENTIAL EXPOSURES TO CHLORINE OR HYDROGEN CHLORIDE VAPOR.

ANALYSIS OF THE COMPARISON WITH CONTROL GROUP A BY YEAR OF HIRE REVEALED A SIGNIFICANTLY ELEVATED ODDS RATIO FOR HAVING BEEN FIRST EMPLOYED PRIOR TO 1950 (5.27); ALTHOUGH NOT SIGNIFICANT, THE ODDS RATIO FOR THE COMPARISON WITH CONTROL GROUP B WAS ALSO ELEVATED (2.81). UPON CLOSER SCRUTINY, IT WAS NOTED THAT 20 OF THE 24 CASES (83%) BEGAN EMPLOYMENT AT DOW, TEXAS DIVISION BETWEEN 1940 AND 1946 (THE PLANT BEGAN OPERATIONS IN 1940).

ALTHOUGH NOT STATISTICALLY SIGNIFICANT IN EITHER OF THE COMPARISONS, THE ODDS RATIO FOR HAVING BEEN A SALARIED EMPLOYEE AT THE TIME OF TERMINATION WAS ELEVATED (2.18; 1.46). SINCE CONTROL GROUP B WAS PARTIALLY MATCHED WITH THE CASES ON PAY STATUS, IT WAS NOT UNEXPECTED THAT THE ODDS RATIO FOR THIS COMPARISON WOULD BE LOWER THAN THAT FOR THE COMPARISON WITH CONTROL GROUP A.

THE ANALYSIS OF DURATION OF EMPLOYMENT WITH DOW, TEXAS DIVISION REVEALED SIGNIFICANTLY ELEVATED ODDS RATIOS FOR EMPLOYMENT FROM 1 TO 5 YEARS (4.79; 6.64) AND SIGNIFICANTLY DECREASED ODDS RATIOS FOR EMPLOYMENT GREATER THAN 10 YEARS (0.30; 0.14). THIS INDICATES THE CONTROLS WERE MORE LIKELY THAN THE CASES TO HAVE BEEN EMPLOYED GREATER THAN 10 YEARS. OF THE 24 PRIMARY BRAIN TUMOR CASES, 10 WERE EMPLOYED LESS THAN 5 YEARS AND 4 OF THESE WERE EMPLOYED LESS THAN 1 YEAR.

ANALYSIS OF OTHER VARIABLES

A REVIEW OF THE ACUTE CHEMICAL EXPOSURE FILE FOR A HISTORY OF MEDICAL TREATMENT FOR OVEREXPOSURE INDICATED ONLY 5 OF THE CASES HAD SUCH A HISTORY AND ONLY TWO OF THESE WERE EXPOSED TO THE SAME CHEMICAL, CHLORINE. BECAUSE OF THE SMALL NUMBERS, NO STATISTICAL ANALYSIS WAS PERFORMED.

REVIEW OF THE MEDICAL RECORDS FOR SMOKING AND ALCOHOL HISTORIES WAS DISAPPOINTING AND DID NOT PROVIDE SUFFICIENT DATA FOR ANALYSIS. ALTHOUGH NOT STATISTICALLY SIGNIFICANT, THE CASES WERE LESS LIKELY THAN THE CONTROLS TO HAVE HAD A POSITIVE HISTORY OF SALK POLIO VACCINATION RECORDED IN THEIR IMD MEDICAL FILE ($\hat{R}_{M-L} = 0.60$).

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DISCUSSION

THE RESULTS OF THIS CASE-CONTROL STUDY DO NOT READILY SUGGEST AN ASSOCIATION BETWEEN HAVING HELD A JOB ASSIGNMENT IN ANY PARTICULAR DEPARTMENT OR PROCESS AREA AND SUBSEQUENT DEATH FROM BRAIN TUMOR. WHILE THERE IS A WEAK ASSOCIATION WITH EMPLOYMENT IN A MAGNESIUM PRODUCTION DEPARTMENT, THIS DOES NOT SUGGEST ANY CHEMICAL AGENT WHICH COULD BE CAUSALLY RELATED. PRIOR TO 1963

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SOME PERSONNEL HAD THE POTENTIAL FOR INTERMITTENT SO_2 EXPOSURE; HOWEVER, THE WORK HISTORIES DID NOT PROVIDE ENOUGH DETAILED DESCRIPTION TO DISCRIMINATE THIS. SOME EXPOSURE TO ELECTROMAGNETIC FIELDS COULD BE EXPECTED IN BOTH CHLORINE AND MAGNESIUM PRODUCTION; ANIMAL STUDIES HAVE SUGGESTED A RELATIONSHIP BETWEEN EXPOSURE TO HIGH ENERGY MAGNETIC FIELDS AND CEREBRAL GLIOSIS; HOWEVER, THERE IS A CLEAR LACK OF EPIDEMIOLOGIC DATA ADDRESSING THIS TOPIC. THE TENDENCY FOR THE ODDS RATIO TO DECREASE WITH AN INCREASING LATENCY PERIOD FURTHER WEAKENS ANY ASSOCIATION WITH THE MAGNESIUM PROCESS.

WHILE ANIMAL STUDIES HAVE SUGGESTED BOTH ACRYLONITRILE AND VINYL CHLORIDE ARE CAPABLE OF INDUCING CENTRAL NERVOUS SYSTEM TUMORS, AND SEVERAL EPIDEMIOLOGIC STUDIES HAVE SUGGESTED AN ASSOCIATION BETWEEN BRAIN TUMOR AND VINYL CHLORIDE EXPOSURE, IT IS INTERESTING TO NOTE THAT NONE OF THE CASES IN OUR STUDY EVER HAD A DOCUMENTED JOB ASSIGNMENT IN A VINYL CHLORIDE DEPARTMENT (VINYL CHLORIDE MONOMER HAS BEEN PRODUCED AT THIS SITE SINCE 1948). THIS LATTER FINDING IS CONSISTENT WITH RESULTS PUBLISHED IN A RETROSPECTIVE MORTALITY STUDY OF VINYL CHLORIDE WORKERS IN DOW, TEXAS DIVISION.

AS MENTIONED, DEVELOPING CHEMICAL AGENT SPECIFIC EXPOSURE PROFILES WAS DIFFICULT FOR CRAFTSMEN SINCE THEIR TRADE CAN CARRY THEM TO ANY PROCESS AREA. THUS, CRAFTSMEN COULD HAVE HAD INTERMITTENT EXPOSURE TO VINYL CHLORIDE AND OTHER ORGANIC CHEMICALS. THE ANALYSES OF HAVING HELD A JOB ASSIGNMENT IN A MAINTENANCE DEPARTMENT OR IN THE BOILER, PIPE OR MACHINE SHOPS DID NOT INDICATE A GREATER PROPORTION OF CRAFTSMEN IN THE CASE

POPULATION, AND WE HAVE NO REASON TO BELIEVE THEY HAD DIFFERENT EXPOSURES THAN DID CRAFTSMEN IN EITHER OF THE TWO CONTROL POPULATIONS.

ALTHOUGH NOT STATISTICALLY SIGNIFICANT, A CONSISTENT FINDING WAS AN ELEVATED ODDS RATIO FOR HAVING BEEN A SALARIED EMPLOYEE AT THE TIME OF TERMINATION OF EMPLOYMENT. AT LEAST TWO OTHER STUDIES OF OCCUPATIONAL GROUPS HAVE NOTED AN INCREASED RISK OF DEATH FROM BRAIN TUMOR AMONG SALARIED (OR WHITE COLLAR) EMPLOYEES. CONSIDERATION OF SOCIOECONOMIC VARIABLES IN FUTURE STUDIES OF BRAIN TUMOR MAY BE INDICATED.

RECENT INTEREST IN THE RELATIONSHIP BETWEEN SALK POLIO VACCINATION AND HUMAN BRAIN TUMOR HAS CENTERED ON THE VACCINE CONTAMINANT OF THE LATE 1950'S AND EARLY 1960'S, SV40 AND ITS ONCOGENIC PROPERTIES. THE APPARENT ISOLATION OF SV40-LIKE PAPOVAVIRUS FROM A CULTURED HUMAN GLIOBLASTOMA HAS HEIGHTENED THIS INTEREST. WE FOUND A DECREASED RISK; BUT OUR ANALYSIS OF A HISTORY OF SALK POLIO VACCINATION IS SOMEWHAT LIMITED AS THE IMD RECORDS ARE LIKELY TO BE INCOMPLETE IN THIS REGARD. THOSE INDIVIDUALS WHO TERMINATED EMPLOYMENT BEFORE THE VACCINATION PROGRAM CONTRIBUTE NO INFORMATION TO THIS ANALYSIS ALTHOUGH THEY COULD HAVE RECIEVED THE VACCINE ELSEWHERE.

A SIGNIFICANT FINDING WAS THE DECREASED ODDS RATIO FOR HAVING BEEN EMPLOYED AT DOW GREATER THAN 10 YEARS. THIS FINDING IS UNDERSTANDABLE IN THE COMPARISON WITH CONTROL GROUP A SINCE THIS GROUP IS WEIGHTED TOWARD EMPLOYEES WHO WERE VESTED. CONTROL GROUP B, HOWEVER, WAS CHOSEN FROM A POOL OF CONTROLS RANDOMLY

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SELECTED FROM THE WORK HISTORY FILE. THE APPARENT LACK OF ASSOCIATION WITH LONGER EMPLOYMENT WOULD ARGUE THAT, IF THERE WERE A CAUSATIVE AGENT, THE EXPOSURE WOULD BE ACUTE AND FROM A POINT SOURCE RATHER THAN A CHRONIC EXPOSURE. THE AVAILABLE DATA DID NOT SUPPORT THIS HYPOTHESIS.

PROBABLY THE MOST STRIKING FINDING WAS THE ASSOCIATION WITH FIRST EMPLOYMENT PRIOR TO 1950, AND THAT 20 OF THE 24 CASES WERE FIRST EMPLOYED BETWEEN 1940-1946. WHILE IT IS GENERALLY ASSUMED THAT HYGIENIC CONDITIONS WITHIN THE CHEMICAL INDUSTRY IN THE EARLY 1940'S WERE QUITE DIFFERENT THAN THEY ARE PRESENTLY, THE LACK OF A COMMON DOCUMENTED WORK EXPERIENCE AMONG THE CASES DID NOT ALLOW US TO IMPLICATE A PARTICULAR PROCESS AREA OR CHEMICAL.

TO FURTHER INVESTIGATE THE APPARENT RELATIONSHIP BETWEEN THE CASES AND YEAR OF FIRST EMPLOYMENT AT DOW, TEXAS DIVISION WE EXAMINED THE DISTRIBUTION OF THE EVER EMPLOYED POPULATION BY YEAR OF HIRE. NEARLY 18,000 HIRES WERE RECORDED FOR THE PERIOD 1940-1946, APPROXIMATELY 40 % OF THE EVER EMPLOYED POPULATION. THE YEARS 1940-1946 REPRESENT AN UNUSUAL PERIOD IN TERMS OF HIRING PRACTICES IN AMERICAN INDUSTRY. AS WORLD WAR II PROGRESSED AND YOUNG PEOPLE WERE DRAFTED, INDUSTRY TURNED TO THOSE NOT ELIGIBLE TO SERVE IN THE ARMED FORCES: THE OLD, THE DISABLED, AND FEMALES. OUR RECORDS INDICATE THE AVERAGE AGE OF THOSE HIRED BY DOW TEXAS DURING THIS PERIOD WAS ABOUT 10 YEARS OLDER THAN HIRES AT OTHER PERIODS.

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USING HIRING DATA, WE MADE SOME PRELIMINARY CALCULATIONS OF THE NUMBER OF EXPECTED DEATHS FROM PRIMARY INTRACRANIAL NEOPLASMS AMONG THE 1940-1946 NEW HIRE COHORT WHICH SUGGEST THERE MAY BE NO EXCESSIVE RISK. THESE CALCULATIONS ARE MADE BASED ON FOUR ASSUMPTIONS: THE MEDIAN AGE AT HIRE OF THE COHORT WAS 31.5 YEARS, 80% WERE WHITE MALES, THE DEATH RATE FROM COMPETING CAUSES OF DEATH WAS COMPARABLE TO THAT OF THE GENERAL POPULATION AND 64% OF CNS TUMORS RECORDED BY THE NATIONAL CENTER FOR HEALTH STATISTICS WERE PRIMARY INTRACRANIAL TUMORS. THIS YIELDED 24.4 EXPECTED DEATHS IN THE 1940-1946 NEW HIRE COHORT VERSUS 20 OBSERVED.

(SLIDE 14: SUMMARY OF CONCLUSIONS)

IN CONCLUSION, THIS CASE-CONTROL EPIDEMIOLOGIC STUDY OF DEATHS FROM PRIMARY INTRACRANIAL NEOPLASMS AT DOW, TEXAS DIVISION, ALTHOUGH SOMEWHAT LIMITED IN SCOPE AND STATISTICAL POWER, HAS FAILED TO DEMONSTRATE AN ASSOCIATION WITH A JOB ASSIGNMENT IN ANY SPECIFIC PROCESS AREA. THERE WAS AN APPARENT RISK ASSOCIATED WITH YEAR OF HIRE PRIOR TO 1950; HOWEVER, PRELIMINARY CALCULATIONS SUGGEST THAT THE BRAIN TUMORS OBSERVED TO DATE MAY NOT EXCEED THE NUMBER ONE MIGHT EXPECT BASED ON GENERAL U.S. POPULATION MORTALITY STATISTICS. FURTHER STUDIES AIMED AT CONFIRMING OR REFUTING AN EXCESS RISK ARE UNDERWAY.

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SUMMARY VERSION

A Progress Report: The Investigation of Brain Tumors
at the Texas Division of Dow Chemical

Gordon R. Reeve
J. William Lloyd
Victor Alexander
Sanford F. Leffingwell

N Y 15 37-24 OCT 1980
RECEIVED DOW CHEMICAL

INTRODUCTION

The current investigation of brain tumors at Dow Chemical in Freeport, Texas was an outgrowth of a similar investigation involving a petrochemical plant in nearby Texas City, Texas. As part of that investigation scientists from the Occupational Safety and Health Administration (OSHA) and the National Institute for Occupational Safety and Health (NIOSH) reviewed the death certificates of brain cancer cases among adult male residents of the three county area proximate to the Texas City plant. In one of the counties, Brazoria County, Dow Chemical was listed on the death certificate as "usual employer" for one third of the malignant brain tumor deaths. Although Dow Chemical has been the largest single employer in Brazoria County for the past forty years, this observation was sufficiently striking to warrant further investigation.

What follows is a progress report of the first six months of the government's investigation of brain tumors at Dow Chemical. For ease of presentation, the components of the investigation will be discussed under three major headings:

- Preliminary Estimates of Risk;
- Additional Case-Ascertainment; and
- More Definitive Estimates of Risk With Isolation of Risk Factors.

PRELIMINARY ESTIMATES OF RISK

County-Based Case-Control Study

To determine whether or not former Dow employees were over-represented among the brain tumor deaths in Brazoria County and to arrive at preliminary estimates of risk of brain tumor among Dow employees, NIOSH and OSHA conducted a case-control study based on Brazoria County deaths. To distinguish this study from other case-control studies of Dow employees it will be referred to as the county-based case-control study.

The cases included in the study represent the complete set of reported brain tumor deaths among adult male residents of Brazoria County in the years from 1964 to 1977. The cases were initially identified by searching computer tape copies of the Texas Bureau of Vital Statistics file of all Texas deaths from 1964 to 1977. The group of deaths satisfying the following criteria were selected as potential cases:

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1. County of residence was Brazoria County;
2. Sex was male;
3. Age at death was 20 years or greater; and
4. Cause of death was coded by state nosologists as a primary intracranial neoplasm (ICDA 8th Revision codes 191, 192.9, 225.0, 238.1)

The death certificates of the potential cases were then reviewed by a NIOSH contracted nosologist to verify the accuracy of the state-assigned ICDA codes. Two of the potential cases were excluded on the basis of this review; bringing the total number of cases included in the study to 25.

Controls were selected from a copy of the Texas data base identical to the one used to identify the cases except that it lacked the data of the 1977 Texas deaths. Each case was assigned four matched controls according to the following selection criteria.

1. County of residence was the same as case.
2. Sex was the same as case.
3. Race was the same as the case except for one case who was of Spanish surname but assigned white controls.
4. Year of Death was the same as the case except for cases who died in 1977, they were assigned controls in 1976. This modification was necessary because a control group sampling frame for 1977 was not available.
5. Age at death was within 1 year of the case except for three cases. Two of which were assigned controls within 2 years of the cases' ages at death. The third case was assigned controls within 3 years of the case's age at death. This modification was necessary due to a limited number of deaths within their particular age/race strata.
6. Cause of death was not a primary intracranial neoplasm, i.e. the state assigned ICDA code does not equal any of the codes defining a case.

In order to determine past employment at Dow Chemical, the death certificates of all 125 cases and controls were examined for mention of Dow Chemical as "usual employer".

The maximum likelihood estimate of the odds ratio¹ was used to determine whether employment at Dow was associated with an increased risk of death due to brain tumor. The test for statistical significance was of the two-tailed Mantel-Haenszel Chi¹. The level of statistical significance was set at the 0.90 level and 90% confidence intervals were calculated. Analyses were conducted which included stratification by tumor type and by race.

The maximum likelihood estimate of the odds-ratio indicated a 2 1/2-fold increased risk of death due to brain tumor among those decedents with Dow Chemical listed as usual employer on the death certificate. The detailed results appear in Table 1. The odds-ratio for all brain tumors, all races was 2.67 with a 90% confidence interval ranging from 1.17 to 6.10. The odds-ratio for the brain tumors among whites was 3.20 with a 90% confidence interval ranging from 1.38 to 7.45. The odds-ratios for all malignant brain tumors was 2.40, with a 90% confidence interval ranging from 1.01 to 5.69, as was the odds ratio and corresponding 90% confidence interval for malignant brain tumors among whites.

Refinement of the County-based Case-Control Study

Although the county-based case-control study demonstrated a 2 1/2 fold risk of brain tumor given Dow employment, this finding was based entirely on information appearing on death certificates. Unfortunately, occupational information on death certificates is frequently scanty or unrepresentative of a decedent's usually varied occupational history. For this reason the data of the county-based case-control study was reanalyzed using company personnel records to determine whether any of the cases and controls had been employed by Dow. Upon matching with the personnel records the initial percentage of former Dow employees among the brain tumor cases was increased from 32% to 41%. A corresponding increase was seen in the controls, from 15% to 24%. It was interesting that all of the Dow cases identified by death certificate were subsequently verified by personnel record matching.

As this study was a minor variation of the initial county-base case-control study, all of the components of the study design remained the same, with the exception of the following two items. The 1976 controls for 1977 cases were replaced by selecting 1977 from a newly available updates to the Texas death files from 1977 to 1979. A search of these updates for additional Brazoria County brain tumor deaths produced two additional cases, bringing the total number of cases in the study to 27. The case-control analyses again demonstrated an increased risk of death due to brain tumor given employment at Dow Chemical. The computed odds-ratios and their respective 90% confidence intervals for the various stratifications by tumor type and race appear in Table 2.

The odds-ratios of perhaps greatest relevance are those for all tumors (malignant and benign), whites only and malignant tumors, whites only. For all tumors, whites only, the odds-ratios was 2.41 with a 90% confidence interval extending from 1.12 to 5.20. The odds-ratios for malignant tumors, whites only, was 1.98 with a 90% confidence interval extending from 0.87 to 4.51.

ADDITIONAL CASE ASCERTAINMENT

The preliminary risk estimates warranted further investigation which began with additional case ascertainment.

The primary thrust of these case ascertainment activities was the manual matching of the Dow personnel records with a computer-selected set of deaths due to brain tumor. The Texas Bureau of Vital Statistics data base and one ancillary data file were searched for all reported deaths due to brain tumor among residents of Brazoria and its neighboring counties. The deaths identified by these searches represented all deaths due to brain cancer from 1950 to 1964 and all deaths due to brain tumor from 1964 to 1979 among residents of Harris, Galveston, Brazoria and Matagorda Counties. These deaths were then matched against the personnel records of all former Dow employees, estimated at 37,000 records. The preliminary matches were scrutinized for accuracy of the match with the personnel by government and company representatives. The death certificates of the preliminary matches were reviewed by a NIOSH contracted nosologist to verify the accuracy of the state-assigned cause of death codes. Matches must have passed both reviews before being designated as a case.

A number of other cases were identified by a variety of activities which included the following:

1. Review of death certificates on file in the company medical department;
2. Search of county death certificate files; and
3. Follow-up of unsolicited leads.

The death certificate of each potential case identified by one of these activities was matched with the respective personnel record and scrutinized for correct nosology before being considered a case.

When the additional cases ascertained by the various methods just described were added to the cases ascertained as part of the county-based case-control study, the number of cases totaled 25. All of the cases were white males. As seen in Figure 1, the ages at death ranged from 37 to 70 years, with 40% of the cases dying between 50-59

at death. The distribution of deaths as depicted in Figure 2 spanned a 28 year calendar period beginning in 1951 and ending in 1977.

Confirmation of histologic diagnosis of the cause of death is being sought.

Distributions of the cases by date of hire and calendar period of employment demonstrated two noteworthy characteristics. As seen in Figure 3, the majority of the cases were hired prior to 1950. More specifically, 84% of the cases were initially hired from 1940 to 1946. Equally as striking is the observation that 68% of the cases were concurrently employed for the calendar period from 1942 to 1944 and 56% for the calendar period from 1947 to 1952. The full span of this distribution is presented in Figure 4. Certainly, investigation of unusual characteristics of employees hired in the early 1940's and of plant condition during the peak work periods of the cases seem warranted.

Limited case ascertainment will continue as long as the investigation is still open, with any newly ascertained cases being added to the investigation.

MORE DEFINITIVE ESTIMATES OF RISK WITH IDENTIFICATION OF RISK FACTORS

The preliminary findings have linked employment at Dow to a 2-fold risk of death due to brain tumor. A series of 25 brain tumor cases among its former workers ascertained. However, such a generalized indication of risk in itself does not facilitate identification of risk factors which may present avenues for elimination of the, as yet unknown, but suspected hazard. Consequently, additional studies designed to refine the initial estimates of risk and to attempt to identify risk factors have or will be undertaken.

Numerous relationships will be investigated in attempting to refine the initial risk estimates and identify risk factors. Obviously, the traditional relationships involving exposures to particular agents will be investigated. Other factors to be investigated include those pertaining to the biologic plausibility of any observed associations between particular exposures and disease; specifically, duration of exposure as an approximation of dose and latency from first exposure to manifestation of disease in recognition of the time necessary for tumor induction and proliferation. For this particular situation where the plant has been in operation for more than 40 years, additional temporal relationships should be investigated in case the risk of brain tumor at the plant varied over time, perhaps as a result of process changes. The distribution of the cases by periods of

concurrent employment would tend to justify exploration of such relationships.

In most situations this set of investigations could be accomplished using standard cohort study methods. Data for the entire population at risk would be collected and automated. Follow-up would be conducted to ascertain all deaths in order to determine person-years at risk and to identify brain tumor deaths. Expected brain tumor deaths would be estimated for selected subgroups of the population at risk using a life table program based on U.S. general population rates. Finally, a standardized mortality ratio (SMR) would be calculated by dividing the observed brain tumor deaths by those expected deaths. Alternately, many of the sought after risk estimates, especially those involving exposures to particular agents, could also be obtained by standard case-control study.

In this situation, however the number and storage mode of the company's personnel records significantly affected the design of the additional studies. Approximately 7,000 persons are currently employed at the plant. When the former employees are included, the total population potentially at risk is 44,000. Of this group, the personnel records of more than 37,000 former employees are not automated and are stored on microfiche. The problems associated with building and manipulating an analytical data base derived from this set of records, were considered in the design of studies to refine risk estimates and identify risk factors.

The study design chosen circumvents the apparent data management problems by using a 5% sample of the employee population on which to base a cohort study and a case-control study.

This sample-based cohort study represents a modest departure from standard epidemiologic methods. Using a representative 5% sample, all but one of the steps to determine expected deaths will proceed in the standard manner, i.e. build a data base of all members of the 5% sample, ascertain deaths by vital status follow-up and calculate expected deaths due to brain tumor using a life table program. The modest variation in methodology for estimating the expected deaths will be the adjustment of the expected mortality experience of the 5% sample to represent 100% of the plant workforce; the expected deaths of the 5% sample are all multiplied by a factor of twenty.

The observed brain tumor deaths will primarily consist of the cases ascertained by methods previously described. If, however, new cases are discovered serendipitously or in the course of ascertaining the vital status of the 5% sample, they will be added to the set of observed cases. Any cases discovered among the 5% sample will be added one by one without any amplification or adjustment for the fact

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that they were derived from the follow-up of a 5% sample. Despite this, these SMRs should still provide minimal estimates of risks due to possible underascertainment of deaths in the total population for certain causes of death. In addition to the sample-based SMR for brain tumors, SMRs will be calculated for malignant brain tumors and stratifications by duration of employment, time periods of employment and latency.

In order to reduce the reconstruction of detailed work histories, risk associations involving exposure to particular production processes or chemical agents will be investigated using traditional case-control study methods. If such associations were investigated using the sample-based cohort, over 2,000 work histories would need to be reconstructed. Using a case-control approach only 135 up to 270 work histories would be required depending upon the number of control groups and matched controls per case.

The cases for this in-plant case-control study would consist of those brain tumor deaths already ascertained and any new cases discovered prior to completion of the study. The sets of matched controls will be selected from the 5% sample of all current and former employees. Because the detailed demographic variables and work history summaries for the 5% sample have been automated, it is now possible to select closely matched controls by key parameters such as, date of hire, age at hire, and duration of employment.

At this point, the sample-based cohort study is nearing completion and it is anticipated that selection of controls for the case-control study should be made in the near future. With the completion of these two studies the primary avenues of study of brain tumors will have been exhausted. Perhaps the results of these studies will provide definitive answers concerning the risk of brain tumors in this plant and if the risk is elevated, the causal factors.