Toxic Substance Exposure and Multiple Myeloma: A Case-Control Study [1,2]

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ABSTRACT—By means of a population-based, multicenter case-control investigation, cenain toxic substances were evaluated as risk factors for multiple myeloma Interviews were completed on 698 subjects with newly diagnosed multiple myeloma. and 1,683 controls were selected from the same geographic areas as those of the cases. Respondents were asked if they had ever been "highly" exposed" to one or more of a list of toxic substances or to other substances not on the list. With the aid of a toxicologist. responses were then categorized into 20 exposure groups. Those who reported past exposure to pesticides had an estimated relative risk of 26 for multiple myeloma (95% confidence interval (CI) = 1.5-4.6). Subjects exposed to a variety of compounds commonly used by painters had an estimated relative risk of 1.6 (95% CI = 1.1-2.4). An increased risk also was found for those who were exposed to sources of carbon monoxide (relative risk= 1.8. 95% CI = 1.0-3.2). Associations of borderline statistical significance were found for metals and/organically high polymers (plastics and elastomers). No statistically significant associations were seen for exposure to fertilizers; dyes and inks; alkalies: acids other caustic substances; chemical asphyxiants: aliphatic, chlorinated. or aromatic hydrocarbons; aldehydes and ketones: ethers; esters; oils: dusts; or asbestos.—JNCI 1986; 76:987-994.

From clinical and epidemiologic investigations, some preliminary evidence exists that multiple myeloma may be associated with certain occupational exposures. Farmers may be prone to the development of this cancer, as suggested by several studies (2-5). In one of these reports, an increased risk was related to use of pesticides (5). Myeloma may occur excessively in workers exposed to metals (1, 6, 7), plastics (8).rubber (9, 10), petroleum Products (11-13), and asbestos (1, 14-17). Other surveys have found an excess of myeloma among wood workers (1, 12, 18), leather workers (12, 19). and painters (20). The following analysis was performed to further evaluate possible associations between exposure to some of these substances and the risk of developing multiple myeloma.

SUBJECTS AND METHOOS

The results in this paper come from data generated by a population-based, collaborative case-control study of multiple myeloma. The investigation was carried out in four parrs of the United States: 1) King County and Pierce County (WA); 2) Davis County, Salt Lake County, and Weber County (UT); 3) the three counties comprising Metropolitan Detroit (MI); and 4) the five counties comprising Metropolitan Atlanta (GA). This analysis dealt with data obtained &om 698 subjects with newly diagnosed multiple myeloma and from 1,683 controls drawn from the general population of the study areas.

Cases.—All persons under 80 years of age with multiple myeloma diagnosed between July 1, 1977, and June 30, 1981, were identified by the cancer registries serving the four areas. (All registries were participants in the SEER Program of the National Cancer Institute, Bethesda, MD.) To be eligible for the study, a case was required to reside in one of the study areas at the time of diagnosis. Cases were distributed by age as follows: Two percent were under 40 years of age, 6% were between 40 and 49 years of age. 22% were between 50 and 59 years of age, 37% were between 60 and 69 years of age. and 33% were 70 or more years of age. Most of the cases were derived from Detroit (51%), with smaller proportions

ABBREVIATIONS USED: CI = confidence interval(s); SEER = Surveillance, Epidemiology, and End Results.

[1] Received April 24, 1985; revised November 7, 1985: accepted December 26, 1985.

[2] Supported in part by Public Health Service grant 1-N01CA-35679 from the Division of Extramural Activities, National Cancer Institute.

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[10] We are grateful to Dr. David Eaton, Department of Environmental Health, School of Public Health and Community Medicine, University of Washington. for his advice on the toxicologic aspects of the study: to Carol Ure, Project Coordinator. for assisting in the study; to Jonathan M. Liff tor computer programming assistance: and to Carolyn Burns and Anne Peterson for their help in the preparation of the manuscript. Data from the Cancer Surveillance System and the assistance of its staff are appreciated.

coming from Washington State (26%). Atlanta (13%), and State of Utah (10%). Of all the cases of multiple myeloma ascertained at the four SEER Program centers and fulfilling these criteria, interview data were obtained from 698 (89%). Information was not obtained for the following cases: 23% due KO physician refusal; 33% due to patient refusal; and 44% due KO miscellaneous reasons, e.g., had moved or could not otherwise be contacted by the SEER Program center. Of the Detroit cases 6% refused to participate, while the proportions in Washington State, State of Utah, and Atlanta were lower (3, 2, and 1%, respectively).

Controls.—While the control group consisted of individuals selected at random from the same geographic areas as those of the cases, the method of control selection varied according to the study area. In Washington State, a population survey using standard area sampling methods was conducted in 1979. King County and Pierce County were divided into 175 contiguous geographic areas of approximately equal population size. Two sampling units averaging four households each were randomly selected from each area. Members of the household were then asked to provide a household census. Of persons 50-64 years of age, 1 in 9 served as a control, while all persons 65-79 years of age were interviewed.

In the other three areas, random-digit telephone-dialing techniques were used to identify controls. In Utah. random samples of working telephone numbers in the study area were called. If a number proved KO be residential, a census of the household by age and sex was taken. When a household member of eligible age was identified, a second random-sampling procedure was applied to determine whether that person would become a potential control, with the selection probability depending on the estimated overall age and sex distribution needed among controls to resemble the Utah cases. For each myeloma case, 2 controls were later drawn at random from among the potential controls of comparable age (same 5-yr age group) and sex. In Atlanta and Detroit, random-digit-dialing techniques based on the Waksberg method (*21*) were used. For each myeloma case, a series of telephone numbers to be called was generated by appending random numbers to the initial digits of the case's telephone number. The resulting numbers were then telephoned until a person of the same age (≤5 yr), sex, and race was identified. In all three study areas for which random-digit dialing was used, up to six to nine calls were made to a telephone number selected at random before the number was abandoned, including attempts during daytime, evening, and weekend hours.

Overall, 1,683 controls (83%) completed an interview. Of the controls not interviewed, 79% refused and 21% did not participate for miscellaneous reasons, e.g., had moved or could not be contacted by the SEER Program center.

Interviews.—Trained interviewers administered a standardized questionnaire to each study participant. For individuals who had died or were too ill to be interviewed, a family member was located to provide information.

Of the 698 case interviews, 68% were obtained directly from the subject. whereas 99% of the 1,683 control interviews were provided by the subject. Because the reported frequency of several exposures differed between self-respondents and proxy respondents, separate analyses were conducted according KO respondent status. The principal results were shown both for comparison of all cases with controls and for comparison of self-respondent cases with controls.

The interviews focused on factors hypothesized as being relevant to the etiology of multiple myeloma (chronic antigenic stimulation, allergies, drug histories,

TABLE 1.—*Substances included in exposure categories*

Exposure category	Major substances included
Acids	Muriatic, hydrochloric. sulfuric. chromic, nitric, and acetic acid; other miscellaneous acids
Aldehydes and ketones	Formaldehyde. ketones. acetone
Aliphatic hydrocarbons	Gasoline. diesel, butane, propane. ethylene. acetylene. kerosene
Alkalies	Ammonia. sodium chlorate, caustic soda. lime. cement
Aromatic hydrocarbons	Benzene, toluene, xylene. creosote
Asbestos	Asbestos insulation, asbestos on brake shoes, asbestos shipyard
Carbon monoxide	Diesel, jet fuel, and automobile exhaust; coal fumes: smoke
Chemical asphyxiants	Hydrogen cyanide, hydrogen sulfide
Chlorinated hydrocarbons	Carbon tetrachloride, trichloroethylene, methylene chloride
Dusts	Cotton. textile. rock. wood. silica. coal, plant. and animals dusts: fiberglass dust: insulation material dust
Dyes and inks	Dyes, beautician and/or hairdressing products. inks
Esters	Nitroglycerine, phosphate esters
Ethers	Ether
Fertilizers	Fertilizers, nitrous soda fertilizer
Metals	Cast iron, lead vapors and liquid, arsenic, gold, manganese. brass fumes, copper powder and fumes, molybdenum fumes, mercury vapors and liquid, tin. silver, beryllium. cadmium
Oils	Oils, greases, grinding fluid
Organically high polymers	Plastic and rubber compounds
Other caustic substances	Chlorine. sulfur. fluorine, and nitrogen compounds: phosgene; ozone
Paint and paint-related products and/or other organic solvents	Paints, paint thinners and removers. lacquers, lacquer thinners, varnish, varnish removers, shellacs. glues. adhesives, other solvents
Pesticides	Pesticides, insecticides, organophosphorus and organochlorine compounds, arsenical insecticides, pyrethrum, herbicides, rodenticides

radiation and chemical exposures, and occupation) in addition to demographic variables such as race, marital status, education, and religion. The question pertinent to this report read as follows: "In your daily life, at home. at work, or elsewhere, was there ever a time when you were highly exposed to products or fumes such as . . . ?" This question was followed by the possible responses: "Gasoline," "turpentine," "alcohol (other than liquor)," "cleaning solvents (carbon tetrachloride, etc.)," "oil (type)," and "other (specify)." If this question was answered affirmativeiy for any exposure, the interviewee was then asked to recall the year in which the exposure first occurred.

Formation of exposure categories.—Without knowledge of case–control status, all of the responses to "other (specify)" were hand tabulated and grouped into 20 exposure categories with the aid of a toxicologist. (See table 1 for a listing of the major substances included in each category.) Affirmative responses to the substances gasoline, cleaning solvents, benzene, and oil were included in the aliphatic hydrocarbon, chlorinated hydrocarbon, aromatic hydrocarbon, and oil-exposure categories, respectively. Certain responses indicating substances or occupations in which several exposures were possible were placed in more than one category. For example. persons reporting exposure to coke oven fumes were classified as being exposed to carbon monoxide. 'aromatic hydrocarbons, and chemical asphyxiants. The responses requiring placement into more than one exposure group are detailed in "Appendix."

Analysis.—Three variabies (age, sex, and race) were identified as potential confounders, since they had been the basis for matching (or frequency matching) in at least one study area and since they were associated with disease status a priori. Odds ratios adjusted for these factors were then calculated for each study area. With one exception (noted below), these area-specific odds ratios did not differ from each other to a statistically significant degree for any of the exposures shown in table 2; accordingly, only summary estimates that combined results across all four areas were shown. Study area, however, was treated as a fourth confounder because of the varying ratio of cases to controls among the four areas. All four confounders were controlled for simultaneously by using the Mantel-Haenszel stratified analysis procedure (22). We then computed the 95% CI. for the resulting Mantel-Haenszel pooled odds ratios, by Miettinen's method (23). The Mantel-Haenszel chi-square statistic was also calculated for the adjusted odds ratios (22). Adjusted odds ratios were also calculated for individuals first exposed 1–19, 20-39, and 40 or more years before interview, in comparison to individuals who did not record an exposure. These associations were assessed by Mantel's test for trend (24).

As described below, stratified analyses suggested the possible importance of pesticides: paint, paint-related products, and/or other organic solvents; metals; and organically high polymers. For these exposures, logistic regression was also used to estimate adjusted odds ratios (25). Adjustment was made for age, sex, race, study site, and education as a measure of socioeconomic status. Since the results from that analysis agreed closely with the results for the stratified analysis procedure, only the results from the stratified analysis procedure were presented.

TABLE 2.—*Risk of multiple myeloma according to substance exposure,* in *comparison of all cases* with *controls*

Exposure category[a]	Percentage reporting exposure among:		Adjusted odds ratio[b]	
	All cases. $n=698$	Controls. $n=1,683$	Estimate	95%CI[c]
Acids	2.9	2.5	1.0	0.6–1.9
Aldehydes and/or ketones	1.2	1.2	0.7	0.2–2.1
Aliphatic HC	15.6	16.3	0.9	0.7–1.2
Alkalies	2.4	1.8	1.0	0.5–1.9
Aromatic HC	2.7	4.3	0.6	0.3–1.0
Asbestos	1.0	0.6	1.3	0.5–3.1
Asphyxiants	0.4	0.7	0.7	0.2–2.5
Carbon monoxide	3.9	3.4	1.8	1.0–3.2
Chlorinated HC	13.2	14.0	0.9	0.6–1.1
Dusts	3.3	3.5	1.0	0.6–1.8
Dyes and inks	1.3	0.7	1.9	0.8–4.6
Esters	0	0.2	—	—
Ethers	0.6	0.4	1.2	0.3–4.3
Fertilizers	0.6	0.1	3.0	0.6–15.3
Organically high polymers	2.0	1.2	2.0	0.9–4.1
Metals	5.6	4.3	1.5	1.0–2.3
Oils	14.9	16.9	1.0	0.7–1.3
Other caustics	0.9	1.8	0.5	0.2–1.3
Paints and/or solvents	7.3	4.8	1.6	1.1–2.4
Pesticides	4.0	1.5	2.6	1.5–4.6

[a] HC=hydrocarbons.
[b] Mantel-Haenszel summary odds ratio estimate, adjusted for age (10-yr groups), sex. race (white. black, other), and study site. —=≈0.
[c] Test-based 95%CI for adjusted odds ratio.

RESULTS

Table 2 shows that 4% of all persons with multiple myeloma were reported to have been exposed to pesticides, in contrast to only 1.5% of controls (adjusted odds ratio = 2.6, 95% CI = 1.5-4.6). As for most other exposures, the adjusted odds ratio was slightly higher (2.9) when self-respondent cases were compared to controls (table 3). The adjusted odds ratio was also found to vary among study areas as follows: Atlanta, 1.8; Detroit, 2.2: State of Utah, 15.5; and Seattle, uncomputable for lack of any exposed controls. There was no clear evidence of a trend toward an increasing or a decreasing risk according to time since first exposure, however. Table 4 shows the specific pesticides reported by persons with such exposures. Because of the small number of subjects in each category, no firm conclusions can be drawn concerning the particular class or classes of pesticides responsible for the overall increase in risk.

Subjects exposed to substances in the category that included paint, paint-related products, and other organic solvents also had an increased risk of myeloma (adjusted odds ratio for all cases = 1.6, 95% CI = 1.1-2.4). Although the results are not shown in detail, there was little variation in the degree of excess risk according to time since first exposure. There appeared to be modest positive associations between myeloma and exposure either to paint and paint-related products or to other organic solvents (table 4), although firm inferences are precluded by small numbers of subjects with these exposures. For carbon monoxide, a positive association was apparent if responses of self-respondents only were considered (adjusted odds ratio = 1.8, 95% CI = 1.0-3.2).

Evidence was also found of a modest increase in myeloma risk for persons reporting exposure to various metals (adjusted odds ratio for all cases = 1.5, 95% CI = 1.0-2.3), although this association was of borderline statistical significance. A similar suggestive result was obtained for organically high polymers (adjusted odds ratio for all cases = 2.0, 95% CI = 0.9-4.1). There was a decrease in risk with increasing time since first exposure for metals and organically high polymers, but these trends fell short of statistical significance. Findings shown in table 4 indicate that no single subcategory of metals or of organically high polymers accounted for the apparent excess risk for persons reporting exposure to either class of substances. However, results not shown suggested that the excess risk associated with metal exposure varied according to race: For whites, the adjusted odds ratio was 2.1 (95%CI = 1.3-3.4), while for blacks it was 0.6 (95%CI = 0.2-1.4).

Table 2 also shows increases in myeloma risk for those exposed to substances in two other categories (dyes and inks, fertilizers), but the associations might well have arisen by chance. There was little evidence of any increase in risk for those exposed to alkalies, acids, other caustic substances, chemical asphyxiants, aliphatic hydrocarbons, aldehydes and ketones, ethers, esters, chlorinated hydrocarbons, aromatic hydrocarbons, oils, dusts, or asbestos.

Additional analyses (not shown) indicated very little change in the results shown in tables 2 and 3 if only

TABLE 3.—*Risk of multiple myeloma according to substance exposure, in comparison of self-respondent* cases with *controls*

Exposure category[a]	Percentage reporting exposure among:		Adjusted odds ratio[b]	
	Self-respondent cases, n = 477	Controls, n = 1,683	Estimate	95%CI[c]
Acids	3.9	2.5	1.5	0.8–2.8
Aldehydes and/or ketones	1.5	1.2	1.1	0.4–3.6
Aliphatic HC	17.8	16.3	1.1	0.8–1.5
Alkalies	2.9	1.8	1.2	0.6–2.5
Aromatic HC	3.4	4.3	0.8	0.5–1.4
Asbestos	1.0	0.6	1.3	0.4–3.8
Asphyxiants	0.4	0.7	0.7	0.2–29
Carbon monoxide	5.0	3.4	1.9	1.1–3.2
Chlorinated HC	14.7	14.0	1.0	0.7–1.4
Dusts	3.8	3.5	1.2	0.7–2.3
Dyes and inks	1.5	0.7	1.9	0.7–5.3
Esters	0	0.2	—	—
Ethers	0.6	0.4	1.1	0.3–4.9
Fertilizers	0.6	0.1	3.2	0.5–19.5
Organically high polymers	2.1	1.2	2.0	0.9–4.6
Metals	6.3	4.3	1.8	1.1–2.9
Oils	15.7	16.9	1.0	0.8–1.4
Other caustics	1.0	1.8	0.7	0.2–2.1
Paints and/or solvents	8.2	4.8	1.8	1.2–2.7
Pesticides	4.4	1.5	2.9	1.5–5.5

[a] HC = hydrocarbons.
[b] Mantel-Haenszel summary odds ratio estimate, adjusted for age (10-yr groups), sex, race (white, black, other), and study site.
— = ~0.
[c] Test-based 95%CI for adjusted odds ratio.

TABLE 4.—*Type of exposure for pesticides, paint and paint-related products and/or other organic solvents, metals, and organically high polymers*

Type of exposure in each category	No. (%) for: Cases, n=698	Controls, n=1,683
Pesticides		
Pesticides in general: pesticides, pest sprays, mosquito sprays, cotton poison, bug sprays	9 (2.7)	12 (0.7)
Organophosphorus compounds: diazinon, malathion, Chlorthion, parathion	2 (0.3)	5 (0.3)
Organochlorine compounds: DDT, chlordane, benzene hexachloride, heptachlor, toxaphene	9 (1.3)	8 (0.5)
Arsenical pesticides	3 (0.4)	5 (0.3)
Herbicides: weed killers, defoliage gas used in Vietnam, 2.4-D weed killer, agent orange	4 (0.6)	2 (0.1)
Paint and paint-related products and/or other organic solvents		
Paint and paint-related products: paints, paint thinners and removers, lacquers, lacquer thinners, varnish, varnish removers, shellacs, refinishing materials, glues and/or adhesives	40 (5.7)	69 (4.1)
Other organic solvents: variety of unspecified solvents	14 (2.0)	13 (0.8)
Metals		
Welding: welding fumes, welding gas, steel welding, arc welding, electric arc welding	10 (1.4)	21 (1.2)
Soldering: soldering fumes, lead soldering, soldering breadboards for computers	3 (0.4)	3 (0.2)
Metal plating: acid plating, plating shop chemicals, fumes from acid electroplating	3 (0.4)	4 (0.2)
Foundry dust, fumes, smoke	1 (0.1)	12 (0.7)
Other metal exposures*	24 (3.4)	34 (2.0)
Organically high polymers		
Plastics: epoxy resins, plastics, vinyl materials, polystyrene, polyethylene	10 (1.4)	15 (0.9)
Elastomers: rubbers	4 (0.6)	6 (0.4)

* Iron, lead vapors and liquid, arsenic, gold, manganese, brass fumes, copper powder and fumes, molybdenum fumes, mercury vapors and liquid, tin, silver, beryllium, cadmium, toxic metal solution, metal frames, metal shavings, and metals at work.

exposures beginning 5 or more years before the interview were considered. For the eight toxic substances listed in table 2 to which at least 3% of cases reported exposure, analyses were also performed to determine the strength of association between myeloma risk and a history of exposure to a combination of two such substances. Although limited by small numbers of exposed cases, the results of these analyses suggested that those combinations involving pesticides were associated with approximately a threefold increase in myeloma risk. This increase was quite similar to that shown in tables 2 and 3 for any pesticide exposure, suggesting little modification of any toxic effectof pesticides by joint exposure to other substances considered.

DISCUSSION

Numerous potential limitations to this study should be noted. First, the positive results may have been due in part to recall bias, particularly since exposure information was derived from an open-ended question rather than from a separate question for each category. As described by Sackett (*26*), cases of a given disease may have enhanced recollection of exposure to a potential cause because of "rumination" about possible explanations for their having been stricken by the disease. However, if this form of questioning did result in such bias, one might expect increased odds ratios for most, if not all, of the exposures. In fact, only a few exposures were found to be positively associated with disease. Recall bias mav also have resulted from the higher proportion of proxy respondents for cases compared with controls. Proxy respondents were probably less likely to be aware of or to recall a significant exposure. The most likely consequence of this inequality would be an underestimate of the actual disease–exposure relationship when all cases were compared with controls. In fact, the results demonstrated just that: Most of the adjusted odds ratios were slightly higher when self-respondent cases were compared with controls.

Another potential source of error was the classification of responses into exposure categories. It is unlikely that all subjects accurately recalled all relevant exposures. Furthermore, judgments had to be made for several responses as to the most likely substances encountered in each instance (see "Appendix"). For example, a person who stated exposure to welding fumes was considered to have been exposed to both metals and phosphine. While it was probable that most subjects who listed welding fumes encountered phosphine at certain times, there were surely some cases or controls who were nonetheless falsely classified as exposed. However, with

the assumption that these errors occurred randomly and were independent of case–control status, the most likely consequence of such misclassification would be to diminish and not to increase the apparent degree of association between disease and exposure. Systematic bias on the part of the investigators was avoided by classifying exposures without knowledge of case or control status.

In addition, these results came from a large data set containing responses to many questions. When one examines a large number of disease–exposure relationships, there will be some statistically significant associations found by chance alone. It is possible some of the positive associations were due to this phenomenon. Similarly, the finding of statistically significant heterogeneity of effect among study areas for pesticides may have emerged on this basis, since this finding was the only instance of such heterogeneity among 20 exposures considered. For this reason, further study of these positive associations is warranted before firm conclusions can be reached.

Pesticides

The largest increased risk was for subjects who acknowledged past exposure to pesticides. The results of several studies suggest that 1 occupational group with high exposure to pesticides, farmers, may be at increased risk for the development of multiple myeloma (*1-5*). In two studies, significantly increased proportionate mortality ratios were found for white male farmers in Washington State (*1*) and the State of Iowa (2). Four of the studies involved comparison of the death certificate statement of occupation for men who died of myeloma and for men who died of other causes, and each found the former group to have a higher proportion of farmers than the latter group (3, *5*). In a more recent case-control study in British Columbia, a significant increase in myeloma risk was found for subjects working in agriculture (*4*). The present study also provided suggestive evidence of such an association: With restriction of consideration KO self-respondents only, the adjusted odds ratio for myeloma in relation to the subject having lived on a farm was 1.3 (95% CI = 1.0-1.6).

Also, one of the studies based on death certificates (*5*) showed a significant increase in risk for farmers who had lived in counties in which high use of both insecticides and herbicides was experienced, but it showed no significant increase in risk for those who resided in counties in which use of these compounds was low.

The carcinogenic potential of pesticides has been documented in other work. Many commonly used pesticides are known to be carcinogens in experimental animals, and several others are suspected of being carcinogens (27). Furthermore, pesticides that are not themselves carcinogenic may have an additive that is carcinogenic (27); and several of the pesticides have the potential to react with nitrite to form carcinogenic N-nitroso compounds (28).

Paints and Paint-Related Products and/or Other Organic Solvents

The results of this study suggest that subjects exposed to paints and solvents have an increased risk of myeloma. Products in this category usually contain a mixture of compounds including aromatic, chlorinated, and aliphatic hydrocarbons; ketones; ethers; and esters. With the possible excepuon of some of the organic solvents, these products are used frequently by painters. When the solvents were eliminated from consideration, there were still more cases than controls who were exposed to the substances in this category.

Only two studies were found in the literature in which the association between painters and hematologic cancers were examined (*20,* 29). On the basis of census reports of occupation and cancer for England, Adelstein (20) calculated a standardized mortality ratio of 126 for multiple myeloma among painters and decorators. Viadana (*29*) studied 1,345 white males with leukemia and 1,237 controls from New York State, Baltimore (MD), and Minnesota. Painters working in the construction industries had an incidence rate of leukemia estimated to be three times the rate for nonpainters.

Metals

The overall association between metal exposure and myeloma risk was not statistically significant in this study; but stratification by race showed that whites had a significant twofold increase in risk, while no increase was found for blacks. Whereas this finding could signify an inherent racial difference in susceptibility to the effect of metals, the potential exists that, with so many race-specific contrasts possible, this result emerged by chance alone.

Insufficient numbers of exposed subjects precluded analysis according to type of metal, thereby making comparisons with the literature difficult, since most studies have attempted to look at specific metals. In a proportionate mortality study in Washington State, Milham Jr. (*1*) reported a slight excess of myeloma deaths among white male smelter workers. Most of the individuals studied worked in a large copper smelter in Tacoma (WA). A similar study showed a Significant increase in mortality for males employed as composing room workers in Washington (DC) (6). Composing room workers are mainly exposed to inorganic lead, both particulate and vapor. A case-control study conducted at a Swedish copper smelter demonstrated an odds ratio of 4.6 ($P = .02$) for exposure to arsenic, but the cases included persons with leukemia as well as persons with myeloma (7).

Organically High Polymers

Exposure to these compounds may involve their unreacted constituents, a variety of additives, degrada-

tion products, or fully reacted polymers. Since subjects did not specify the circumstances under which exposure occurred, little can be said about the agent(s) responsible for the increased estimated risk. One way to approach this difficulty is by a separate analysis for plastics and elastomers, since different additives are used in the production of these two types of compounds. However, in this study both plastics and elastomers appeared to be related to disease.

The results may support other findings in the literature. Mason (8) found higher age-adjusted myeloma death rates for white males in U.S. counties in which plastic and synthetic fiber manufacturing took place relative to deaths for white males in control counties. A cohort analysis of white male rubber workers revealed an excess of lymphoreticular cancers, which included both lymphatic cancers and myeloma cases (9). An additional follow-up study examined the cancer mortality of female workers in a rubber-manufacturing plant. There was a slight excess of multiple myeloma deaths, but the analysis was based on small numbers (10).

Other Exposures

There are no previous reports of the association found between myeloma and the carbon monoxide-exposure category. The substances included involved exposure to several combustion productions in addition to carbon monoxide. Major pollutants were probably carbon dioxide, nitrogen oxides, sulfur oxides, hydrocarbons, and particulates. The increased risk could be due to carbon monoxide, one of the other combustion products, or any possible combinations. Preliminary surveys suggest that myeloma mortality may be excessive in U.S. counties involved in petroleum manufacturing (11) and metal-related occupations with cutting-oil exposure (12). In another report. proportionate mortality rates for myeloma increased as years of membership increased in the Oil, Chemical, and Atomic Workers Union in Texas (13). However, in the present study no positive associations were found for the hydrocarbons or oils. The positive associations lor dyes and inks, and fertilizers, were based on extremely small numbers and are therefore difficult to interpret. Multiple myeloma has been noted to occur in men occupationally exposed to asbestos (14-17), but the odds ratio of 1.3 observed here supports only a weak relationship at most.

CONCLUSION

On the basis of this study's findings, special attention might be paid to multiple myeloma in occupational epidemiologic studies of workers exposed to pesticides, paint and paint-related compounds, and carbon monoxide. Further research also appears warranted to assess the strength of any association between myeloma and particular types of pesticides, especially those in current use.

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APPENDIX RESPONSES REQUIRING PLACEMENT INTO MORE THAN ONE EXPOSURE CATEGORY

Responses indicating substances or occupations that can result in more than one exposure were placed in more than one exposure category. These responses are listed 1–13 and are followed by the exposure categories in which they were placed. The potential exposures of the substance or occupation follow each appropriate exposure category.

1) Coke oven fumes, smoke from coke ovens
   a) Carbon monoxide: carbon monoxide
   b) Aromatic hydrocarbons: benzene
   c) Chemical asphyxiants: hydrogen sulfide and hydrogen cyanide
2) Welding. welding fumes. welding gas, steel welding
   a) Metals: brass. lead, chromium
   b) Other caustic substances: phosphine
3) Arc welding, arc welding fumes
   a) Metals: variety of metals
   b) Other caustic substances: ozone
4) Electric arc welding
   a) Metals: lead, manganese, molybdenum, zinc
   b) Other caustic substances: ozone. fluorine. nitrogen dioxide
5) Fumes from acid electroplating
   a) Metals: arsenic, barium, chromium, cobalt, lead, mercury, molybdenum. nickel, selenium, zinc
   b) Alkalies: ammonia, lime, sodium hydroxide, potassium hydroxide
   c) Acids: formic, nitric, sulfuric acids
   d) Other caustic substances: carbon disulfide, fluoride compounds, nitrogen dioxide, ozone
   e) Chemical asphyxiants: hydrogen cyanide
   f) Chlorinated hydrocarbons: trichloroethylene
   g) Dusts: graphite dust
6) Metal plating, acid plating, chemicals: plating shop
   a) Metals: molybdenum, zinc
   b) Acids: variety of acids
7) Galvanizing
   a) Metals: arsine, arsenic, brass, lead, zinc
   b) Alkalies: ammonia
   c) Acids: anhydrous hydrochloric acid, sulfuric acid
   d) Chlorinated hydrocarbons: trichloroethylene
8) Soldering fumes, lead soldering. soldering breadboards for computers
   a) Metals: arsine, cadmium, copper, lead
   b) Chemical asphyxiants: hydrogen cyanide
9) Metal extractor
   a) Metals: variety of metals
   b) Alkalies: ammonia
10) Vulcanizing tires
   a) Metals: barium. tellurium
   b) Alkalies: ammonia
   c) Other caustic substances: sulfur chloride, tetramethylthiuram disulfide
   d) Chemical asphyxiants: hydrogen sulfide
   e) Aromatic hydrocarbons: amino compounds of benzene
11) Foundry dust. fumes, smoke
   a) Metals: aluminum. nickel, tellurium. titanium, zirconium
   b) Acids: phosphoric acid
   c) Other caustic substances: sulfur dioxide, fluorine compounds
   d) Carbon monoxide: carbon monoxide
   e) Aliphatic hydrocarbons: acetylene
   f) Aldehydes and ketones: formaldehyde
   g) Aromatic hydrocarbons: creosols
   h) Dusts: graphite dust
12) Dry cleaning fumes
   a) Other caustic substances: carbon disulfide
   b) Aliphatic hydrocarbons: naphtha
   c) Ethers: dichloroethyl ether. ethyl ether, cellusolve
   d) Chlorinated hydrocarbons: carbon tetrachloride, dichloroethylene, ethylene dichloride, methyl chloride, methyl chloroform, perchloroethylene, propylene dichloride, trichloroethylene
13) Laundry fumes
   a) Acids: acetic, formic, oxalic acids
   b) Other caustic substances: chlorine, fluorine