Cancer patients often ask their physician whether there are any factors in their family history, life style, or work environment that might have increased the risk of developing their type of tumor. When clinicians consult the literature about oncology, toxicology, and epidemiology for answers to questions such as this, they soon discover that the information can be extensive and complicated and that guidance may be needed for the interpretation of some of the data. This report will review the association of benzene exposure with myeloma.

Since the first cases of acute myelogenous leukemia (AML) were reported in workers exposed to high concentrations of benzene in shoe manufacturing and rotogravure plants, there have been extensive investigations of the role of benzene in the causation of the hematologic malignancies. Data to be presented below convincingly link high-level benzene exposure to the causation of AML. Case reports of another hematologic malignancy, multiple myeloma, in persons exposed to benzene prompted additional studies to determine whether benzene might also be involved in the causation of this tumor.

The purposes of our appraisal are to update, review, and summarize studies of the association of benzene with myeloma and to illustrate the use of the criteria developed by Sir Austin Bradford Hill in the evaluation of the role of benzene in the causation of multiple myeloma. We will also review advances in the detection of specific chromosome lesions in myeloma cells and those associated with drug and chemical exposures.

Myeloma originates with the malignant transformation of a B lymphocyte that has undergone V(D)J recombination and somatic hypermutation of its Ig heavy and light chain genes and, almost always, isotype switch recombination (IgM myeloma is rare). This clone is committed to the production of a unique monoclonal Ig (abbreviated as monoclonal- or M-protein). The clone derived from the transformed B lymphocyte must grow to approximately 1 billion cells before sufficient M-protein is produced to allow detection in a serum electrophoresis pattern. Subjects are asymptomatic during the initial phase (monoclonal gammopathy of undetermined significance [MGUS]), when a small M-protein is present in the serum, without bone lesions, renal failure, or anemia, and the marrow contains less than 10% plasma cells. More than 95% of the subjects discovered to have an M-protein in a screening study of a population will be found to have MGUS. Follow-up of 241 MGUS subjects at the Mayo Clinic for 24 to 38 years showed that only 26% progressed to a symptomatic B-lymphocyte malignancy, with bone destruction, bone pain, and other manifestations of these malignancies. The studies to be reviewed here deal only with the association of benzene with multiple myeloma: the association of benzene with MGUS has not been evaluated.

Detailed molecular analyses of the reciprocal 11;14 breakpoints and the productive switch recombination breakpoint in the myeloma cell line U266 clearly indicate that, at least in this one example that has been fully characterized, the aberrant 11;14 rearrangement resulted from an error occurring at the time and is related to the process of productive isotype switch recombination. These translocations are characteristic in that t(4;14) and t(14;16) have only been described in myeloma samples; similarly, a t(11;14) translocation occurring in the switch region has only been described in myeloma samples. Many of these translocations are not detected by conventional karyotypic analysis, although recent analyses using reverse transcription-polymerase chain reaction (RT-PCR), multicolor spectral karyotypes, and dual-color interphase fluorescent in situ hybridization indicate that these translocations occur at a similar high frequency in primary patient material. Myeloma is also characterized by frequent trisomies of chromosomes 3, 5, 7, 9, 11, 15, 19, and 21 and monosomy 13.

Although the first report of multiple myeloma appeared in 1844, the disease has presented problems in classification in the past and, consequently, in analysis as well. Historically, multiple myeloma was classified as a bone tumor until the sixth revision of the International Classification of Diseases (ICD), which was published in the late 1940s. Since then, multiple myeloma has been assigned a unique rubric (ICD 203) in the broad category of “neoplasms of the lymphatic and hematopoietic tissues” ICD 200-209, which includes non-Hodgkin lymphoma, Hodgkin disease, and various types of leukemia.

According to the National Center for Health Statistics (NCHS), more than 8,000 Americans die from multiple myeloma every year. In 1994, the National Cancer Institute (NCI) estimated that 12,000 new cases were diagnosed in the United States. Multiple myeloma is a disease of older age. The NCI Surveillance, Epidemiology, and End Results (SEER) Program reports that the incidence increases rapidly with age to reach 52/100,000 in caucasian men more than 85 years of age and to reach 33/100,000 in caucasian women 80 to 84 years of age. Multiple myeloma, unlike other lymphatic and hematopoietic malignancies, is more common in blacks than in caucasians. The age-adjusted incidence rate for caucasians is 4.1/100,000 and for blacks is 9.1/100,000. The lowest incidence rates are...
for Americans of Japanese (1.7/100,000) and Chinese (2.3/100,000) descent. The most distinctive feature of myeloma is the late age of onset, with a median age at diagnosis of 72 years of age, which is somewhat older than the median age at diagnosis of all cancers. Thus, age and race have an important influence on the incidence of myeloma. The strong influence of race on the incidence of myeloma and the occurrence of familial clusters of multiple myeloma cases suggest that genetic factors may be involved in determining who will develop this disease. Other risk factors for multiple myeloma (eg, autoimmune disorders, chronic immune stimulation, and ionizing radiation) have also been considered. The general epidemiology of multiple myeloma has been discussed recently in 2 reviews.

EXPOSURE, METABOLISM, AND TOXICITY OF BENZENE

Benzene is a versatile industrial chemical. It is a natural component of crude and refined petroleum products. It is also formed in the combustion of organic materials. Benzene is used primarily as a raw material in the manufacture of synthetic organic chemicals. In the past, benzene was used extensively as an organic solvent. It was also an important component of paint, thinners, adhesives, and degreasing compounds. Although it is rarely used in commercial products today, it is still present in many organic compounds as a contaminant.

Exposure to benzene is not limited to the occupational setting. Nonoccupational exposure originating from the general environment or derived from personal lifestyle is not uncommon. The investigations of the US Environmental Protection Agency have shown that the major route of personal exposure is through air. Living close to major fixed sources of benzene (eg, oil refineries, storage tanks, and chemical plants) had no effect on personal exposure. For smokers, the overwhelming source of benzene exposure is mainstream cigarette smoke. According to the International Agency for Research on Cancer (IARC), benzene in cigarette smoke has been measured at levels between 47 and 64 parts per million (ppm). Ambient air benzene concentrations in urban areas have been recorded as high as 182 parts per billion (ppb) in Los Angeles, 98 ppb in Toronto, and 179 ppb in London. Surprisingly, benzene content in certain foods items is relatively high: 500 to 1,900 µg/kg in eggs and 120 µg/kg in Jamaican rum.

Benzene itself is not toxic. It must be broken down by enzymes in the liver into metabolites that are potentially toxic. The major toxicity observed in experimental animals (mice, rats, and rabbits) has been on the blood-forming cells of the bone marrow, the hemopoietic system. The most frequently observed toxic effect of heavy benzene exposure in humans and animal models has been depression of blood cell production, in some cases leading to aplastic anemia. Detailed studies of humans, mice, and rats exposed to benzene have shown that, under certain circumstances, it can lead to chromosomal abnormalities, the formation of micronuclei, and sister chromosome exchanges.

Studies of workers chronically exposed to high concentrations of benzene indicate that benzene can cause AML (see below). Although these effects (ie, aplastic anemia, chromosome damage, and leukemogenesis) are indicative of the ultimate effects of benzene on bone marrow, the underlying mechanisms by which they are initiated are not fully understood.

The toxicity of benzene was first tested on experimental animals and tissue cultures of human cells in the laboratory. Unfortunately, there is no good animal model for the AML caused by prolonged high benzene exposure in humans, and because benzene must be converted into toxic metabolites before it can damage hemopoietic cells, it has been difficult to study the underlying mechanism directly in tissue cultures. Despite a great deal of effort, little has been learned about the role of benzene as a potential cause of the hematologic malignancies in the laboratory. In contrast, detailed studies of exposures to benzene in the workplace have yielded much useful information.

The detection of cases of cytopenia, aplastic anemia, and leukemia among shoe and leather workers using adhesives containing up to 88% benzene in Turkey in the 1960s and 1970s provided strong suggestions about the leukemogenic potential of this agent. Average air concentrations experienced by the Turkish shoe and leather workers ranged from 16 to 30 ppm during nonwork hours, with an increase during work hours to 212 ppm, and sometimes as high as 640 ppm, when glues containing benzene were used. Reports of similar cases from Italy among workers in rotogravure plants, where benzene concentrations in the air were estimated to range between 200 and 400 ppm, with peaks up to 1,500 ppm, and in shoe factories increased the concern about benzene. These case reports set the stage for detailed epidemiological studies of the role of benzene as a cause of hematological malignancies.

Based on a crude investigation in the 1970s, Aksoy et al found an excess of leukemia (~2-fold) among Turkish shoemakers using adhesives containing benzene. Exposure data were inadequate for a dose-response analysis. Thus, the only conclusion one can draw from the data is that exposure to benzene at such high levels can increase the risk of leukemia. However, Aksoy et al did make the important observation that the prominent cell-type of the leukemia was AML.

In the past, leukemia was considered as a single statistical category in most occupational epidemiologic studies. This occurred partly because of the historical nomenclature, potential misdiagnoses in some cases, lack of an understanding of the biological mechanisms, the unavailability of cell-type specific rates for comparison, and, most importantly, the paucity of cases by cell-type in individual studies. Recently, epidemiologic studies have demonstrated the importance of cell-type specific analysis in studying leukemia. It has now been recognized that the diseases collectively known as leukemia are several distinct malignancies with different etiologic factors.

The importance of specific cell-types of leukemia has also been recognized by hematologists, who have found that the characteristics of the disease fit a more homogeneous pattern if the leukemias are subdivided on the basis of morphology (eg, lymphocytic or myelogeneous) and the course of the disease (eg, acute or chronic). More recently, specific subtypes, for instance AML, have been associated with distinct chromosome translocations [eg, t(8;21), inv(16), t(15,17), and t(11q23)]. Tumors that share the same chromosome translocations also share similar morphology, prognosis, and response to treatment, and cytogenetics is now recognized as one of the most important prognostic factors in AML. In the subset of AML secondary to inhibitors of DNA topoisomerase II (eg, etoposide), characteris-
tic reciprocal translocations involving the loci 11q23 (MLL) and 21q22 (AML1) have been recognized. These have been postulated to result from site-specific DNA cleavage induced by the topoisomerase inhibitors. The distribution of translocation breakpoints on 11q23 in therapy-related AML has been shown to be distinct from that of AML arising de novo, with a concentration in a region rich in topoisomerase II cleavage sites. Thus, recent advances in other disciplines confirm the epidemiologic observation that leukemia is a group of distinct malignancies that should be analyzed separately.

**CASE REPORTS OF MULTIPLE MYELOMA AND BENZENE EXPOSURE**

Interest in the relationship between multiple myeloma and benzene exposure arises from observations that multiple myeloma involves the bone marrow and that benzene is a recognized bone marrow toxin. In 1970, Torres et al described 2 cases of multiple myeloma in leather workers in Spain who used benzene-containing glues. In 1984, Aksoy et al reported 4 cases of multiple myeloma over a period of 10 years in Turkey in workers who were exposed to benzene. The occupations of these 4 workers included a shoemaker, a plastic factory manager, an airplane technician, and a furniture worker. These 2 reports have been cited frequently as evidence suggestive of as well as supportive of an association between multiple myeloma and benzene exposure. However, case reports alone are insufficient for the determination of causation.

**USING EPIDEMIOLOGY TO IDENTIFY CAUSAL FACTORS IN CHRONIC DISEASES**

To determine the relationship between multiple myeloma and benzene exposure, epidemiologic studies based on well-defined populations of exposed workers were needed. Epidemiologic studies involve the comparison of disease patterns and rates between groups of persons with and without the exposure of interest or groups with varying degrees and/or durations of exposure. The comparison is generally based on risk ratios between the 2 groups (the risk of the exposed workers compared with nonexposed persons). Risk ratios can be standardized mortality ratios (SMR) in cohort studies or odds ratios (relative risks) in case-control studies. A risk ratio greater than 1 may indicate an increased risk. Associated with each risk ratio is a 95% confidence interval. The risk ratio is statistically significant if the 95% confidence interval does not include 1, which means that the observed result is real and probably not due to chance. Case reports, by definition, are incapable of providing any estimate of risk ratio, because the underlying population at risk is not defined. Only properly conducted epidemiologic studies, particularly those with quantitative exposure information, can provide the basic data needed for a causation analysis.

**HILL’S CRITERIA FOR ASSESSING CAUSATION IN CHRONIC DISEASES**

The criteria for assessing causation in chronic diseases, such as cancer, was formulated by Hill more than 3 decades ago and is used by the Surgeon General’s Committee in assessing the relationship between smoking and cancer as well as by IARC in the evaluation of carcinogenicity of substances. Hill’s criteria include the following:

1. The strength of the association. How large is the difference between the incidence of the disease in subjects exposed to the chemical versus the unexposed? Large differences are more likely to be associated with causal factors. Furthermore, the risk ratio must be statistically significant before one can conclude that there is an increased risk, ie, the excess is not likely due to chance.

2. The consistency of the association. Has the association been repeatedly observed in more than one group, in different places, and under different circumstances?

3. The specificity of the association. The association should be specific in terms of both exposure and disease. Nevertheless, it must be remembered that some diseases, such as cancer, can have more than one cause.

4. The temporality of association. The exposure to the chemical must precede the development of the disease. For chronic diseases, because of the usual long latency, recent exposures do not play a significant role in the disease process.

5. Exposure-response relationship in the association. There should be evidence that greater exposures lead to a higher incidence of the disease.

6. Biological plausibility. If the chemical agent is known to cause some biological effect that could lead to the development of the disease in question, it is helpful in establishing causation. However, this feature cannot be demanded in every case, because for many chemicals the biologic mechanisms are unknown.

7. Experimental evidence. With respect to human carcinogens, direct experimental evidence is seldom available. Occasionally, it is possible to draw on semieperimental evidence (mostly resulting from intervention or preventive action). For example, the incidence of acute leukemia in shoe workers began to decrease in Istanbul after the use of benzene in their work was phased out, and no new cases of AML have been detected in the Ohio Pliofilm cohort (see next section) in workers hired after 1950, when the levels of benzene exposure were reduced. These observations support the view that benzene, at high concentrations, was involved in causing AML.

**EPIDEMIOLOGIC STUDIES OF WORKERS EXPOSED TO BENZENE**

In evaluating the causal relationship, if any, between benzene exposure and multiple myeloma, Hill’s criteria must be considered. In particular, the available data must be examined in terms of the strength, consistency, and specificity of the association, as well as the exposure-response relationship, which can be addressed by epidemiologic data directly. In addition, studies of the association of exposure to a chemical with the subsequent development of a relatively rare malignancy such as multiple myeloma require long-term studies of the largest possible sample of exposed people, because the risk of a false-negative result is great.

In studying chronic diseases such as myeloma, which appear to evolve slowly, it is important to follow the study cohort for many years because of the potential problem of latency, ie, the interval between the toxic exposure that injures a B lymphocyte and the eventual development of myeloma. Because this
interval may be of many years duration, the follow-up period must be long enough for the effects of the exposure to become manifest.

One of the frequently cited studies of benzene-exposed workers is a cohort of workers involved in the manufacture of rubber hydrochloride (Pliofilm) in Ohio. This cohort was analyzed on several occasions by the National Institute for Occupational Safety and Health (NIOSH), as well as by others.

The first report was by Infante et al in 1977. The mortality through 1975 of 748 caucasian male workers occupationally exposed to benzene for varying periods between 1940 and 1949 in two Pliofilm manufacturing facilities was evaluated. The vital status of only 75% of the cohort was determined. Causes of death were determined from death certificates. Two populations were chosen as control groups: the first was US caucasian males, and the second was employees at a fibrous glass construction products facility over the same period. For lymphatic and hematopoietic malignancies, there were 9 observed deaths versus 3.34 expected when compared with US caucasian males. This difference was statistically significant and was attributed to an increased leukemia mortality. No analysis was reported for multiple myeloma.

The next analysis of the Pliofilm cohort was conducted by Rinsky et al in 1981. Vital status was obtained for 98% of the original group of 748 men (group 1). A second group of 258 caucasian male workers first employed in departments with benzene exposure between January 1, 1950 and December 31, 1959 (group 2) was added. In group 1, 10 deaths of lymphatic and hematologic malignancy were observed versus 3.03 expected, with 7 leukemia deaths versus 1.25 expected (SMR = 5.60). In group 2, there was 1 death from myelogenous leukemia. This individual started his employment at the plant in May 1950 and died in 1954. The major findings of this analysis confirmed that of the previous report. Again, no analysis was reported for multiple myeloma.

The third report, also by Rinsky et al in 1987, was an update of the earlier report. Benzene levels were estimated for jobs held by the cohort members, and cumulative exposure (ppm-years) was estimated for each worker. A total of 1,165 caucasian males with at least 1 ppm-day of benzene exposure were observed through December 31, 1981. There was a significant increase in deaths from all lymphatic and hematologic neoplasms (15 observed vs 6.6 expected; SMR = 2.27). The increase was due to leukemia (9 observed vs 2.7 expected; SMR = 3.37) and myeloma (4 observed vs 1 expected; SMR = 4.09). The principal findings of this analysis were a positive exposure-response relationship between benzene and all leukemias. On the other hand, no exposure-response relationship was found for myeloma.

A further updated analysis of this cohort was conducted by Paxton et al with vital status follow-up through 1987. For the entire cohort, a significantly increased SMR for all leukemia of 3.60 was found (14 observed vs 3.89 expected). No new cases of myeloma were discovered. Although Paxton et al did not calculate an SMR for multiple myeloma, they stated that, with the increased follow-up time (hence, more expected deaths), the statistical association with myeloma reported by Rinsky et al was “weakened to nonsignificance.” Similar to the previous analysis, a positive exposure-response relationship with leukemia was found. Paxton et al concluded that the leukemia data were consistent with a threshold model (ie, an exposure greater than the threshold is required before the risk of leukemia is increased). It is important to note that both Rinsky et al and Paxton et al grouped all cell-types of leukemia together as a single disease in their analyses (thus violating one of Hill’s criteria: specificity).

Citing recent advances in our understanding of the biological mechanisms of benzene leukemogenesis and observations from recent epidemiologic studies, Wong criticized the lumping of “lymphatic and hematological malignancies” or “leukemias of all cell-types combined” for analysis in the study of the Pliofilm cohort. Each hematological malignancy originates from the malignant transformation of different precursor cells. The malignancies that result are very different, as shown by differences in the course and treatment of acute myelogenous leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, myeloma, and lymphomas that are included in these broad categories. In the absence of specific data, it cannot be assumed that the same chemical is capable of causing all of these different neoplasms. Whether the same chemical can cause more than one disease can only be demonstrated through analyses specific to each individual disease in question. In other words, Hill’s criterion of specificity must be met before a causation conclusion can be drawn. This issue has been addressed by a number of investigators.

Table 1 shows that, for the total cohort, 6 deaths from AML were observed versus 1.19 expected. The SMR of 5.03 was significantly elevated, with a 95% confidence interval (95% CI) of 1.84 to 10.97. Furthermore, there was a strong exposure-response relationship, with an SMR of 98.37 for those with 400 or more ppm-years. On the other hand, the exposure-response analysis also shows a threshold. The risk of developing AML was not increased in workers exposed to less than 200 ppm-years. As stated by Wong, had more realistic exposure

### Table 1. AML by Cumulative Benzene Exposure in a Cohort of Pliofilm Workers

<table>
<thead>
<tr>
<th>Cumulative Exposure in ppm-years</th>
<th>Observed Deaths</th>
<th>Expected Deaths</th>
<th>Standardized Mortality Ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>1</td>
<td>0.84</td>
<td>1.19</td>
</tr>
<tr>
<td>40-200</td>
<td>0</td>
<td>0.35</td>
<td>0</td>
</tr>
<tr>
<td>200-400</td>
<td>2</td>
<td>0.07</td>
<td>27.21*</td>
</tr>
<tr>
<td>400+</td>
<td>3</td>
<td>0.03</td>
<td>98.37*</td>
</tr>
<tr>
<td>Totals</td>
<td>6</td>
<td>1.19</td>
<td>5.03*</td>
</tr>
</tbody>
</table>

Data from Wong. *P < .01.*
estimates been used in the Pliofilm study, the AML threshold would have been higher (between 370 and 530 ppm-years).

For cell types other than AML, the Pliofilm study does not provide sufficient cases for any meaningful analysis. The cell-type with the second largest number of cases was CML, consisting of only 2 deaths. One of the 2 CML cases was employed at the plant for 1 month in 1948 and died 2 years later in 1950. Given the slow progression of the disease (ie, long latency), this case could not have been related to exposure at the plant (Hill’s criterion of temporality). Thus, only AML was associated with benzene exposure in the Pliofilm study.

Recent laboratory studies of the effect of benzene metabolites on the growth regulation of myeloid cell progenitors by Iorns et al and others offer a biological mechanism to explain the selective increase in AML (Hill’s criterion of biological plausibility). These investigations have shown that hydroquinone (a benzene metabolite) increases the recruitment or stimulation of myeloid progenitor cells that respond to a specific myeloid growth factor (granulocyte-macrophage colony-stimulating factor [GM-CSF]), thereby increasing the number of these cells at risk of developing leukemia. This effect, on the other hand, has not been shown for growth factors associated with other progenitor cells.

Wong concluded that analysis specific for AML shows the importance of taking specificity of disease into consideration in causation analysis. His investigation shows that previous studies based on a combination of all types of leukemia have set the estimated threshold too low on one hand and underestimated the risk for exposure above the threshold on the other.

In addition to AML, Wong also reanalyzed the updated Pliofilm cohort with respect to myeloma. The results are reproduced in Table 2. For the total cohort, 4 deaths from myeloma were observed, versus 1.37 expected; the corresponding SMR of 2.91 was not statistically significant. More importantly, there was no exposure-response relationship. In fact, 3 of the 4 deaths occurred in workers in the lowest exposure category. One of these workers was employed at the plant for only 4 days, and the other 2 workers were employed for 9 months and 1.5 years, respectively.

Thus, in this Pliofilm cohort, a significant increase in the risk of developing AML was observed in benzene-exposed workers, and there was a strong exposure-response relationship between cumulative benzene exposure and the risk of AML. Furthermore, all AML deaths occurred among workers who were exposed before 1950, after which benzene exposure at these plants was markedly reduced. According to Rinsky et al., "(the) employees’ 8-hour time-weighted average exposures were within the recommended standards in effect at the time."

The benzene threshold limit value (TLV) was reduced from 100 to 50 ppm in 1947 and was further reduced in 1948 to 35 ppm. It can be assumed that exposure after 1950 would have been much lower than that in the early or mid-1940s. No deaths from AML have been observed among the Pliofilm workers employed after 1950. Furthermore, in the Pliofilm study there was no evidence for a causal relationship between benzene exposure and the risk of developing leukemias other than AML or the risk of developing multiple myeloma.

In the United States, there is another often-cited cohort study of workers exposed to benzene. Wong reported the mortality experience of a cohort study of more than 7,000 chemical workers in the United States. Most of these workers were exposed to benzene in the 1940s and 1950s, with some whose first exposure occurred in the 1920s and 1930s. Furthermore, some of these workers were exposed to relatively high benzene levels in the past (in the range of 50 to 100 ppm). There were 3 deaths from multiple myeloma among the workers exposed to benzene. The expected deaths were estimated to be 2.58, with adjustment for age and race. The corresponding SMR was 1.16, with a 95% CI of 0.24 to 3.39. Thus, a significantly increased mortality from multiple myeloma was not observed in this cohort of chemical workers exposed to benzene.

There are 2 additional small cohort studies of benzene workers in the United States. Bond et al reported only 1 death due to multiple myeloma among 594 chemical workers in Michigan who were exposed to benzene. The investigators stated that the multiple myeloma death “did not represent an excess over expectation.” In another small study, Decoufle et al also reported only 1 death from multiple myeloma in 259 petrochemical workers who were exposed to benzene at a petrochemical plant in Baltimore. Although these 2 studies were small and no firm conclusion could be drawn from them alone, neither provided any support for a causal relationship between benzene exposure and multiple myeloma.

Similar results have been reported in studies from other countries as well. Paci et al reported significantly elevated risks from both aplastic anemia and leukemia in a cohort of more than 2,000 Italian shoe workers who were exposed to glues containing more than 70% benzene by weight, but no death due to multiple myeloma. It is interesting to point out that an Italian law was introduced in 1963 limiting the use of benzene. The benzene content in the glues used by Italian shoe workers was reduced to less than 2%. No increase of leukemia or aplastic anemia was reported among those who began their employment after 1964 (Hill’s criterion of “experimental” evidence resulting from intervention).

Recently, a large-scale cohort study of more than 74,000 Chinese workers in a variety of occupations and industries (predominately painters) who were exposed to benzene as well as to other chemicals was completed by scientists from China and the US National Cancer Institute. The observation period was from 1972 to 1987. A total of 1,369 deaths were reported. There was a significant increase in mortality from AML. Mortality from aplastic anemia was also significantly elevated. On the other hand, no death was due to multiple myeloma (SMR = 0; 95% CI, 0 to 3.2). Therefore, the cohort studies of Italian and Chinese workers exposed to relatively high benzene

<table>
<thead>
<tr>
<th>Cumulative Exposure in ppm-years</th>
<th>Observed Deaths</th>
<th>Expected Deaths</th>
<th>Standardized Mortality Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>3</td>
<td>0.93</td>
<td>3.21</td>
<td>0.66-9.39</td>
</tr>
<tr>
<td>40-200</td>
<td>0</td>
<td>0.30</td>
<td>0</td>
<td>0.00-12.29</td>
</tr>
<tr>
<td>200-400</td>
<td>0</td>
<td>0.10</td>
<td>0</td>
<td>0.00-36.89</td>
</tr>
<tr>
<td>400+</td>
<td>1</td>
<td>0.04</td>
<td>25.17</td>
<td>0.63-139.83</td>
</tr>
<tr>
<td>Total</td>
<td>4</td>
<td>1.37</td>
<td>2.91</td>
<td>0.79-7.45</td>
</tr>
</tbody>
</table>

Data from Wong.
levels (as indicated by the increased risk of leukemia or aplastic anemia) do not provide any evidence for a causal association between benzene exposure and multiple myeloma.

Another source of data for assessing the health effects of benzene exposure is the petroleum industry. Exposure to hydrocarbons in the petroleum industry includes inhalation of vapors and dermal contact with crude oil, feedstocks, intermediate products during refining, and end products such as gasoline in marketing or distribution.44 Many of these products contain varying amounts of benzene. Therefore, workers in the petroleum industry constitute a valuable database to assess the relationship between multiple myeloma and benzene exposure.

Although there are numerous studies of petroleum workers, there are only 2 studies with adequate quantitative exposure data. In a relatively large cohort study of distribution workers, exposure to gasoline vapor was measured in terms of total hydrocarbons (THC).67,68 The benzene component in gasoline vapor is highly correlated with total hydrocarbons. Based on more than 400 industrial hygiene samples reported by the International Agency for Research on Cancer, which were collected under a variety of environmental conditions, benzene concentration in gasoline vapor is approximately 1.6% of that of total hydrocarbons.44 Mortality from multiple myeloma in this cohort of distribution workers was examined by various exposure indices (job category, length of exposure, cumulative exposure, and cumulative frequency of peak exposure [an episode of exposure in excess of 500 ppm THC lasting 15 to 90 minutes]) in a subsequent nested case-control study by Wong et al.69 Analyses were based on both the Mantel-Haenszel procedure and conditional logistic regression (ie, internal comparisons). The major results are summarized in Tables 3 and 4. In general, drivers can be considered to have higher exposure than the others. As indicated in Table 3, the relative risk of multiple myeloma for drivers was 0.91 (95% CI, 0.21 to 3.96). Similarly, none of the exposure indices were found to be associated with multiple myeloma risk (Table 4). In particular, the risk ratios were 0.96, 1.00, and 1.00 for length of exposure, cumulative exposure, and cumulative frequency of peak exposure, respectively.

A similar nested case-control study of lymphohemopoietic cancers in Canadian distribution workers was conducted by Schnatter et al.70 Exposures were measured in terms of cumulative exposure and intensity of exposure. No relationship between multiple myeloma and exposure to total hydrocarbons or benzene was found. For example, with respect to benzene exposure, the risk ratios were 1.00, 0.44, 1.44, and 0 for cumulative exposure categories 0.0 to 0.90, greater than 0.90 to 9.9, greater than 9.9 to 9.99, and greater than 9.99 ppm-years, respectively.

Recently, the results of a record-linkage study of approximately 19,000 service station workers in 4 Scandinavian (Denmark, Norway, Sweden, and Finland) countries were reported.71 No increased multiple myeloma risk was found: among men, the standardized incidence ratio (SIR) was 0.6 (9 observed v 15.99 expected), with a 95% CI of 0.3 to 1.2, and among women, no multiple myeloma case was observed (1.65 expected).

Finally, to determine the risk of multiple myeloma, data from cohort studies of petroleum workers (the majority being refinery workers) were reviewed and pooled by Wong and Raabe.72 The methodology of pooled, or meta-analysis, of cohort studies has been described elsewhere.73,74 A total of 22 cohort mortality studies of petroleum workers in the United States, the United Kingdom, Canada, and Australia, which satisfied certain criteria, were included in the pooled analysis. Authors of these studies were contacted, and data on the number of observed deaths and age-specific person-years of observation were requested. Data from individual studies were combined in a pooled analysis (meta-analysis). In addition to the pooled analyses, results for individual cohorts, most of which have never been reported before, were also presented. The combined multinational cohort consisted of more than 250,000 petroleum workers, and the observation period covered an interval of 55

Table 3. Relative Risk and 95% CI of Multiple Myeloma by Job Category in a Nested Case-Control Study of Gasoline Distribution Workers

<table>
<thead>
<tr>
<th>Job Category</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plantmen</td>
<td>0.55</td>
<td>0.15-2.10</td>
</tr>
<tr>
<td>Warehousemen</td>
<td>1.82</td>
<td>0.32-10.4</td>
</tr>
<tr>
<td>Laborers</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Mechanics</td>
<td>0.45</td>
<td>0.05-3.81</td>
</tr>
<tr>
<td>Clerks/Office</td>
<td>0.29</td>
<td>0.04-2.28</td>
</tr>
<tr>
<td>Foremen/Super</td>
<td>1.92</td>
<td>0.43-8.59</td>
</tr>
<tr>
<td>Maintenance</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Drivers</td>
<td>0.91</td>
<td>0.21-3.96</td>
</tr>
<tr>
<td>Loaders</td>
<td>1.0</td>
<td>0.11-9.51</td>
</tr>
<tr>
<td>Others</td>
<td>0.80</td>
<td>0.21-3.06</td>
</tr>
</tbody>
</table>

Data from Wong et al.69

Table 4. Conditional Logistic Regression Analysis of Risk of Multiple Myeloma and Exposure to Total Hydrocarbons in a Nested Case-Control Study of Gasoline Distribution Workers

<table>
<thead>
<tr>
<th>Model</th>
<th>Variables in Model</th>
<th>β</th>
<th>SE (β)</th>
<th>( \chi^2 )</th>
<th>P</th>
<th>RR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Length of exposure (yrs)</td>
<td>-0.038778</td>
<td>0.034580</td>
<td>1.257</td>
<td>0.262</td>
<td>0.96</td>
</tr>
<tr>
<td>2</td>
<td>Cumulative exposure (ppm-years)</td>
<td>-0.000536</td>
<td>0.000732</td>
<td>0.536</td>
<td>0.464</td>
<td>1.00</td>
</tr>
<tr>
<td>3</td>
<td>Cumulative frequency of peak exposure</td>
<td>0.000046</td>
<td>0.000052</td>
<td>0.790</td>
<td>0.374</td>
<td>1.00</td>
</tr>
<tr>
<td>4</td>
<td>Length of exposure (yrs)</td>
<td>-0.033747</td>
<td>0.038630</td>
<td>0.763</td>
<td>0.382</td>
<td>0.97</td>
</tr>
<tr>
<td>5</td>
<td>Cumulative exposure (ppm-years)</td>
<td>-0.000218</td>
<td>0.000755</td>
<td>0.083</td>
<td>0.773</td>
<td>1.00</td>
</tr>
<tr>
<td>6</td>
<td>Cumulative frequency of peak exposure</td>
<td>0.000153</td>
<td>0.000089</td>
<td>2.980</td>
<td>0.048</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Cumulative exposure (ppm-years)</td>
<td>-0.001228</td>
<td>0.0001040</td>
<td>1.381</td>
<td>0.240</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Cumulative frequency of peak exposure</td>
<td>0.000088</td>
<td>0.000065</td>
<td>1.850</td>
<td>0.174</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Data from Wong et al.69

*Relative Risk (RR) corresponding to an increment of 1 unit of the independent variable.
years from 1937 to 1991. A total of 205 deaths from multiple myeloma were observed, compared with 220.93 expected, which were derived from respective national mortality rates. The corresponding SMR was 0.93 and the 95% CI was 0.81 to 1.07 (Table 5). Additional analyses were performed by type of facility and industrial process. Stratum-specific SMRs (95% CIs) were 0.92 (0.77 to 1.09) for refinery workers and 0.93 (0.69 to 1.23) for distribution workers. The pooled analysis indicates that petroleum workers are not at an increased risk of multiple myeloma as a result of their exposure to benzene, benzene-containing liquids, or other petroleum products in their work environment.

Further supporting evidence that there is no causal relationship between exposure to benzene or benzene-containing solvents and multiple myeloma can be derived from population-based case-control studies. In a US NCI case-control study consisting of 100 multiple myeloma patients in the Baltimore area, Linet et al. reported a risk ratio of 1.1 (95% CI, 0.4 to 3.7) for benzene exposure. In a second case-control study sponsored by NCI, Morris et al. compared the occupational exposure histories of 698 patients with newly diagnosed multiple myeloma in Washington, Utah, Michigan, and Georgia to their controls. For those exposed to aromatic hydrocarbons (including benzene), a risk ratio of 0.6 (95% CI, 0.3 to 1.0) was reported.

Case-control studies from other countries also support the finding of no causal relationship between multiple myeloma and benzene exposure from American studies. Based on a study of 131 multiple myeloma patients in Sweden, Flodin et al. reported a risk ratio of 1.0 (95% CI, 0.6 to 1.8) for exposure to solvents. The second Swedish study, based on 275 multiple myeloma patients in the northern part of the country, was reported by Eriksson and Karlsson. No increased risk was reported for occupational exposure to organic solvents (risk ratio of 0.5; 90% CI, 0.38 to 1.21). Two case-control studies of multiple myeloma in Denmark were reported by Heineman et al. and Pottet et al. The first study consisted of 1,098 male multiple myeloma patients. For those with probable exposure to organic solvents, the risk ratio was 0.9 (95% CI, 0.7 to 1.2), and for those with probable exposure to benzene in particular, the risk ratio was 0.8 (95% CI, 0.6 to 1.1). The second study consisted of 1,010 female multiple myeloma patients. The risk ratio for probable exposure to organic solvents was 0.6 (95% CI, 0.2 to 1.4). The last case-control study was reported by Cuzick and De Stavola from the United Kingdom. The exposure histories of 399 multiple myeloma patients in England and Wales were compared with those of matched controls. An analysis by length of exposure to “solvents/benzene” did not show any upward trend. Although no numerical risk ratio was presented in the report, the investigators stated that “excess risks were not found amongst individuals exposed to solvents.” Thus, these case-control studies support the results from cohort studies of benzene or petroleum workers that there is no increased risk of multiple myeloma associated with exposure to benzene or solvents containing benzene (Hill’s criterion of consistency).

### CONCLUSIONS

Based on a thorough analysis of the existing scientific data according to well-established criteria, the following conclusions can be made:

1. There is strong evidence linking high levels of exposure to benzene with an increased risk of developing acute myelogenous leukemia. The evidence for this association satisfies all of Sir Austin Bradford Hill’s criteria, and the relationship can be judged as causal in nature. Furthermore, cell-type specific analysis indicates that the threshold is most likely around 370 to 530 ppm-years.

2. In contrast, there is no scientific evidence to support a causal relationship between exposure to benzene or other petroleum products and the risk of developing multiple myeloma.

### REFERENCES


### Table 5. Multiple Myeloma in a Multinational Cohort of More Than 250,000 Petroleum Workers by Country and Industrial Division

<table>
<thead>
<tr>
<th>Country and Industrial Division</th>
<th>Observed Deaths</th>
<th>Expected Deaths</th>
<th>SMR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Refinery</td>
<td>116</td>
<td>120.01</td>
<td>0.97</td>
<td>0.81-1.17</td>
</tr>
<tr>
<td>US, UK, and Canada Refinery</td>
<td>145</td>
<td>157.91</td>
<td>0.92</td>
<td>0.77-1.09</td>
</tr>
<tr>
<td>US, UK, and Canada Distribution</td>
<td>48</td>
<td>51.46</td>
<td>0.93</td>
<td>0.69-1.23</td>
</tr>
<tr>
<td>US and Canada Production and pipeline</td>
<td>6</td>
<td>9.27</td>
<td>0.65</td>
<td>0.23-1.42</td>
</tr>
</tbody>
</table>
| US, UK, Canada, and Australia All divisions | 205 | 220.93 | 0.93 | 0.81-1.07

Data from Wong and Raabe.
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64. Decoufle P, Blattner WA, Blair A: Mortality among chemical workers exposed to benzene and other agents. Environ Res 30:15, 1983
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