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THE APPLICATION OF EPIDEMIOLOGY TO THE PREVENTION OF OCCUPATIONAL CANCER

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ABSTRACT

Epidemiology attempts to establish a quantitative causality which is essential in preventive medicine strategies for occupational cancer. By studying carefully exposure effect relationships and populations at risk, subtle causes of occupational cancer can be identified. The nature of epidemiological reasoning and the criticism of this methodology are outlined. Using combined epidemiological and industrial hygiene data, a quantitative risk assessment of a lifetime exposure of workers to benzene and its association with leukemia is presented. In a population of 1,000 workers exposed for a working lifetime to 100 ppm benzene vapor, 140 excess deaths from leukemia would occur. At a lifetime exposure of 10 ppm, it is calculated that 14 excess leukemia deaths would occur. Because the current legal standard is 10 ppms for occupational exposure, this epidemiological risk assessment indicates that an unexpectedly large number of excess leukemia deaths will result in a population of workers exposed to 10 ppm.

INTRODUCTION

In the prevention of occupational cancer, the function of epidemiology is to establish and quantitate causality. Through

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the exploration and defination of exposure-effect relationships, epidemiologists seek to identify the causes of occupational cancers; to determine the populations at greatest risk; and hence to provide a scientific basis for regulatory, medical and other forms of intervention.

In this report, we shall first discuss the rules of evidence which have been developed for assessing causality in epidemiologic studies of occupational cancer. Then, we shall present a specific example -- that of the association between exposure to benzene and subsequent death from leukemia -- to illustrate the application of epidemiologic techniques to the prevention of occupational malignancy.

The Nature of Epidemiologic Reasoning

Physicians and epidemiologists have traditionally approached the establishment of causality through a process of inductive reasoning (1-3). That is to say, they begin with scattered bits of data -- a clinical observation, the results of a toxicologic study, or an exposed worker's report of the occurrence of symptoms. From those fragmentary data, they develop a hypothesis, which attempts to explain the development of disease by attributing its origin to one or more causes or risk factors. In the simplest situation, a single cause if postulated -- a cause which is sufficient by itself to produce the disease in an exposed person (4). An example might be the suggestion put forth on the basis of the observation of

four cases of angiosarcoma of the liver (ASL) in a small group of men employed in a single department of a plastics manufacturing plant that their common exposure to vinyl chloride monomer (VCM) was the cause of their tumors; (5) subsequent epidemiologic and toxicologic studies confirmed the validity of that hypothesis. In other more complex instances, a hypothesized cause may require the concomitant action of other risk factors to produce its effect, or it may be unable to exert its effect unless certain pre-existing conditions (necessary causes) are met. For example, the suggestion in experimental toxicology that certain substances, such as the phorbol esters act as tumor promoters in animals already predisposed to development of cancer as a result of their prior exposure to a tumor inducer, constitutes an example of this more complex sort of causal hypothesis (6).

It is important to realize that the establishment of a causal hypothesis in medicine, in epidemiology, or for that matter in any branch of science is frequently a tenuous process (3). It depends on imagination, on insight, and the ability to reach beyond the data which are immediately at hand. At times, indeed, the establishment of a new causal hypothesis may be truly revolutionary in nature if it involves a serious break with previously held scientific dogma (7).

Once a hypothesis has been proposed, then the work of the epidemiologist is to test it, to determine whether or not it provides an adequate explanation of observed reality.

Criticisms of Epidemiology

Because epidemiologic studies almost inevitably take place after exposure has occurred, and because they evaluate events in the murky, imperfectly controlled world of human affairs, some critics have argued that epidemiology can never prove anything -- that the process of inductive reasoning in epidemiology is too tenuous to be believable, and that the data are too "soft" and too unreliable ever to permit the drawing of causal inferences.

Particularly ingenious arguments along those lines have been developed by apologists for the tobacco industry in their efforts to refute the studies which demonstrate a causal relationship between cigarette smoking and lung cancer in man. For example:

> "Epidemiology, like astronomy, is largely an observational rather than an experimental science and hence the scope for planned and controlled intervention by the investigator is usually either limited or absent. Precautions that are routine in properly conducted experiments are unattainable in epidemiology. Inbred strains of the human species are not available and strict standardization of environmental conditions throught the lifespan is inconceivable. Even randomization -- which can often be used to mitigate differences between experimental and control groups of animals -- is seldom possible when investigating the causes of diseases in man."(8)

Or again:

> "Epidemiology cannot prove cause and effect. All if can demonstrate is a relationship. The nature of the relationship, causal or otherwise, has to be worked out by other methods, usually experimental."(9)

In pursuing their logic further, those critics have argued that predisposition, rather than causation accounts for the fact that certain members of the population both smoke cigarettes and also develop lung cancer. For example:

> "Any observed differences...with respect to health outcomes may not, in fact, be the result of smoking, but may instead be due to other more basic factors (e.g., those of a genetic origin)... In other words, one can reasonably maintain the view that smokers are constitutionally different from non-smokers, and that such constitutional factors cause such individuals both to smoke to develop lung cancer. Under this plausible hypothesis, then, smoking is an outcome variable just like lung cancer, being a manifestation of the constitutional factors possessed by people who choose to smoke."(10)

The nature of those proposed constitutional factors has been further elucidated:

> "Smokers are biologically older than non-smokers"...[Smoking is associated with] "other correlated habits, such as

drinking, living it up, staying out late, wenching, etc., i.e. a certain style of life the totality of which may increase the 'rate of living."(11)*

In similar fashion, spokespersons for the lead industry have argued that the association observed in children between low-level exposure to lead and neuropsychological dysfunction may not reflect causality, as has been suggested by the results of several epidemiologic analyses;(13-15) instead those spokespersons argue that children who receive poor parental care in homes of low socioeconomic status may be predisposed both to lead exposure as well as to diminished cerebral function.(16)†

Establishing Causality - Qualitative Aspects of Data Evaluation

The above criticisms have been a powerful goal to epidemiologists.

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* The tobacco industry's criticisms have largely been laid to rest by the demonstration of a strong dose-response relationship between the amount of tobacco smoked and the frequency of lung cancer, and also by the observed decline in lung cancer mortality following cessation of smoking. (12)Further, it is important to note that the tobacco industry has been able to develop no firm evidence for the existence of the predisposition which they claim.(1)

+ The lead industry's criticisms have been addressed in epidemiologic studies which have consistently found a positive dose-response relationship between degree of lead exposure and severity of neuropsychological impairment. Evidence for the existence of that relationship has persisted even when numerous socioeconomic and familial factors were held constant either through matching or through multivariate analysis.(13) Further corroboration of these observations is anticipated to result from several prospective studies now under way of neuropsychological development in children exposed to lead in utero.

Their refutation has stimulated eloquent rebuttals, defending the ability of medicine and epidemiology to establish cause-and-effect relationships. For example:

> [We should not] "throw up our hands in despair, settle the cigarette in the corner of our mouths and decline to draw any conclusions from the available observational data.

"It is a good deal more difficult to control variables in observational than in experimental material, so that the experimental method has unravelled and will continue to unravel mysteries before which uncontrolled observation could be powerless. But there is no difference in principle. There are no such categories as first-class evidence and second-class evidence. There are merely associations, whether observational or experimental, that, in a given state of knowledge, can be accounted for in only one way or in several different ways...To distinguish between statistical association on the one hand and relationships that are established by experimentation on the other, without any reference to alternative variable that are present in one case but not the other, seems to us to be neither good statistics, good science, nor good philosophy -- though it may be good red herring."(17)

Additionally, this debate has fostered the development of a set of reasonably well standardized criteria for examining data pertaining to cause-and-effect. (3, 17-19) The use of these criteria serves to reduce uncertainty and imprecision in data analysis and thus "to carry our understanding beyond the

level of intuition".(3)

The first step in the systematic evaluation of data from a series of human studies is, of course, to evaluate individually the results of each separate report. The strengths and weaknesses of each study must be considered, and also the potential for the existence of bias must be assessed in each.(20) Note should be made as to the care with which the methods of each study are described. Although it may be stretching a point to say that all studies with carelessly described methodologies are careless studies, it is nevertheless true that studies with well described methodologies tend to be the better reports in the published literature and ought to receive appropriate weighting. A useful series of guidelines for the documentation of epidemiologic methods was provided in 1981 by the Interagency Regulatory Liaison Group;(21) these guidelines may be used as a yardstick against which to assess published studies.

Particular scrutiny must be applied to the evaluation of studies which have been reported to show "negative results", that is, studies which report an apparent absence of evidence for a hypothesized causal relationship between exposure and effect.(22) Such studies need to be searched for such obvious flaws as dilution (the inclusion of unexposed people in an allegedly exposed group of persons), misclassification, omissions (for example, of retirees),(23) or premature examination of subjects for diseases which may require the passage of many years of so-called

induction-latency between exposure and first appearance of clinical illness; many cancers, for example, may require an induction-latency period of as long as 30 to 40 years between first exposure and ultimate manifestation. In addition, the statistical power of each "negative study" needs to be assessed. The statistical power of a study is defined as the probability that the study will be able to demonstrate an effect if an effect, such as excessive disease or death, is indeed present in a population.(24) An example of a formal statement on statistical power is provided by a recently published study of leukemia mortality in naval shipyard workers exposed to ionizing radiation; the authors of this study reported explicitly that their work had a power (or probability) of 99 per cent to be able to detect a 3-fold excess of leukemia mortality, had such an excess been present in the study population at the time of the study.(25) The absence of an explicit statement regarding statistical power weakens the impact of a 'negative' study. A power statement, i.e., a statement of the statistical limitations of a study ought to be a sine qua non in all descriptions of epidemiologic methodology.(21)

An excellent summation of the approaches used for the evaluation of clinical and epidemiologic studies is provided by the International Agency for Research on Cancer (IARC),(26) as follows:

> "An analytical study that shows a positive association between an agent and an effeft may be interpreted as implying causality

to a greater or lesser extent, if the following criteria are met: (a) there is no identifiable positive bias (By 'positive bias' is meant the operation of factors in study design or execution which lead erroneously to a more strongly positive association between an agent and disease than in fact exists. Examples of positive bias include, in case-control studies, better documentation of exposure to the agent for cases than for controls, and, in cohort studies, the use of better means of detecting cancer in individuals exposed to the agent than individuals not exposed); (b) the possibility of positive confounding has been considered (By 'positive confounding' is meant a situation in which the relationship between an agent and a disease is rendered more strongly positive than it truly is as a result of an association between the agent and another agent which either causes or prevents the disease. An example of positive confounding is the association between coffee consumption and lung cancer, which results from their joint association with cigarette smoking); (c) the association is unlikely to be due to chance alone; (d) the association is strong; and (e) there is a dose-response relationship.

Analytical epidemiological studies that show no association between an agent and a cancer ('negative' studies) should be interpreted according to criteria analogous to those listed above: (a) there is no identifiable negative bias;

(b) the possibility of negative confounding has been considered; and (c) the possible effects of misclassification of exposure or outcome have been weighed.

In addition, it must be recognized that in any study there are confidence limits around the estimate of association or relative risk. In a study regarded as 'negative', the upper confidence limit may indicate a relative risk substantially greater than unity; in that case, the study excludes only relative risks that are above this upper limit. This usually means that a 'negative' study must be large to be convincing. Confidence in a 'negative' result is increased when several independent studies carried out under different circumstances are in agreement.

Finally, a 'negative' study may be considered to be relevant only to dose levels within or below the range of those observed in the study and is pertinent only if sufficient time has elapsed since first human exposure to the agent. Experience with human cancers of known etiology suggests that the period from first exposure to a chemical carcinogen to development of clinically observed cancer is usually measured in decades and may be in excess of 30 years.

After the assessment of each individual report has been completed, it is possible to begin a comprehensive review of the literature in which the many published studies describing the health effects due to a particular agent are considered col-

Table 1. CRITERIA FOR DETERMINING CAUSALITY IN EPIDEMIOLOGIC STUDIES*

-- The strength of the association

-- Its consistency (or reproducibility)

-- Its temporality (exposure must precede effect)

-- Its biological gradient (existence of a dose-response phenomenon)

-- Its specificity

-- Its biological plausibility, and coherence in regard to the generally known facts about the disease under study

* From Hill (reference 27)

lectively. The best known guidelines for this exercise are those developed by Hill (27) during the debate on smoking and lung cancer (Table 1). Hill recommends that the following factors be considered in determining whether or not an observed association represents causality:

-- The Strength of the Association

The strength of an association between exposure and effect

is measured in terms of relative risk. Relative risk may be expressed in terms of a proportionate mortality ratio (PMR), an odds ratio (in case-control studies), or a standardized mortality ratio (SMR) (in cohort studies). The stronger is a measure relative risk, the greater the likelihood that an observed association is causal in nature. Monson(28) has offered the following guide to the assessment of relative risk:

Relative Risk		Strength of Association
0.9 - 1.0	1.0 - 1.2	None
0.7 - 0.9	1.2 - 1.5	Weak
0.4 - 0.7	1.5 - 3.0	Moderate
0.1 - 0.4	3.0 - 10.0	Strong
0.1	10.0	Infinite

In evaluating relative risks, it is important to note the actual numbers of observed and expected cases as well as their ratio.(29) If the expected number is very small (fewer than 2 or 3 cases), then even a very high relative risk must be evaluated with caution, for rates based on small numbers tend to be statistically unstable and are subject to substantial random variation.(22)

It is necessary also to be cognizant of the so-called "healthy worker effect" in evaluating relative risks. This term describes the underestimation of mortality of a working

population which typically results from the selection into active work of only those members of a population who are free of obvious defects and free of chronic debilitating disease. As a result of the healthy worker effect, the overall relative risk of a working population tends to be below that of the general population particularly in the youngest age groups and in the early years of employment. Because of the healthy worker effect, even relative risks less than 1.0 (SMR of 100) may, in some instances, be of concern; for example, an SMR for a particular cancer of 120 in a population with an overall (all causes) SMR or 75 must be regarded with suspicion.

Finally, the possible influences of such confounding factors as cigarette smoking need to be considered in any assessment of relative risk in an occupational study. Calculations based on the relative risk of lung cancer associated with smoking and on the fraction of smokers in typical working populations indicate that relative risks for lung cancer, above 2.0 can seldom be explained by confounding with smoking.(30)

-- The Consistency (Reproducibility of the Association)

Causal influences are strengthened by the repetition of the findings "by different persons, in different places, circumstances and times."(27) The reproducibility of findings

consitutes one of the strongest arguments for the existence of causality. The International Agency for Research on Cancer has gone so far as to state that "the most convincing evidence of causality comes when several independent studies done under different circumstances result in 'positive' findings".(26)

-- The Temporality of the Association

It is most important in making an inference of causality, to determine that exposure preceded illness. When latency periods are involved, exposure must have commenced early enough to have produced an effect by the time of the study; a reasonable criterion to use in making that judgement is that exposure must have begun at least earlier than half the mean latency period.(22) It is important to realize that cross-sectional studies are seldom capable of establishing temporality.

-- The Biological Gradient of the Association (Dose-Response Relationship)

If a factor is causally related to a disease, the risk of developing the disease should be related positively to the extent and severity of exposure to the factor.(31) In chronic disease of long latency, cumulative exposure to a factor may need to be summed over many years.(32) Although the criterion of dose-response is extremely useful in asses-

sing causality, it must be noted that occasions arise in which a confounding factor may be so intermingled with an exposure that their effects cannot be separated even by application of this criterion. Examples include exposure to multiple toxic metals in smelter workers at risk of lung cancer, and the intertwined roles of "age at first birth" and "age at first lactation" in the etiology in women of breast cancer.(31) Also, paradoxes occur occasionally in analyses of dose-response. For example, a higher frequency of occupational disease will be seen sometimes in short-term than in long-term workers. This apparent contradiction is explained by recognition of the fact that duration of employment serves only as a surrogate measure of actual exposure; some heavily exposed entry level workers may actually experience greater total exposure to a toxin than long-term workers in cleaner jobs. Finally, some agents actually appear to produce greater disease risk at lower doses. For example, low doses of ionizing radiation appear to produce higher risks of thyroid cancer than higher radiation doses.(31)

Related to dose-response is the concept that very strong evidence for causality is provided when a change in exposure brings about a change in disease frequency.(22) The decrease in risk of lung cancer which follow cessation of smoking is a good example of this sort of evidence.(12) This type of evidence can also be obtained in interventive epidemiological studies.

-- The Specificity of the Association

The term specificity refers to the notion that if a particular exposure is associated with only one disease and vice versa, then there exsists strong evidence for a causality. Examples of one-to-one correspondence abound in the study of infectious disease - measles, diphtheria, smallpox -- but are less common in noninfectious diseases which tend to be of multifactorial origin. Reasonable examples of specificity in chronic disease might, however, include mesothelioma in persons exposed to asbestos and bladder cancer in persons exposed to certain aromatic amines such as benzidine.

Specificity is not as essential criterion of causality.(1) The presence of specificity argues for causality, but its absence does not exclude it.(29)

-- The Biological Plausibility, the Association and Its Coherence in Regard to Generally Known Facts About Disease Under Study

Hill insisted strongly that a proposed causal relation not conflict seriously with knowledge of the biology and pathophysiology of a disease under study. Although this criterion is not absolute, there is no question that an epidemiologic inference as to causality is strengthened by the finding of similar findings in experimental studies and by the demonstration of consistency between epidemiologic results and

some underlying biological mechanism. Exposure to ionizing radiation, for example, causes increased incidences of numerous cancers not only in man, but also in a variety of animal species. It has been demonstrated that the ability of ionizing radiation to react with and alter the structure of deoxyribonucleic acid (DNA), the fundamental genetic material, almost certainly underlies and explains its carcinogenic potential.

At the conclusion of the process of qualitative evaluation of the available human studies, it should be possible to state the degree of evidence which exists for causality. The International Agency for Research on Cancer (IARC) has offered the following semiquantitative classification of degrees of evidence:(26)

"Sufficient evidence" for causality in human studies is "that which provides a causal association between exposure and cancer or other illnesses".

"Limited evidence" for causality in "that which indicated a possible carcinogenic [or other disease-producing] effect in humans."

Benzene and Leukemia

Studies which examine the association between occupational exposure to benzene and subsequent death from leukemia illustrate the application of epidemiology to the prevention of occupational

cancer. The association between benzene exposure and leukemia was first recognized in a series of case reports published from the 1890's to the 1960's. To evaluate this association more systematically, the National Institute for Occupational Safety and Health (NIOSH) undertook a combined epidemiologic and industrial hygiene study.(33,34) The epidemiologic study employed a retrospective cohort design. It examined a population of 1,006 non-salaried white male workers who had been exposed to airborne benzene vapors at two rubber plant in Ohio. The only chemical present at these plants which was known to be associated with blood dyscrasias was benzene.

The study population was divided into two groups. Group 1 consisted of 748 men who worked at least 1 day between January 1, 1940 and December 31, 1949, in a department with benzene exposure. Group 2 consisted of 258 men who first worked in a department with benzene exposure between January 1, 1950 and December 31, 1959.

Vital status follow-up was conducted to June 30, 1975. Vital status was ascertained for 98% of the cohort. The remaining 2% were considered to be alive as of the study end-date. Death certificates for all known deaths were obtained and coded by a qualified nosologist according to the rules of the International Classification of Disease Adapted for Use in the United States (ICDA) in effect at the time of death, and were then converted to 7th revision codes. A NIOSH life-table

computer program was used to calculate expected numbers of deaths by cause within 5-year age and 5-year calendar time periods.(32) Age- and calendar-specific United States white male death rates were used as referrents. Observed and expected cause-specific mortalities were compared using a 2-tailed test of significance based upon the Poisson distribution.

Industrial hygiene information concerning atmospheric concentrations of benzene vapor at the first plant was available to NIOSH from several sources.

The Industrial Commission of Ohio: On November 19, 1946, representatives of the Industrial Commission of Ohio visited this plant. A letter dated November 21, 1946, stated:

> "The presses have been completely enclosed and the exhaust systems now in operation are so efficient that the characteristic odor of benzol could not be detected in the area. Tests were made with benzol detectors and the results indicate that concentrations have been reduced to a safe level and in most instances range from zero to 10 or 15 parts per million."

As a result of an occupational disease claim, an industrial hygiene engineer visited the plant on December 15, 1955. His report, dated December 27, 1955, stated:

> "The company has used a great deal of ingenuity in exhausting

all operations where benzol vapors are liable to get into the air. Practically all of the operations take place in a closed system. The company has made repeated tests and the benzol concentration is kept below 35 ppm. On certain operations the concentrations may go up momentarily for a few moments but the company has never found more than 200 ppm in these exposures. When the exposure is above 35 ppm, even momentarily, employees are required to wear a chemical cartridge respirator."

The corporate medical director in a review of the same disease claim stated in an internal memorandum dated February 22, 1956, that:

"...the patient's story was that considerable amounts of benzol vapors were inhaled. The facts concerning the working environment are contained in the Industrial Hygienist's report indicate that the concentration is kept below the 35 parts per million. Indeed it is my opinion that in general working areas these vapors are below 10 parts per million."

The Ohio Department of Health: On January 17, 1956, an industrial hygiene engineer of the Ohio Department of Health conducted an investigation at this locality. His report stated:

"Local exhaust ventilation is used throughout the process to capture benzol vapors at potential escape points. The processing and material conductance is maintained within

complete enclosures and the reactions are carried out within sealed vessels."

Employees are required to wear chemical cartridge respirators during any exposure to benzol in those working areas known through air check to contain concentrations of benzol above recognized safe values."

The University of North Carolina: The Occupational Health Studies of the University of North Carolina conducted industrial hygiene surveys of this facility during 1973-74. Concerning the mixing room their report stated:

"Levels of 0 to 29 ppm of benzene were measured in this area where one man is required to spend approximately 10 minutes, four times per shift to monitor the mixing operation. The exposure level for an eight-hour day in this area might average slightly over 10 ppm. The TLV, on a time-weighted basis is not exceeded, because the area is not continuously occupied; the ceiling value, however, may be exceeded from time to time."

Location Two

Limited information was available for an industrial hygiene at this locality.

"Plant One": On April 27, 1948, the Ohio Department of Health

conducted an industrial hygiene survey. The report stated:

> "Various type machines such as dryers, spreaders, mixers, etc. are all exhausted. There are, however, a few areas of the plant and a few conditions wherein an employee might be subjected to an extremely high concentration of benzol. The benzol test taken at the front end of the dryer showed 120 parts per milllion. The employees working on this dryer are well aware of the toxicity of benzol and have been instructed to, and do, wear respirators when they are required to enter the front end of this dryer. The door which leads into the dryer is marked, indicating that respirators must be donned before entrance. This dryer is #C. A spreader, also #C, contains an effective exhaust system but a test showed 120 parts per million under the dam. Again, employees use respirators whenever they enter this spreader."
>
> "In a test taken at the top of a (benzene storage) tank, the test showed 500 parts per million of benzol. The information obtainable seemed to indicate that one or more employees would spend approximately 1 hour per day at these tanks."

"Plant Two": The Ohio Department of Health report stated:

> "The company is installing a new (rubber hydrochloride) unit in this plant; and while it is far from complete, one can see that adequate exhaust systems will be used to eliminate high concentrations."

As knowledge of benzene toxicity increased, recommended environmental levels were continually revised downward as follows:

Year	Recommended Standard
1941	100 ppm
1947	50 ppm 8-hour time-weighted average (TWA)
1948	35 ppm 8-hour TWA
1957	25 ppm 8-hour TWA
1963	25 ppm 8-hour ceiling
1969	10 ppm 8-hour TWA

Our analysis of the available environmental data lead us to the conclusion that although there were occasional excursions above recommended limits, for the most part, employees' 8-hour time-weighted average exposures to benzene were within the recommended standard in effect at the time of the exposure.

RESULTS OF THE MORTALITY STUDY

Group 1

Among the cohort who worked at least 1 day in a benzene-exposed department at either location between 1940 and 1949, there were 180 deaths from all causes, compared with an expected number of 161. Although not statistically significant, this increased number of deaths from all causes was nevertheless unanticipated, since in an industrial population one normally observes fewer

than the expected total number of deaths.

Moreover, there was a statistically significant excess of deaths from malignancies of the lymphatic and hematopoietic system (ICDA codes 200-205). Ten such cases were observed versus 3.03 expected ($p < 0.01$) (Table 1). When leukemias (ICDA code 204) were considered alone, seven cases were observed vs. 1.25 expected ($p < 0.001$). Although the ICDA code for leukemia encompasses lymphatic, myeloid, and monocytic leukemias, all seven cases were of the myeloid or monocytic cell types, as ascertained by death certificate designation. Five of these seven cases were seen by one hematologist, who confirmed the diagnosis.

Of the 748 workers included in Group 1, 437 (58%) had exposure to benzene for less than a year. Because only 1 day of exposure qualified a worker for entry into the cohort, individuals with short duration of exposure contributed a large proportion of the total person-years at-risk used to calculate the expected number of death. Inclusion of these persons with brief exposures served to lower the calculated risk of death from leukemia from what it would have been if a requirement for minimum duration of exposure had been imposed. When exposure to benzene is examined in terms of duration, a sharp increase in the SMR is seen among the group of workers exposed for longer than 5 years. For those persons who had attained 5 or more years of exposure, five leukemia deaths were observed, while only 0.23

was expected (SMR = 2100). Also for those with more than 10 years of employment, 3 leukemia deaths were observed, whereas only 0.09 were expected (SMR = 3300).

The observed excess of leukemia deaths remained evident when the Group 1 cohort (1940-1949) was divided according to location and the locations examined separately. At Location One, two cases of leukemia were observed vs. 0.58 expected, yielding an SMR of 345. At Location Two, five cases were observed vs. 0.67 expected, yielding an SMR of 345. At Location Two, five cases were observed vs. 0.67 expected, yielding an SMR of 746. Thus, both locations considered as independent cohorts experienced an excess of leukemia deaths.

Group 2

Among the cohort who first worked in a benzene-exposed department between 1950 and 1959, there were 49 observed deaths from all causes compared to 56 expected (SMR = 87). In group 2, one case of leukemia was observed vs. 0.46 expected (SMR = 217).

Conclusion

These data show a strong association between occupational exposure to benzene and death from leukemia. They suggest strongly that the association is causal. They therefore form a basis for preventive action.

From the combined epidemiologic and industrial hygiene data obtained in this study it was possible to undertake a quantitative assessment of the risk of leukemia in workers exposed for a working lifetime (40 years) to benzene vapors. In this risk assessment, it was calculated that in a population of 1000 workers exposed for a working lifetime to 100 ppm benzene vapor, 140 excess deaths from leukemia would occur.(35) Similarly, at a lifetime exposure of 10 ppm, it was calculated that 14 excess leukemia deaths would occur.

Because 10 ppm is the current legal standard for occupational exposure to benzene, and because this epidemiologic risk assessment indicates that an unacceptably large number of excess leukemia deaths will result in a population of workers exposed to benzene vapor for a working lifetime at that level, there exists a scientific justification for lowering the current legal standard for occupational exposure to benzene. If epidemiologic data help to bring about that reduction, then epidemiology will have assisted in the prevention of occupational cancer.

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