

# HARTLEY & O'BRIEN WHITE PAPER ON MULTIPLE MYELOMA

## Medical Background

The word "myeloma" means a tumor of the bone marrow. Most people develop many bone marrow tumors, hence the name "multiple myeloma." Multiple myeloma is a neoplasm of mature and immature plasma cells.<sup>1</sup> These plasma cells characteristically cause destruction of bone, leading to such troublesome complications as bone pain, compression, fractures, hypercalcemia and renal damage.<sup>2</sup> Abnormal radiographs of the skeleton are found in 80 percent or more of patients at diagnosis. Multiple punched-out osteolytic lesions involving the red bone marrow are typical.<sup>3</sup> Complete remission is rare, and a possible cure has been reported in only a few cases.<sup>4</sup> With standard therapy the clinical disease phase lasts an average of only 3 years. Virtually all patients with multiple myeloma succumb to their malignancy.<sup>5</sup> Based on all cases diagnosed in the geographic regions included in the U.S. SEER Program during 1983 to 1990, 5-year relative survival rates were 29 and 27 percent among men and women, respectively, and for blacks and whites, respectively.<sup>6</sup>

Multiple myeloma is a disease of old age. Onset of the disease prior to age 40 is rare; thereafter age-specific incidence rates rise exponentially with age, with the rate of increase less rapid at older ages.<sup>7</sup> The incidence rate for males and females over the age of 80 is 65 and 37 per 100,000.<sup>8</sup> Since 1950, age adjusted mortality rates have risen continuously. The increase in the incidence of multiple myeloma from the 1950's to 1989 was among the highest observed for any cancer during that time interval.<sup>9</sup> According to the National Center for Health Statistics more than 8,000 Americans die from multiple myeloma every year. The median age at diagnosis is 72, somewhat older than the median age at diagnosis of all cancers.<sup>10</sup> The National Cancer Institute estimated that 12,000 new cases of multiple myeloma were diagnosed in the United States in 1994. The age-adjusted incident rates for whites is 4.1 per 100,000, and for blacks 9.1 per 100,000.<sup>11</sup> The lowest incidence rates are for Americans of Japanese and Chinese descent (1.7 per 100,000 and 2.3 per 100,000 respectively).<sup>12</sup>

## Peer-reviewed studies suggesting exposures/employments associated with multiple myeloma:

- Exposure to Engine Exhaust
- Exposure to Benzene
- Exposure to Creosote
- Job Classifications involving Solvent Exposure

## Exposure to Engine Exhaust.

Exhausts from various engines (diesel and gasoline) have been associated with the development of multiple myeloma. The following studies support such an association.

A large, population-based, multicenter case-control study of American multiple myeloma cases has demonstrated a statistically significant increased risk (OR 1.8, CI 1.0-3.2) among individuals exposed to **diesel, jet fuel, and automobile exhausts, coal fumes,** and smoke, after adjustment for age, sex, race, and study site.<sup>13</sup>

A case-control study of 131 Swedish multiple myeloma cases found a doubling of risk among cases with occupational exposure to **engine exhaust**, a risk which remained significant (RR 2.1, CI = 1.2-3.9) after adjustment for a number of potential confounders, including age, fresh wood, creosote, concrete and brick work, sulfonil urea, gamma radiation, ex-smoking, farming, and gender.<sup>14</sup>

A case-control study of 1,098 Danish males with multiple myeloma investigated occupation and exposures as potential associations. The investigators reported a 30% increase in the relative risk of contracting multiple myeloma for workers possibly exposed to **diesel exhausts**, although this finding was not statistically significant.<sup>15</sup>

A population-based case-control study of 275 multiple myeloma cases in northern Sweden showed increased risk in relation to **engine exhausts** (working with tractor, power saws, or as drivers), power saws, road workers, lumberjacks, and afforestation workers (RR 1.38, CI = 0.92-2.09). The relative risk remained elevated after accounting for other exposures.<sup>16</sup>

A Danish case-control study of females diagnosed with multiple myeloma between 1970 and 1984 has shown increased risk for those individuals with possible or probable exposure to **exhaust fumes**.<sup>17</sup>

A Swedish cohort study of 14,225 truck drivers, exposed primarily to **diesel exhaust** demonstrated increased risks for all hemolymphopoietic malignancies, lymphatic leukemia and multiple myeloma, during the years 1970 to 1980. The risk for multiple myeloma was statistically significant (SMR 4.39, CI 1.42-10.24).<sup>18</sup>

Recently, a large case-control study of death certificates in 12,148 male multiple myeloma cases by the National Cancer Institute, found statistically significant increased risk among operators of graders and dozers compared to age-, race-, and gender-matched controls who were primarily exposed to **engine exhausts**.<sup>19</sup>

## Persons exposed to solvents.

Individuals exposed to solvents are at a greater risk of developing multiple myeloma. The medical and scientific literature is replete with reports of workers exposed to solvents that have developed multiple myeloma. It is thought that the contamination of the solvents with benzene is the reason for the elevated risks.

A 1972 study based on census reports of occupation and cancer in England, revealed an SMR of 1.26 for multiple myeloma when the occupation was **painters and decorators**.<sup>20</sup>

A cohort mortality study of 416 Swedish **paint manufacturers**, with at least 5 years of exposure to **organic solvents** between 1955 and 1975, showed an increased risk for death from all hemolymphopoietic malignancies. There was also a statistically significant increased risk for death from multiple myeloma (OR 5.49, CI 1.13-16.06), with evidence of increased risk with increased level of exposure. All of the multiple myeloma cases occurred more than 15 years from first exposure, with exposure periods ranging from 15 to 43 years.<sup>21</sup>

In a study of 327 multiple myeloma cases within the Kaiser Permanente Medical Care Program, only 150 were found to have occupational information in their medical records. Despite the paucity of exposure information increased risks for multiple myeloma were detected for **painters** (6 cases v. 2 expected) and carpenters (10 cases v. 5 expected).<sup>22</sup> A case-control study of 399 English patients with multiple myeloma showed increased risk among painters. The incidence of multiple myeloma for individuals in **painting** among the cases was 3.8%, and that among the controls was 2.0%, almost a doubling of the percentage.<sup>23</sup>

A case-control study of New Zealand multiple myeloma cases showed a statistically significant increased risk among painters (OR 1.95, CI 1.05-3.65), especially among **spray or car painters**, and especially among workers under age 60 (OR 4.23, CI = 1.80-9.91).<sup>24</sup>

A multicenter study of American myeloma cases has shown a significant increased risk in workers exposed to paint-related products, including **solvents and paint thinners** (OR 1.6, CI = 1.1-2.4).<sup>25</sup>

Lifetime job histories from a population-based, case-control study were analyzed to investigate the relationship between multiple myeloma and employment in various occupations and industries. An elevated risk for multiple myeloma was observed among persons ever employed as **painters**, odds ratio (OR) = 2.1 [95% confidence interval (CI) = 1.2-3.6]. The OR increased to 4.1 [95% CI=1.8-10.4] for those employed for 10 or more years.<sup>26</sup>

## Benzene.

Benzene has been associated in various case reports and epidemiologic studies with multiple myeloma.

Case reports of multiple myeloma in **benzene-exposed** individuals include two reported by Torres, *et al.* and four cases reported by Aksoy.<sup>27</sup> In 1983, Decoufle' suggested the possibility that multiple myeloma could be linked to **benzene** based on a chemical plant cohort mortality study.<sup>28</sup>

Professor Aksoy stated in 1985 that "today there seems to be sufficient data to incriminate **benzene as a potent carcinogenic agent causing . . . multiple myeloma . . .**"<sup>29</sup>

An elevated, although imprecise, odds ratio of 1.2 (95% CI=0.4--3.6) for multiple myeloma and **benzene exposure** was reported by Linet in a Baltimore, Maryland hospital study. When Linet and co-workers examined the hospital data for cases involving **petroleum products** and multiple myeloma, a statistically significant increased adjusted odd ratio of 3.7 (95% CI=1.3--10.3) was found.<sup>30</sup>

The NIOSH study of the Pliofilm **benzene-exposed** cohort found an elevated statistically significant risk of multiple myeloma in 1987.<sup>31</sup>

Heineman, *et al.* reported an adjusted odds ratio of 1.4, again imprecise (95% CI=0.9--2.1) for multiple myeloma and probable benzene exposure among Danish men. Heineman also reported an age-adjusted odds ratio of 1.4 (95% CI=1.0--1.9) when exposure to **oil products** and multiple myeloma was examined.<sup>32</sup>

An update of cancer mortality among workers with **benzene exposure** at Monsanto's Sauget, Illinois plant observed elevated, albeit imprecise, rates of multiple myeloma (SMR = 2.3, 95% CI= 0.7--9.4).<sup>33</sup>

## **Creosote exposure.**

Workers exposed to coal tar products (**coal tar, creosote, pitch**) have been shown to have excess risk for hemolymphopoietic malignancies, including multiple myeloma.<sup>34</sup>

In the Flodin case-control study of 131 cases of multiple myeloma, a crude relative risk of 6.0 (p<0.01) was calculated for multiple myeloma among workers exposed to creosote. The risk remained significantly elevated after adjustment for age, ex-smoking, gender, and exposure to fresh wood, exhaust, concrete and brickwork, sulfonyleurea, gamma radiation, and farming. The authors characterized creosote exposure as "potent in its effect" on the risk for multiple myeloma.<sup>35</sup>

If you wish to discuss a diagnosis of multiple myeloma and a potential exposure please use the contact page or call Hartley & O'Brien at 1-800-363-8591.

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<sup>1</sup> John Foerster, Multiple Myeloma in *Wintrobe's Clinical Hematology* Vol. 2, 2219 (G. Richard Lee, et al. eds., 9th ed. 1993); Dan L. Longo, Plasma Cell Disorders in *Harrison's Principles of Internal Medicine*, Vol. 2, 1621 (Kurt J. Isselbacher, et al. eds. 13th ed. 1994).

<sup>2</sup> Reiner Bartl, Bertha Frisch, and Wolfgang Wilmanns, Bone and Marrow Findings in Multiple Myeloma and Related Disorders in *Neoplastic Diseases of the Blood* 477, 492 (Peter H. Wiernik, et al. eds., 3d ed. 1996), citing, R. A. Kyle, E. D. Baryd, *The Monoclonal Gammopathies: Multiple Myeloma and Related Plasma-Cell Disorders*. Charles C. Thomas, Springfield, 1976; R. Bartle, B. Frisch, Biopsy of Bone in *Internal Medicine: An Atlas and Sourcebook*. Kluwer Academic Publishers, Dordrecht, 1993; H. Ludwig, *Multiplés Myelom*. Springer, Berlin, 1982; R. A. Kyle, J. Jowsey, P. J. Keely, et al., Multiple myeloma and bone disease, *N. Eng. J. Med.* 293:1334 (1975); R. S. Weinstein, Bone involvement in multiple myeloma, *Am. J. Med.* 93:591 (1992); J. A. Kanis, A. J. P. Yates, R. G. G. Russell, Hypercalcaemia and skeletal complications of myeloma in *Multiple Myeloma and other Paraproteinaemias* 307 (I. W. Delamore ed. 1986).

<sup>3</sup> *Id.* citing, R. Bartle & B. Frisch, *Biopsy of Bone in Internal Medicine: An Atlas and Sourcebook*. Kluwer Academic Publishers, Dordrecht, 1993.

<sup>4</sup> *Id.* at 499, citing, R. A. Kyle. 1988. IgD multiple myeloma: a cure at 21 years. *Am. J. Haematol.* 29:41.

<sup>5</sup> Bart Barlogie, Plasma cell myeloma in *Williams Hematology* 1109, 1123 (Ernest Beutler, et al. eds., 5th ed. 1995).

<sup>6</sup> L. A. G. Ries, B. A. Miller B. F. Hankey et al., (eds.) SEER Cancer Statistics Review: 1973-1991, National Cancer Institute, NIH Pub. No. 94-2789, Bethesda, 1994.

<sup>7</sup> Linda M. Pottern, et al. Epidemiology of Multiple Myeloma in *Neoplastic Diseases of the Blood* 441, 443 (Peter H. Wiernik, et al. eds., 3d ed. 1996), citing, S. S. Devesa, D. T. Silverman, J. L. Young, Jr., et al. 1987. Cancer incidence and mortality trends among whites in the United States, 1947-1984, *J. Nat'l Cancer Inst.* 79:701.

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<sup>9</sup> Linda M. Pottern, et al. Epidemiology of Multiple Myeloma in *Neoplastic Diseases of the Blood* 441 (Peter H. Wiernik, et al. eds., 3d ed. 1996), citing, S. S. Devesa, Descriptive epidemiology of multiple myeloma in *Epidemiology and Biology of Multiple Myeloma* 3 (G. I. Obrams & M. Potter eds. 1991); B. A. Miller, L. A. G. Ries, B. F. Hankey et al., (eds.) SEER Cancer Statistics Review: 1973-1990, National Cancer Institute, NIH Pub. No. 93-2789, Bethesda, 1993.

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<sup>11</sup> L. A. G. Ries, B. A. Miller B. F. Hankey *et al.*, (eds.) SEER Cancer Statistics Review: 1973-1991, National Cancer Institute, NIH Pub. No. 94-2789 , Bethesda, 1994.

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