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THE EVOLUTION OF CHRONIC HAZARD EVALUATION

TED ROBINSON and RALPH YODAIKEN*

Office of Occupational Medicine, OSHA-DOL, 200 Constitution Avenue, N.W., Washington, DC 20210 (U.S.A.)

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Summary

The advent of modern epidemiology has been briefly reviewed from the early observational studies to the nested case control technique. While the cohort study has been neglected, many of the significant milestones in epidemiology have been reviewed. The lessons learned from the investigations of nickel, asbestos, benzene, chromates, smoking and many other hazards which were too long ignored must be applied, otherwise the tragedies of the past will recur. To accomplish the preventive goals inherent in occupational medicine, cooperation between industry, government, physicians and scientists is necessary. Toxicological, epidemiological and medical research must continue to improve our understanding of environmental hazards. New chemicals or new uses of old agents should be assumed to be potentially hazardous and worker exposure kept to a minimum until the long risk assessment process indicates otherwise.

Introduction

The evaluation of chronic workplace hazards is a difficult and often perplexing task by virtue of its very nature. The time necessary for an adverse effect to manifest itself can be decades and the actual dose, that is the amount, intensity and duration, of the offending agent may be relatively low compared to other non-toxic or less toxic occupational exposures. Chronic hazards, such as most human carcinogens, are not easily or rapidly identified with certainty because frequently the essential epidemiologic data are "soft", that is, less well established than "hard" verifiable, scientific data. The observational, unlike the experimental, epidemiologist does not have strict control over all environmental conditions. Instead, he or she must rely on the best possible study design, control of biases and the concurrence of other well conceived studies to reach defendable conclusions. Consequently the exposed population reaps no immediate benefit from an epidemiologic study and more often than not the scientific as well as the lay establishment is skeptical of the conclusions drawn.

*Author to whom correspondence should be addressed.

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History is replete with examples of convincing epidemiologic data, painstakingly collected and studiously ignored.

Chronic hazard evaluation is one of the most challenging fields in medicine. The plethora of new chemicals entering the workplace each year requires the occupational health physician to have the suspicion and penetrating insight of a Holmesian detective, the basic science knowledge of a toxicologist and the computerized data analysis skills of an epidemiologist. Since the breadth and depth of all of these skills is beyond the capability of most individuals, a team approach is advantageous. Epidemiologists, industrial hygienists, toxicologists, physicians and many others [1] combine to facilitate the prevention of disease. It is instructive to examine the evolution of occupational medicine in the context of these disciplines.

Developments in epidemiology

The techniques of epidemiological investigation are well known and have been appreciated for some time. These vary from the *case report* (a single case) to the *prospective cohort* that is a defined population that is, or will be exposed or not exposed and followed for a number of person-years. Perhaps the most noteworthy use of the *case report* was Percival Potts' description of scrotal cancer in chimney sweeps [2]. This description and more recently studies of liver angiosarcoma illustrate that the usefulness of the case report should not be underestimated and this paper will discuss this technique extensively.

Reports of angiosarcoma of the liver, an extremely rare malignancy, in vinyl chloride workers in the mid 1970's caused an almost immediate shift to remedial regulatory action without the need for long prospective studies [3,4]. The prior reports of experimentally induced tumors were helpful [5], but the case reports were most valuable because of their relevance to human disease. In this instance, the rarity of the disease was a great advantage and helped reinforce the value of case reports. They can establish causality, heighten interest in the association between exposure and disease and lead to more definitive studies if evaluated in perspective.

The beginning of modern epidemiology can be traced to the 1600's and has its roots in combating infectious disease. John Graunt analyzed the Bills of Mortality of London to arrive at patterns of death and laid the foundation for development of the life table [6], an invaluable technique in mortality investigations. While the next 200 years showed little progress in this area, the general growth of science in the 18th century fostered the development of the *comparative study*. This type of investigation frequently merely compared the pretreatment and post-treatment condition of the patient. Another strategy was to do this for several proposed treatments and compare the relative effect of each. Known since the 1500's, its popularity increased in the 1700's primar-

ily due to the successful evaluation of treatments for such diseases as scurvy and typhus fever.

In 1834, P.C.A. Louis included the comparative method in an "Essay in Clinical Instruction" that may have indicated, even in his day, the need for *randomization* [7]. He suggested that this approach could be used to study the cause of diseases and applied it to his study of tuberculosis in 1844. In another study of the distribution of tuberculosis among letterpress printers in London, William Augustus Guy developed a new technique, the 2×2 table (example below), and a relative risk estimate which is very similar to the odds ratio widely accepted today [7]. The odds ratio or relative odds, is an approximation of the relative risk of disease among the exposed compared to the unexposed and will be dealt with in more detail. Subsequent to this study in 1843, medicine and epidemiology combined to uncover the bacteriological causes of disease, frequently by using this comparative method. However, the truly modern case-control was not seen until Lane–Claypon reported on breast cancer in 1926 [7,8]. This investigation used separate study groups, the cases with breast cancer and the controls *without*, for comparison.

The latter part of the nineteenth century evidenced stagnation in the development of epidemiologic methods. Since the great concern was the etiologic organism rather than any etiologic exposure, control groups were not a component of the well known Henle–Koch postulates. In other words, selecting matched control subjects was not considered and from a practical point of view probably beyond the capability of the investigators of that period. Notable advances were made, however, by a few individuals such as William Farr who was appointed Compiler of Abstracts of England in 1839. For the next 30 years, he built upon Graunt's work and organized a system of recording mortality information. He was the first to investigate systematically the relationship between occupation and cause of death. Farr conceptualized the *standardized mortality ratio* (SMR) in a study of earthenware workers and this contribution to occupational epidemiology has remained invaluable [6]. The SMR is a means of correcting the death rate of a population by standardizing for age. Thus, an older population with a higher death rate can be compared to a younger one by correcting for age against a standard population. For example, the mortality rate for a specific disease is known for all males of a specific age group in the U.S.A. and is measured against the observed mortality of the study population. Excess deaths due to an exposure or occupation will be apparent.

A contemporary of Farr, John Snow, took advantage of his data compilation to study the etiology of cholera. Farr had found an inverse relation between cholera mortality and the altitude of residence (he mistakenly thought it was the elevation that determined the cholera indicence). Snow, at a time when nothing was known about the organisms that caused cholera, related the number of deaths to the water supply [9]. Using the data of William Farr, he correlated the death rate with the company supplying water. Districts using the

Lambeth Company, which got its water upstream of London, had a much lower cholera death rate than those receiving water from downstream suppliers. John Snow, in this study erected many of the pillars of modern occupational epidemiology. He established an association between an exposure to a specific agent and a disease, used death rates to estimate relative risk, found ways to reduce information bias and the confounding (extraneous; misleading) factor of social class. Although epidemiology had developed slowly to this point, as has been shown, several key elements of occupational epidemiology had been established.

The case-control format had seen some use in the middle of the nineteenth century but it was the sociologists of the 1920's and 1930's who brought it into the 20th century. Constrained by the same lack of controlled experimental approaches that plagued observational epidemiology, they added unexposed control groups for comparison and matched them to the study group for potential confounders such as age, sex and ethnicity. Many continued to expound on the need for controlled experiments in public health. By matching for various characteristics any disparity between the cases and controls was removed. Thus, differences observed in morbidity or mortality between among groups and controls were more likely to be the result of the agent of interest than of confounding factors such as ethnic group, age or sex.

One of the first to employ this technique was Raymond Pearl, who in 1929 published a case-control study on the relationship of tuberculosis to cancer [10]. This study suggested a negative association that implied a protective factor which was subsequently found to be erroneous. This study highlighted several problems with the method and as a result efforts were initiated to solve the major flaws.

Case-control studies

The case-control study, descriptively named by Sartwell in the 1960's has become a popular tool for the investigation of the effects of chronic exposure [11] as shown by the dramatic increase in the number of published case-control reports during the last 30 years [12]. This is due to the increasingly important ability to examine the effects of multiple exposures, associated with rare or common diseases and even rare exposures if they cause a high proportion of the disease. Rare diseases can only be investigated in this manner since a prospective study which follows a cohort of exposed and non-exposed would require an extremely large population base to find the few needed cases.

The primary limitations of case-control studies are selection and recall biases. Techniques for dealing with these limitations have allowed this format to become perhaps, the most popular for chronic hazard evaluation especially for investigations of carcinogenesis where a population based case-control study includes all of the cases in that population. By using control groups numeri-

cally equal to or larger than the study group, valid risk ratios for acquiring cancer can be determined. Sometimes more than one control group is preferred to allow for multiple comparisons and to make the analysis more meaningful [6].

In 1951, Jerome Cornfield showed that relative frequency of exposure data can be used to determine the relative risk of disease [13] by using the cross product of a 2×2 table, the *odds ratio* (Table 1). Cornfield recognized that the way to achieve a true rate and therefore relative risk, was by prospectively studying over a long period of time, exposed and non-exposed groups. He acknowledged, however, that this approach is expensive and time consuming. Furthermore, the frequency of exposure data from cases (diseased) and controls (disease-free) does not necessarily demonstrate the strengtht of the association between exposure and disease. He devised a method of transforming the frequency of exposure data of both cases and controls to a ratio of the risk of disease among exposed and unexposed. Indeed, the odds of exposure in cases divided by the odds of exposure in the controls, is exactly the same as the odds of disease in exposed over the odds in the unexposed. Using exposure and disease data previously published he showed that the prevalence of lung cancer in "white males aged 40–49 is 2.4 times as high among those who smoke ten or more cigarettes a day as among those who do not" [13]. Doll and Hill's 1947 study on smokers is referred to later. He also stated the seemingly obvious. The cases and controls must be representative of diseased and non-diseased populations respectively in order for the risk calculation to be generalized to the overall population. If this condition is not met, the study will have very limited applicability and hence usefulness for projecting risk among the occupational or exposed group as a whole.

Mantel and Haenszel [14], in 1959, published a landmark article which continues to have a monumental effect on epidemiology and, therefore, chronic hazard evaluation. This article promulgated two statistical tests widely used to analyze case-control studies, the *chi square significance test* and a *pooled estimator of relative risk*. Along with Cornfield's odds ratio, these statistical techniques allow the case-control approach to approximate results obtainable in a cohort study and hence, approximate the actual relative risk. Mantel and Haenszel appreciated the fact that in the absence of important biases the case-control approach is preferable. This paper and the work by Cornfield provided the means to control multiple variables so that any remaining incongruity between the cases and controls which would artificially distort the odds ratio could be dealt with. Therefore, measuring the degree of association between exposure and disease became practical without the need for arduous, lengthy cohort studies.

In 1960, Cornfield and Haenszel again reviewed retrospective or case-control studies [15]. They noted that while the prospective or cohort approach leads to the expenditure of a large amount of resources on those who never develop

the disease, the case-control design allows the investigator to study only a small fraction of the non-diseased while obtaining the same number of cases as well as an estimate of the relative risk. An estimate of the true relative risk, the relative odds of disease between the exposed and unexposed, is obtained from the two by two tables as constructed below:

TABLE 1

Example of a 2×2 table for estimating true relative risk

Exposure	Diseased	Disease free	Total
+	A	B	A+B
−	C	D	C+D
Total	A+C	B+D	N

Since A, B, C and D represent the absolute number of people in each category, the incidence rate of disease in the exposed is A/(A+B) and in the unexposed, C/(C+D). The relative risk is the ratio of these, i.e. [A/(A+B)]/[C/(C+D)]. An estimate of the true value is obtained by assuming that the number of those with disease (A and C) is small compared to those who are disease free (B and D) which is the case for most chronic illnesses, particularly in a heatlhy population. Therefore A and C can be neglected in the denominator. The ratio then becomes (A/B)/(C/D) or AD/BC which expressed the odds of acquiring the disease if exposed, compared to acquiring the disease if not exposed and is called therefore, the odds ratio.

A more efficient study design incorporating a case-control study within a cohort is becoming popular. This approach, a *nested case-control study*, allows for better control of selection bias and recall bias [8], which are the major drawbacks of the case-control study. In essence, cohort studies compare exposed populations to non-exposed over a period of time. Case-control studies compare cases with a disease to controls without the same disease. A nested case-control study then, means the selection of cases and controls from a cohort and examines the antecedent (exposure) histories of these groups. This technique emphasizes the cogency of Cole's statement in 1979 that the case-control study can replace the cohort study in many instances.

Strength of association and bias

Sartwell discussed the evidence needed to draw etiologic conclusions between environmental factors and disease [11]. The factors are (a) strength of the association (the frequency with which a factor is associated with a disease compared to the frequency with which it occurs in the absence of the disease),

(b) concurrence of other studies, (c) establishment of a dose–response relationship (a change in the amount, concentration or duration of exposure is related to a change in the outcome), (d) proper chronology between exposure and disease and (e) compatibility with other lines of evidence. The stre ıgth of the association is directly related to the magnitude of the relative risk or odds ratio.

The recent review of statistical analyses of case-control studies by Breslow and Day [12] shows that this type of investigation is probably indispensable in cancer research. Using this approach, relationships between many exposures and disease have been elucidated. For instance, the associations between age at first parturition and breast cancer; diethylstilbestrol and vaginal cancer; exogenous estrogens and endometrial cancer have fallen to the case control approach. In order to reach valid conclusions in this manner however, the study must be well designed and various biases properly dealt with.

Bias in a study can result in a spurious association between disease and the characteristic or exposure of interest which may occur in any of several ways. Sackett has reviewed the major potential biases [16] of case-control studies. One of these, Berkson's paradox, a type of selection bias, was first dealt with by Joseph Berkson in 1946 [17]. He described the distribution of risk of hospitalization among patients who have experienced more than one disease. As W.A. Guy has pointed out, the different probabilities of admission to a hospital for those individuals with disease, without disease and with the characteristic of interest may result in an artificial alteration (bias) in the odds ratio [18]. Berkson asserted that the probabilities of hospitalization for those with multiple diseases is a combination of the rates for each of their illnesses. Consequently, if hospital patients form the study group which is to be compared with a control group, the results must be regarded with reservation because the hospital population is not representative of the overall population. The over-representation of patients with multiple diseases in the hospital population has an effect on the odds ratio because it results in a different hospitalization rate for each cell of the 2×2 table [17]. The first empirical demonstration of the importance of Berkson's paradox came in 1978 after over 30 years of neglect [19]. Roberts and others, calculated the odds ratio for the association between respiratory disease and injury cases. When the general population was used as the basis for the study, an odds ratio of 0.98 was obtained which indicates no association. However, in a hospitalized subset the odds ratio was 1.37, which is a statistically significant difference ($p = 0.05$) in the relative risk between the general population and a hospital population. So if an investigator looked only at hospital patients, he/she may conclude erroneously, that injury is probably caused by respiratory diseases.

Recall bias is another well known problem in case-control studies and may be most important if the exposure is rare or when community controls are used [16]. People of all ages have difficulty in recalling past events, and obviously

the more remote the event, the more likely a recall error can be expected. Recall errors may affect estimates of exposure or estimates of disease and may cause a change in the odds ratio.

Also, prevalence-incidence bias is nearly always a factor in case-control studies of chronic exposure due to the exclusion of persons affected early. If those who become ill soon after exposure change jobs, retire or die, then they would not be a part of the population under study. Thus, the most susceptible may be excluded unless specifically searched for, and therefore the number of cases is artificially reduced causing a reduction in the relative odds.

Once the data are collected and an odds ratio calculated, its significance must be determined. Cole pointed to the over-reliance on the *p*-value and the tendency to use it to establish or refute causality. But the *p*-value is merely the probability that data as extreme as that observed could have been obtained by chance alone and if the *p*-value is small, then the probability that the result was obtained by chance is unlikely. Thus, a *p*-value of 0.01 or 0.05 simply means random variation is not viable as explanation for the results. He asserted that the confidence interval (the range of values within which a mean is thought to lie, with a specified degree of confidence) is a much more valuable test [8]. The confidence interval gives one a given degree of certainty that the parameter (relative risk) is within that interval which is especially useful since Miettinen [20] simplified the confidence interval calculation. Miettinen made other contributions to the design of case-control studies. For instance he asserted that matching improved validity (that is the measure measures what it is supposed to measure), not efficiency (precision) and should be used only for characteristics that are related to the exposure and the disease under study [21]. Matching makes the cases and the controls identical for these factors (e.g. age, sex, ethnic group) and thus, removes this influence on the odds ratio calculation.

Hazard evaluation

The evolution of chronic hazard evaluation can be exemplified by looking at some specific hazards. In 1927, it was first suspected that nickel workers had an increased risk of developing nasal cancers a suspicion which was not verified until Bradford Hill gave his report to the Mond Nickel Company in 1939. This report, completed under contract to the company, was not published in the scientific literature. No further studies appeared until 1958 when Morgan published his observations on respiratory cancer in nickel workers [22] and later on nasal and lung cancer [23].

Bradford Hill's study has shown that the excess risk of nasal cancer was limited to workers actually involved with the carbonyl process and that lung cancer also occurred more frequently in this group. Apart from nasal and lung cancer, using standard population data as a reference, it was calculated that only ten other cancers could have been expected to occur and, in fact, only 11

were observed in this worker population. As a result of these studies, in 1949 nasal and lung cancers occurring in workers engaged "in a factory where nickel is produced by decomposition of a gaseous nickel compound" were placed on the official list of occupational diseases [22]. This study covered only the Clydach plant in South Wales and, thus, only the carbonyl process of nickel refining. The more generalized extent of the hazard was not appreciated and nickel carbonyl was assumed to be the only responsible agent.

The three decades that elapsed between initial and confirmatory studies allowed workers to continue to be exposed to nickel and various dusts and fumes. The premature assumption that the carbonyl process was to blame was tragic and began to be refuted in the early 1950's when an excess of cancer was found among workers in plants where this process was not used. Suspicion now also lies with nickel subsulphide but as NIOSH concluded in its criteria document of 1977, all inorganic nickel should be considered carcinogenic until further data are available [24]. Many similar stories mark the history of environmental medicine.

The elucidation of agents causing lung cancer has contributed greatly to the field of occupational epidemiology. For example, lung cancer had long been suspected to result from exposure to chromates when the first study relating the deaths to the population at risk was reported. In 1950, Baetjer reviewed the literature on respiratory cancer among chromate workers and came to the conclusion that it was far higher than expected [25]. It is difficult if not impossible to prevent occupational disease unless the distribution of risk among specific workers is characterized which allows specific processes, chemical compounds, routes of exposure and workers at risk to be targeted for preventive measures. The history of the association between lung cancer and cigarettes is another important chapter in the development of occupational epidemiology. In the era before World War II, documented lung cancer was rare. During and just after this global conflict, however, it became clear that the incidence among men was rising. Both case-control and cohort studies were initiated to study the etiology of this increase. In 1947, Doll and Hill planned a case-control study to determine the relation between lung cancer and smoking. Their conclusion published in the British Medical Journal in 1950 was not a popular one. They stated, "smoking is a factor, and an important factor, in the production of carcinoma of the lung..." [26]. A cohort study begun by the same investigators in 1951 involved both male and female doctors. Questionnaires were sent to all British physicians regarding their smoking habits. Death certificates of these physicians were collected and the cause of death correlated to smoking habits. These studies [27,28] and others in the 1950's which were built upon the seminal works of Graunt, Farr and Snow, not only showed that cigarette smoking resulted in lung cancer and heart disease in both sexes, but also reinforced the utility of non-experimental methods in the evaluation of environmental or occupational disease.

As noted by Monson [6] the computer has greatly enhanced the collection and analysis of data. The consequent ability to explore weaker associations than were previously practical has encouraged an explosion of epidemiologic studies. Smaller odds ratios can now be detected and excess risk due to lower levels of exposure analyzed. The long term storage of medical and industrial hygiene data facilitates the evaluation of long-term hazards. The epidemiologist is obliged, however, to recognize and if possible correct any weaknesses in the data collection process and remember that without accurate exposure data, analysis of the extent of a hazard becomes imprecise.

Toxicology and industrial exposures

Lead usage may date from 2000 B.C., and in 370 B.C. Hippocrates described the first case of abdominal colic. Arsenic and mercury were known poisons in the fourth century B.C. and Maimonides wrote a toxicology text in the twelfth century. The Egyptians had information on a number of poisons including lead, copper and antimony [29]. Cadmium, however, was not recognized in ores until 1817. Initially, acute toxicities were the major concern but in today's industrial environment subtle, chronic and even sub-clinical effects must be searched out. The literature on metal toxicity has grown recently, especially in the area of carcinogenesis. Friberg reviewed the risk assessment of metal exposure [30], the components of which are risk identification, estimation, evaluation and control.

Toxicological, medical and epidemiological information is essential to identification and estimation, but independent of risk evaluation and control. Therefore, these disciplines are crucial to identifying the hazards and estimating their magnitude, the first steps in the risk assessment process. The process of risk assessment is complicated to some extent by the "no threshold" approach to carcinogens. Risk to very low levels of exposure is an active area of research and basically involves the application of several mathematical models. Measured points of exposure plotted against morbidity/mortality data are extrapolated to zero exposure allowing possible morbidity/mortality to be read against low levels which have not been measured. The linear or "one-hit" model which assumes that one molecule reacting with the cell can cause cancer, is the most conservative. The application of this model will, however, overestimate the risk for non-carcinogens [30]. Therefore knowledge of the mechanism of toxicity and potential carcinogenesis is critical for appropriate regulatory action. The debate concerning the relative value of animal data versus epidemiologic studies continues and is of particular concern to regulatory agencies.

Animal data are critical for mechanistic research and to establish the curve for extrapolation to very low doses. Epidemiologic data are essentially the results of human studies and may confirm or refute animal data. OSHA has

determined that *positive* animal data should supersede *negative* human epidemiologic studies because of the limitations of latency of effect, confounding factors, exposure interaction and individual human variability [31]. Thus, an animal carcinogen is deemed to affect humans until overwhelming data to the contrary are compiled. The pharmacokinetics and pathogenesis of a human carcinogen that does not cause cancer in animal models is harder to evaluate since complete reliance on epidemiologic data is required.

Biological monitoring

Biological monitoring is "a method of anticipating disease by sampling and analyzing solid tissue, tissue fluid, secretions, or excretions and thereby providing the opportunity to take preventive action" [32]. Biological monitoring is an effective means of monitoring *in vivo* levels of toxins and can in some instances, minimize the risk for those exposed, even though it may not always reflect actual absorption [33]. For instance, blood lead levels which are the best means of monitoring recent exposures, do not necessarily correlate with the body burden because lead is stored in bones and sequestered from the circulation. Nevertheless biological monitoring is valuable as a predictor of adverse consequences if done at the proper time. Since elevated *in vivo* levels may occur with acceptable ambient levels, both ambient and biological monitoring are frequently necessary for proper risk assessment.

The importance of toxicological information and biological monitoring for risk assessment is shown by the relatively recent addition of cadmium and beryllium to the list of carcinogens [34]. A recent paper by Enterline and others, shows that even ancient poisons such as arsenic may not be completely understood [35]. A new mathematical model for the conversion of urinary arsenic levels to airborne levels provided the means to demonstrate that the relation between the respiratory cancer Standardized Mortality Ratio (SMR) and airborne arsenic exposure was stronger than seen in any earlier analyses (Fig. 1). The calculated air levels were considerably above those previously projected. This indirect technique of determining airborne levels from urine levels evolved because direct measurements of air levels are usually not available.

While the relationship between respiratory cancer, SMR, and urinary arsenic levels was found to be linear, the slope of the SMR versus air level curve lessens as the ambient levels rise (Fig. 1). The apparent decline in the rate of change of the SMR with increasing air levels of arsenic may be due to a decline in bioavailability of arsenic at higher ambient arsenic levels [35]. The concave upward curve of air arsenic levels versus urinary arsenic levels (Fig. 2) tends to support this, but may only indicate an excretion maximum. The previous linear relation was derived from relatively low level arsenic exposures. At higher levels, the relation may change if bioavailability is altered. Thus, toxicologic,

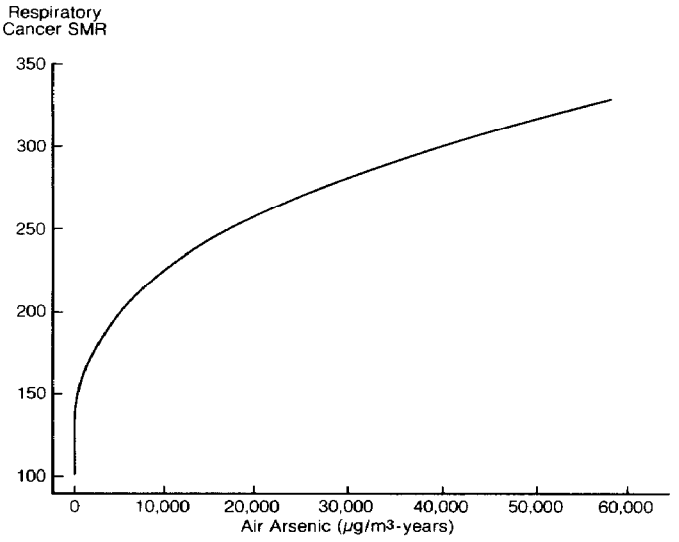

Fig. 1. Cancer SMR vs. airborne arsenic levels (Redrawn from Enterline et al. [35]).

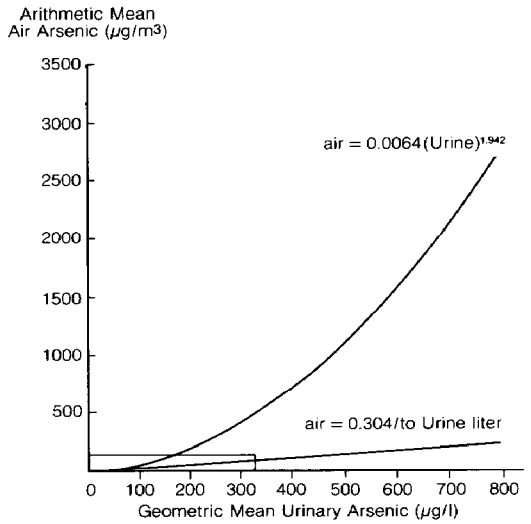

Fig. 2. Best fit lines for air arsenic level based on urinary levels (Redrawn from Enterline et al. [35]).

industrial hygiene and medical data continue to be re-evaluated even for established hazards adding to the burden of evaluating new hazards and illustrating the importance of exposure data.

Work-practices

The value of prompt risk assessment and good work-practices is shown by the following. In 1962, it was noted that an excess of lung cancer occurred in workers employed in an area of a major chemical plant. Reports soon began to appear documenting the carcinogenicity of chloromethyl methyl ether (CMME) and bis-chloromethyl ether (BCME) in animals [36]. A semi-annual screening of workers was initiated in December 1962, which consisted of a 70 mm chest photofluorogram and a questionnaire. A group of men were followed over five years during which time four developed lung cancer. This 8-fold elevation in risk was largely due to the work-practices which allowed exposure levels to be so great that the building had to be evacuated at least 3–4 times on most days because of the vapors. This was not worrisome at the time because BCME was not a known hazard. Had a high index of suspicion for occupational disease and a respect for potential hazards been operative in this instance, many deaths would have been avoided. This could be a harbinger of the disasters yet to happen if exposures are not minimized, and the multiplicity of new and unknown chemicals are not controlled to the greatest degree feasible.

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