Does Benzene Cause Multiple Myeloma? An Analysis of the Published Case–Control Literature

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Two case series and two epidemiological studies in the 1970s and 1980s suggested that benzene exposure might be a risk factor for multiple myeloma. An analysis has now been conducted of the published population-based and hospital-based case–control studies published through mid-1995 that permit examination of the relationship between multiple myeloma and benzene exposure or surrogates for benzene exposure. No increased association was found between multiple myeloma and benzene exposure or exposure to chemical groups that included benzene. The odds ratios from these analyses approximated 1.0. Exposures to petroleum products and employment in petroleum-related occupations did not appear to be risk factors for multiple myeloma. Cigarette smoking, as a surrogate of benzene exposure, was not found to be associated with multiple myeloma, while some studies of products of combustion described as "engine exhaust" did show a significant association with multiple myeloma. *In toto*, the population-based and hospital-based case–control literature indicated that benzene exposure was not a likely causal factor for multiple myeloma. — Environ Health Perspect 104(Suppl 6):1393–1398 (1996)

Key words: benzene, multiple myeloma, case–control studies, petroleum products, solvents, occupational exposures

Introduction

Does benzene cause multiple myeloma? In 1990, Goldstein (*1*) argued that

> it is reasonable, although not scientifically proven, to causally relate benzene exposure to multiple myeloma. The evidence remains less than definitive in that the level of proof of such a relationship does not meet that required for a statement of scientific certainty, although it is rapidly approaching this point.

The evidence then consisted of a few case series of benzene-exposed multiple myeloma cases and of cases in a few epidemiological studies of benzene-exposed workers. The first two case reports of multiple myeloma in benzene-exposed workers were from Torres et al. (*2*) in 1970. A subsequent report of four cases came from Aksoy et al. (*3*) in 1984. The first report of multiple myeloma cases in an epidemiological study of benzene-exposed workers was from Decoufle et al. (*4*) in 1983, and the first (and only) report of a statistically significant excess of multiple myeloma in a cohort of benzene-exposed workers was from Rinsky et al. (*5*) in 1987. Although the four multiple myeloma cases reported by Rinsky et al. in 1987 represented a statistically significant excess in his analysis of Ohio Pliofilm worker mortality through 1981, the subsequent analysis of mortality through 1987 (*6*) found that the mortality risk for multiple myeloma no longer showed a statistically significant elevation. These earlier studies were sufficient to raise the hypothesis that benzene exposure was a risk factor for multiple myeloma but not to test that hypothesis. The current report contains an analysis of the published population-based and hospital-based case–control studies to test that hypothesis.

Multiple myeloma is one of the neoplasms of the lymphatic and hematopoietic system. It is a malignant tumor of the plasma cell that is derived from B lymphocytes and located primarily in the bone marrow. It is differentiated from Hodgkin's and non-Hodgkin's lymphomas and from the leukemias. Previous analysis has demonstrated that acute myelogenous leukemia (AML) and its variants are consistently associated with benzene exposure but that the other leukemias are not (*7*). This report examines whether multiple myeloma and benzene exposure are consistently associated.

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Abbreviations used: ACS, American Cancer Society; AML, acute myelogenous leukemia; CPS II, Cancer Prevention Study II; *ICD, International Classification of Diseases*; SE, Southeast; SEER, Surveillance, Epidemiology, and Results.

Methods and Materials

Study Design and Base

The epidemiological literature examining whether a specific risk factor (exposure) and a specific disease (outcome) are associated consists of cohort studies and case–control studies. In the cohort studies, persons with the exposure and persons without the exposure are followed forward in time to observe the comparative frequencies of specific diseases (or causes of death) among them. In the case–control studies, the histories of persons with the disease and of persons without the disease are examined for the comparative frequencies of prior exposures to various possible risk factors. Case–control studies can be carried out within a geographically specified population, a hospital or clinic or a group of hospitals or clinics, or an exposure cohort.

This analysis is based on the published papers of population-based or hospital-based case–control studies of multiple myeloma that provide risk ratios examining the frequencies of reported exposures to benzene or to surrogates of benzene exposure.

Disease Outcome

Multiple myeloma is a clearly defined malignant neoplasm of the plasma cell characterized by at least two of the following three diagnostic criteria: plasma cell infiltration in bone marrow smears or secretions, definite osteolytic lesions in skeletal X-rays, and monoclonal paraproteins in the serum or urine. Most population-based and hospital-based case–control studies involve multiple myeloma cases in which this diagnosis has been clinically confirmed by pathological and/or clinical review. This is in contrast to cohort studies whose criteria for diagnosis are usually limited to information from the death certificate. Multiple myeloma cases have been coded as 203 in the *International Classification of*

Diseases, Revisions 6 to 8 (ICD), 203.0 in the *ICD, Revision 9*, and C90.0 in the *ICD, Revision 10.*

Exposure Definition

Analysis has been conducted using data from the studies that specified benzene as an exposure variable. Few studies did so. Some studies reported data for larger chemical categories that specifically included benzene, such as solvent/benzene or aromatic hydrocarbons (benzene, toluene, xylene, creosote). Persons included in the categories of exposures to solvents/benzene (or solvents including benzene) or to aromatic hydrocarbons would include those specifically reported as exposed to benzene as well as those whose specific exposure was to a different chemical in that chemical category. Data from some studies present risks associated with exposures to more broadly defined mixtures of chemicals that include benzene. These data are used as surrogates for benzene exposure. They included benzene as a component of gasoline and other petroleum products, benzene as a component of engine exhaust (product of combustion of carbonaceous material), and occupational titles expected to involve exposure to such products. These occupational titles include refinery workers, gas station workers, and mechanics. Benzene exposure surrogates were grouped as petroleum products and constituents, engine exhaust (diesel, gasoline, or unspecified), and petroleum-related employments. The methodology for collecting and interpreting information for exposure ascertainment has varied among the studies.

Search Strategy

A literature search was performed looking for population-based and hospital-based multiple myeloma case–control studies that considered occupational and environmental exposures as possible risk factors. Studies that included information on benzene exposures, surrogates for benzene exposure, or occupational job titles probably associated with benzene exposure were sought. The search was conducted using MEDLINE for the years 1966 to 1995 as well as the *Occupational Medicine Digest* and references cited in identified articles.

This search method yielded the following 13 case–control, population-based, or hospital-based multiple myeloma studies that contained odds ratio or risk ratio analyses for occupational exposures (Table 1). None of the studies contained information on actual measured exposures; all reported exposure classifications on the basis of interview responses or employment information. In some cases, industrial hygienists assessed the likelihood of specific exposures based on available information. Analysis by exposure groupings that might represent exposure to benzene or might be surrogates for exposure to benzene were extracted. The analytic results have been organized into four groups:

- benzene and benzene-specified exposures: benzene (two studies), solvent/benzene (four), aromatic hydrocarbons (one)
- petroleum products or constituents: gasoline (one), petroleum products (one), and oil products (one)
- petroleum products employment: auto mechanic (one), refinery worker (two), and gasoline station/garage worker (two)
- petroleum combustion products: engine exhausts (five), diesel exhausts (one), and gasoline exhausts (one).

Within these 13 studies, 20 odds ratios were placed into the above groupings.

Table 1. Population-based and hospital-based case–control studies of multiple myeloma.

No.	Study	Population	Reference
1	Australia	Tasmania Population Registry	Giles et al. (*8*)
2	Canada	Vancouver Clinic (1972–1981)	Gallaher et al. (*9*)
3	Denmark - F	Danish Cancer Registry (women)	Pottern et al. (*10*)
4	Denmark - M	Danish Cancer Registry (men)	Heineman et al. (*11*)
5	England/Wales	Referral centers (six areas)	Cuzick et al. (*12*)
6	Italy	Greater Milan area hospitals	La Vecchia et al. (*13*)
7	Sweden - 1	Mid and SE Sweden hospital registries	Flodin et al. (*14*)
8	Sweden - 2	Swedish Cancer Registry (1961–1979)	McLaughlin et al. (*15*)
9	Sweden - 3	Four northern counties cancer registry	Eriksson et al. (*16*)
10	United States - 1	Baltimore, MD, hospitals (whites)	Linet et al. (*17*)
11	United States - 2	American Cancer Society – CPS II[a]	Boffetta et at. (*18*)
12	United States - 3	SEER Cancer Registries (four areas)[a]	Morris et al. (*19*); Demers et al. (*20*)
13	United States - 4	Death certificates (24 states)	Figgs et al. (*21*)

[a]CPS, Cancer Prevention Study.

Results

Thirteen studies were found that met the criteria for this analysis. Odds ratios or risk ratios for exposure to benzene or to surrogates for benzene exposure were identified along with their 95% confidence limits where possible (Figure 1). Two of the studies (*11,17*) cited benzene as an analyzed exposure. Three of the studies (*10,14,19*) specified exposures to a chemical group that included benzene. The other studies cited various surrogates for benzene exposure as analyzed exposures.

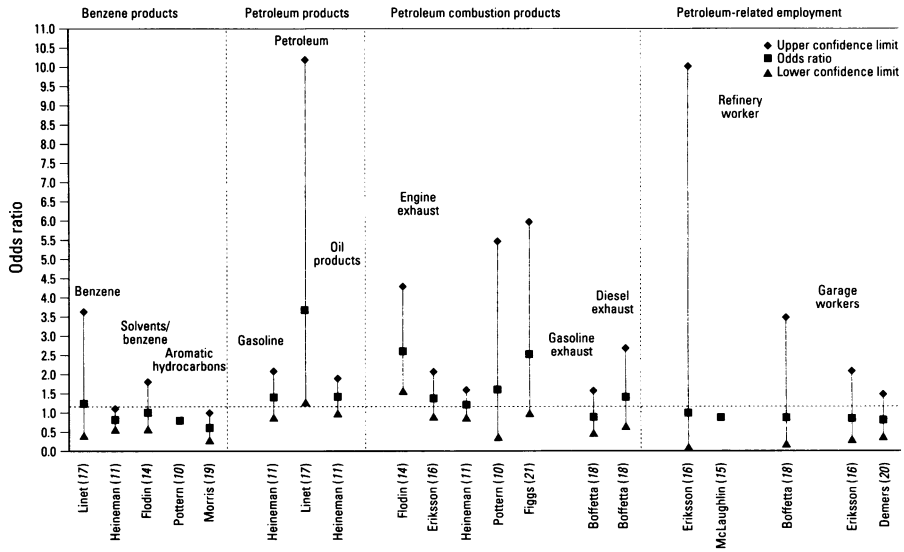

Figure 1. Odds ratio and 95% confidence limits for multiple myeloma and benzene or surrogate benzene exposures.

Benzene Exposures

Benzene. Linet et al. (*17*) reported an adjusted matched odds ratio of 1.2 (95% CI, 0.4–3.6) for multiple myeloma and benzene exposure for 100 Baltimore, Maryland (1975–1982), hospital cases and their controls. Occupational exposures had been directly inquired about in a telephone questionnaire, as had occupational and medical histories. Most of the responders for multiple myeloma cases were proxy responders (spouses, children, or siblings), as the case was either deceased or too ill to be interviewed; most of the responders for the controls were the patients themselves. Their reported crude matched odds ratio without the adjustment for respondent's status (e.g., self vs proxy) was 1.1 (95% CI, 0.4–3.7).

Heineman et al. (*11*) reported an age-adjusted odds ratio of 0.8 (95% CI, 0.6–1.1) for multiple myeloma and probable benzene exposure for 1098 male Danish cases registered in the Danish Cancer Registry (1970–1984) and their matched live population controls. Exposure assessments for 20 major categories of substances and 27 specific substances were made by industrial hygienists using a four-strata classification (none, possible, probable, or unknown) based on employment histories in the records of the Danish Supplementary Pension Fund.

These studies reported odds ratios that were approximately 1 (range 0.8–1.2), indicating no evidence of an increased association between multiple myeloma and benzene exposure.

Solvents/Benzene. Flodin et al. (*14*) published a hospital-based case referent study based on 131 multiple myeloma cases diagnosed in middle and southeast Sweden between 1973 and 1983 and interviewed between 1981 and 1983. Exposure was assessed from the responses on a mailed questionnaire. The crude rate ratio for solvent exposure (including benzene, per personal communication) was 1.0 (0.59–1.8). Pottern et al. (*10*) published a study for 1010 female Danish multiple myeloma cases and their matched controls [a companion study to the Heineman et al. study of male Danish multiple myeloma cases and controls (*11*)] and reported an odds ratio of 0.8 (confidence limits not reported) for exposure to solvents including benzene. Pottern (*10*) and Heineman et al. (*11*) used the same methodology for ascertaining exposure, i.e., exposure assignment by industrial hygienists based on national records of patients' employment histories.

Two studies examined for evidence of a linear trend with duration of exposure to solvents including benzene without calculating an odds ratio for those with exposure. Cuzick et al. (*12*) found neither an excess risk for solvents including benzene nor a linear trend for duration of exposure among their 399 cases and matched hospital controls from England and Wales. Cases and controls were matched by age, gender, and source of medical care. Exposure histories were obtained by interviewers using a detailed questionnaire. Percentages of cases and controls having 1 to 10 years of exposure and having greater than 10 years of exposure were reported. La Vecchia et al. (*13*) reported a case–control study of lymphoid neoplasms in which data for 110 multiple myeloma cases and 396 controls were compared. Occupational histories were obtained from the patients by trained interviewers using a structured interview. A significant positive linear trend for duration (<1 year, 1–10 years, and >10 years) of exposure to solvents/benzene was reported for multiple myelomas after the data were adjusted for age and gender. Analysis of the crude data did not show a significant trend.

Aromatic Hydrocarbons. Morris et al. (*19*) reported an adjusted odds ratio of 0.6 (95% CI 0.3–1.0) for multiple myeloma and exposure to aromatic hydrocarbons based on 698 cases from selected Surveillance, Epidemiology, and End Result (SEER) Registries. These cases had been registered as residents of two counties in Washington State (King and Pierce), three counties in Utah State (Davis, Salt Lake, and Weber), or the metropolitan areas of Detroit, Michigan, and Atlanta, Georgia, for mid-1977 to mid-1981. Aromatic hydrocarbons included benzene, toluene, xylene, and creosote. Occupational histories were obtained by trained interviewers using a standardized questionnaire. Categorization of responses was determined by a toxicologist not familiar with the case–control status of the participant. The adjusted odds ratio had been adjusted for age, sex, race, and study site. Morris et al. (*19*) also reported an adjusted odds ratio for aromatic hydrocarbon exposure when the data were from the self-respondent cases with controls. This adjusted odds ratio was 0.8 (95% CI, 0.5–1.4).

Benzene Surrogates

Surrogates for benzene exposures have been grouped into petroleum products, petroleum combustion products, and petroleum-related employment. The odds ratios are shown both by central tendency (ie., odds ratio) and by dispersion (i.e., 95% confidence limits).

Petroleum Products

Gasoline. Heinemen et al. (*11*) reported an adjusted odds ratio of 1.4 (95% CI 0.9–2.1) for multiple myeloma and probable benzene exposure among Danish men diagnosed between 1970 and 1984.

Petroleum Products. Two studies examined the association between petroleum products and multiple myeloma. Linet et al. (*17*) found a statistically significant increased adjusted odds ratio of 3.7 (95% CI 1.3–10.3) for petroleum exposure in an analysis of matched cases and controls. Heineman et al. (*11*) reported an age-adjusted odds of 1.4 (95% CI 1.0–1.9) for exposure to oil products.

Petroleum Combustion Products

Engine Exhaust. Four Scandinavian studies have examined the association between multiple myeloma and exposure to engine exhaust. Flodin et al. (*14*) found a statistically significant adjusted rate ratio (Mantel-Haenszel point estimate) of 2.6 (95% CI 1.6–4.3) for engine exhaust in a hospital-based case/referent study from middle and south eastern Sweden. This was a primary finding of the study, which found significant associations for engine exhaust, fresh wood, and creosote but not for radiation. Eriksson et al. (*16*) reported a rate ratio of 1.38 (90% CI 0.92–2.09) for engine exhaust in a population-based case–control study of 275 multiple myeloma cases diagnosed in residents of the four most northern counties of Sweden and registered in the Swedish Cancer Registry between mid-1982 and mid-1986. Eriksson included working with tractor or power saw or working as a driver as exposure to engine exhaust. Odds ratios for probable engine exhaust exposure were reported at 1.2 (95% CI 0.9–1.6) for Danish men by Heineman et al. (*11*) and at 1.6 (95% CI 0.4–5.5) for Danish women by Pottern et al. (*10*) from population-based case–control studies derived from the 1970 to 1984 multiple myeloma cases (1098 male and 1010 female cases) in the Danish Cancer Registry.

Figgs et al. (*21*) in a study of death certificates from 24 states reported significantly increased mortality odds ratios for certain groups of workers in certain occupations associated with engines (bus driver, stevedore, moving equipment supervisor,

and grader/dozer operator) and suggested that exhaust exposure might be the associated factor. These mortality odds ratios were generally about 2.5 with 95% confidence ranges from about 1 to 6. However, his most consistently elevated risk groups were teachers, particularly elementary school teachers.

Diesel Exhaust and Gasoline Exhaust. Boffetta et al. (*18*) reported Mantel-Haenszel matched odds ratios of 0.9 (95% CI 0.5–1.6) for gasoline exhaust and of 1.4 (95% CI 0.7–2.7) for diesel exhaust based on the 282 multiple myeloma cases reported in the first 4 years of follow-up of more than 500,000 male and 675,000 female enrollees in the American Cancer Society (ACS) Cancer Prevention Study II (CPS II). Exposure histories had been obtained from personal interviews conducted by volunteers.

Employment-based Exposure

Refinery Worker. Eriksson et al. (*16*) reported a rate ratio of 1.00 (90% CI 0.10–10.06) for refinery workers in northern Sweden, and McLaughlin et al. (*15*) reported a standardized incidence ratio of 0.9 for petroleum refinery employment in Sweden.

Auto Mechanic. Boffetta et al. (*18*) reported a Mantel-Haenszel matched odds ratio of 0.9 (95% CI 0.2–3.5) for employment as an auto mechanic, based on the data from the American Cancer Society CPS II study.

Gasoline Station/Garage Worker. Eriksson et al. (*16*) reported a rate ratio of 0.86 (90% CI 0.34–2.12) for employment as a gasoline station/garage worker in the northern Sweden study. Demers et al. (*20*), in a new analysis of the SEER database reported by Morris et al. (*19*), reported an adjusted odds ratio of 0.8 (95% CI 0.4–1.5) for employment in garage and service station occupations.

Discussion

Two case series and two epidemiological studies reported associations between multiple myeloma and benzene exposure, thus raising the hypothesis that benzene exposure caused multiple myeloma. A search of the epidemiological literature for hospital-based or population-based case–control studies of multiple myeloma cases was conducted seeking information to test that hypothesis.

Two case–control studies reported odds ratios specifically for benzene exposure. Linet et al. (*17*), in a hospital-based study from Baltimore, Maryland, reported an odds ratio of 1.2 for benzene exposure with a 95% confidence interval from 0.4 to 3.6. Heineman et al. (*11*), in a population-based study of Danish males, reported an odds ratio of 0.8 for probable benzene exposure with a 95% confidence interval of 0.6 to 1.1. Both odds ratios approximated 1.

Heineman et al. (*11*) also reported an odds ratio for possible benzene exposure of 1.3 with a 95 % confidence interval of 1.0 to 1.6. This borderline significant association of 1.3 was found when the uncertain benzene exposure category of "possible exposure" was used, while no association was found (0.8) when the more certain benzene exposure category of "probable exposure" was used. Heineman et al. (*11*) further reported a trend toward a lower risk of multiple myeloma with a greater duration of exposure to benzene. These observations are contrary to the expectations for a causal relationship between multiple myeloma and benzene exposure.

Three case–control studies reported odds ratios specifically for exposure categories that included persons specified as having benzene exposure (e.g., solvents or aromatic hydrocarbons). These groups would also include persons whose exposures had been specified as being from a specific substance other than benzene. Pottern et al. (*10*) reported an odds ratio among Danish female cases of 0.8 for exposure to any organic solvents including benzene; Morris et al. (*19*) reported an odds ratio of 0.6 (95% CI 0.3–1.0) for exposure to aromatic hydrocarbons, and Flodin et al. (*14*) reported a risk ratio of 1.0 (95% CI 0.6–1.8) for exposure to solvent, a grouping that included benzene exposure (personal communication). The above studies consistently show no association of multiple myeloma in groups with or without benzene-exposed workers (Figure 2).

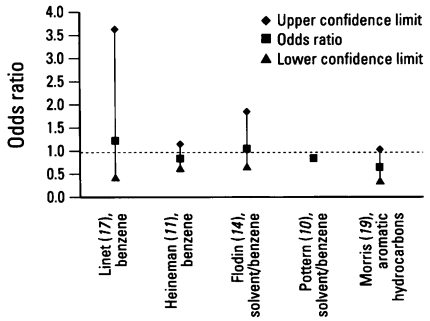

Figure 2. Odds ratio and 95% confidence limits for multiple myeloma and benzene exposure.

Two studies examined for a linear trend in the risk by duration of exposure. Cuzick et al. (*12*) showed a trend toward a lower risk of multiple myeloma with a greater duration of exposure to solvent/benzene, and La Vecchia et al. (*13*) showed a risk for solvent/benzene that was significantly higher only after age and gender adjustment of the data.

In the absence of analyses specifically for benzene exposure, analyses for surrogates of benzene exposure have been reviewed. Because major occupational exposures to benzene come from petroleum products, either directly or from their combustion products, analyses relating to petroleum products, petroleum combustion products, or occupations with petroleum exposure were assessed as surrogates for benzene exposure. Odds ratios for exposures to petroleum products [with one exception—Linet et al. (*17*)] were not significantly increased (i.e., 95 % lower confidence limit > 1.0). Odds ratios for petroleum-related employment rarely exceeded 1.0, and none significantly. In contrast, odds ratios for exposures to petroleum combustion product tended to be somewhat elevated, with two studies showing statistically significant elevations (*14,21*).

Most studies that reported odds ratios for multiple myelomas and benzene exposure also reported odds ratios for multiple myelomas and benzene surrogate exposures. Linet et al. (*17*) reported a nonsignificant odds ratio for benzene exposure of 1.2 and a statistically significant odds ratio of 3.7 for petroleum exposure. Heineman et al. (*11*) reported a nonsignificant odds ratio for probable benzene exposure of 0.8 and nonsignificant odds ratios for oil products and for gasoline exposures of 1.4. Flodin et al. (*14*) reported a rate ratio of 1.0 for the category that included benzene exposure (solvents) and a significantly elevated rate ratio of 2.3 for the benzene surrogate exposure category of engine exhaust. Finally, Pottern et al. (*10*) reported a nonsignificant odds ratio for probable benzene exposure of 0.8 and a nonsignificant odds ratio for engine exhaust of 1.6. If benzene exposure were the etiological agent expressed by the odds ratio for the benzene surrogates, the odds ratio for the benzene exposure would be expected to exceed the odds ratio for the surrogate benzene exposure. Since the opposite is observed (Figure 3), it is unlikely that benzene exposure is the explanatory factor.

The above analyses have demonstrated that the population-based and hospital-based

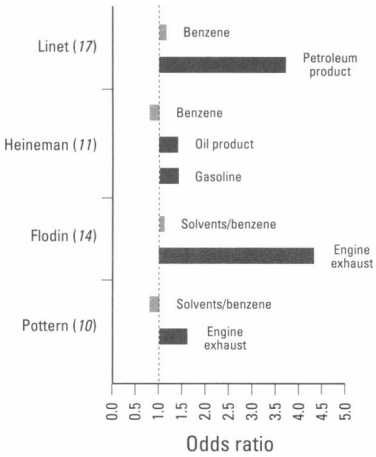

Figure 3. Odds ratio of multiple myeloma associated with benzene and surrogate benzene exposure.

case–control studies for multiple myeloma generally do not show a significant association for benzene exposures, mixed benzene exposures, petroleum products exposures, or petroleum-related employments. These results do not lead to a finding that benzene is a cause of multiple myeloma.

Exposures to petroleum combustion products, however, tend to have somewhat elevated odds ratios, some of which show statistically significant elevations. Since products of combustion consist of a wide range of carcinogenic and noncarcinogenic constituents, no particular constituent can be positively distinguished. However, as in the studies by Heineman et al. (*11*) and Pottern et al. (*10*), the odds ratio for probable benzene exposure was less than 1.0 and for probable engine exhaust or exhaust gases was greater than 1.0; therefore benzene exposure, is unlikely to be the explanatory factor.

The methodologies for exposure ascertainment have varied among the studies. Most studies begin with a work history retrospectively obtained by interview (*13*), telephone (*17*), or mail (*14*). Some studies began with concurrently developed work histories maintained by government agencies (*11,14*). Authors have used external evaluators to categorize occupational information based on the expertise of a toxicologist (*14*) or of industrial hygienists (*11,14*) or have relied on the assessment of the interviewee (*17*). The area of validation of exposure ascertainments is a developing field.

Cigarettes and automobiles are the major sources of human exposure to benzene (*22*). Three of the case–control studies (*14,17,18*) have been analyzed for multiple myeloma risk from cigarette smoking. All three found odds ratios that are less than one (0.78, 0.8, and 0.9, respectively). These results are consistent with the results of most other studies that examined the relationship between cigarette smoking and multiple myeloma and found no association (*23–27*) contra Mills et al. (*28*) in contrast to the studies showing a relationship between cigarette smoking and acute myelogenous leukemia, which is known to be related to benzene exposure. Since cigarette smoking is often considered a surrogate of benzene exposure in cancer causation studies, this generally consistent observation weighs against both benzene as a causal agent and products of combustion as a causal agent.

The causes of multiple myeloma are not clear. The population-based and hospital-based case control studies of multiple myelomas do not generally show consistent patterns of excess risk for any particular occupation or chemical exposure except possibly for some aspect of agriculture. A number of researchers (*9,12,13,15,16,18*) reported positive associations for farming or agriculture. Others, however (*19*), reported a positive association for pesticide; and Linet et al. (*17*) found no association with agriculture. Further, Linet et al. (*17*) reported a significant association with asbestos exposure; Morris et al. (*19*) and Cuzick et al. (*12*) found nonsignificant associations; and Boffetta et al. (*18*) found a nonsignificant reduction. Occupations generally not thought of as associated with marked chemical exposures frequently show the strongest associations with multiple myeloma. Giles et al. (*8*) found a significant association only for cases that worked in administrative occupations; Pottern et al. (*10*) found the most significant associations for women who worked in the home (household help, mother's helper, and "Mrs./homemaker"); and Figgs et al. (*21*) found that teachers were the group that most consistently had an elevated risk. Among nonoccupational factors, Flodin et al. (*14*) and Boffetta et al. (*18*) report a significant positive association for diabetes mellitus, but Gallaher et al. (*8*) and Cuzick et al. (*12*) did not.

Thus, causal agents for multiple myeloma have not been found. Nonetheless, in spite of the reports from the 1970s and 1980s that suggested an association between multiple myeloma and benzene exposure, review of the population-based and hospital-based case–control studies in the mid-1990s reveal that benzene exposure is unlikely to be a causal agent for multiple myeloma. The odds ratios for those studies that have examined benzene exposure are approximately 1.0. Exposures to chemicals in categories containing benzene, exposures to petroleum products, and employment in petroleum-related occupations do not appear to be risk factors for multiple myeloma. Products of combustion described as "engine exhaust" have a suggested association, while products of combustion described as "cigarette smoking" do not, cigarette smoking often being considered a surrogate for benzene exposure. Much of the literature on risk factors for multiple myeloma is ambivalent. The current published case–control literature on benzene exposure is not ambivalent and does not indicate that benzene exposure is a risk factor for multiple myeloma.

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