Exhibit 221

Mortality among United States Coast Guard Marine Inspectors

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ABSTRACT. Work history records and fitness reports were obtained for 1 767 marine inspectors of the U.S. Coast Guard between 1942 and 1970 and for a comparison group of 1 914 officers who had never been marine inspectors. Potential exposure to chemicals was assessed by one of the authors (RP), who is knowledgeable about marine inspection duties. Marine inspectors and noninspectors had a deficit in overall mortality compared to that expected from the general U.S. population (standardized mortality ratios [SMRs = 79 and 63, respectively]). Deficits occurred for most major causes of death, including infectious and parasitic diseases, digestive and urinary systems, and accidents. Marine inspectors had excesses of cirrhosis of the liver (SMR = 136) and motor vehicle accidents (SMR = 107), and cancers of the lymphatic and hematopoietic system (SMR = 157), whereas noninspectors had deficits for these causes of death. Comparison of mortality rates directly adjusted to the age distribution of the inspectors and noninspectors combined also demonstrated that mortality for these causes of death was greater among inspectors than noninspectors (directly adjusted ratio ratios of 190, 145, and 198) for cirrhosis of the liver, motor vehicle accidents, and lymphatic and hematopoietic system cancer, respectively. The SMRs rose with increasing probability of exposure to chemicals for motor vehicle accidents, cirrhosis of the liver, liver cancer, and leukemia, which suggests that contact with chemicals during inspection of merchant vessels may be involved in the development of these diseases among marine inspectors.

MARINE INSPECTORS of the U.S. Coast Guard inspect merchant vessels to ascertain the integrity of the hull, machinery, and equipment on board. During these inspections they enter cargo tanks, void spaces, cofferdams, and pumprooms, where they may encounter the hazards of oxygen deficiency and exposure

to a variety of chemicals. These chemicals may include acrylonitrile, carbon tetrachloride, ethylene dibromide, ethylene dichloride, benzene, gasoline, styrene, toluene diisocyanate, tetrachloroethylene, and trichloroethylene.[1,2] Because potential exposure to these and other chemicals exists, the Coast Guard established a Committee on Maritime Hazardous Materials to evaluate safety and environmental protection issues for the transport of hazardous materials. The Committee found little information available regarding the health of marine inspectors.

To obtain information on the health status of marine inspectors, the Coast Guard sought the assistance of the National Cancer Institute (NCI) in the conduct of an in-depth analysis of the health status of marine inspectors. A collaborative study of the mortality experience of marine inspectors was undertaken and results are presented herein.

Methods

Marine inspectors were identified from annual registries of Coast Guard officers and enlisted personnel. Information available from the registries included name, rank, date of birth, service number, designator number, job category, and class year. For comparison, a group of noninspectors was selected and matched to marine inspectors for registry, rank, and year that rank was achieved. Personnel files at the National Personnel Record Center in St. Louis, Missouri, and at the U.S. Coast Guard Headquarters in Washington, D.C., were accessed to obtain demographic information and complete work histories for marine inspectors. Information obtained included social security number, date of birth, race, sex, place of birth, type and date of termination from the Coast Guard, year of commission, and duties and dates of assignment at each duty station (from semi-annual fitness reports). For noninspectors, demographic information and dates of entry and exit from Coast Guard personnel files were obtained, but detailed information on jobs and duties was not abstracted. The duty records for noninspectors, however, were scanned to ensure that they contained no marine inspection duties.

The cohort is composed of all persons who performed marine inspection duties between 1942 and 1970 and suitable referents. Marine inspectors and referents were traced to January 1, 1980, to determine vital status. Vital status was ascertained through records from the Coast Guard personnel office, Veterans Administration, Social Security Administration, credit bureaus, and motor vehicle departments. For those persons deceased, death certificates were obtained and underlying causes of death were determined by an experienced nosologist, who used the rules in effect at the time of death and who assigned rubrics of the 8th Revision of the International Classification of Diseases.

The level of exposure to chemicals while a marine inspector was estimated by one of the authors (RP) using information from description of duties, duty station, and rank. A four-point rating scale (no exposure, low, moderate, and high exposure) was used. Nonexposed persons generally held administrative positions. Low exposure was assigned to staff with duties that occasionally required vessel inspections. Moderate exposure was assigned to inspection duties that did not regularly include hull structures, and regular inspection of hull structures in geographic areas where chemicals were not major items of cargo. High exposure was generally reserved for persons who performed hull inspections at ports where vessels transported chemicals. A cumulative exposure score was calculated by summing the product of the four-point rating scale and duration (mo) in each job. All referents were classified as nonexposed. Because marine inspectors inspect ships and barges that haul a variety of products, and because it was impossible to reconstruct the actual exposure history of any subject, we could not assess exposure to specific chemicals. The proportion and mix of products conveyed by ships and barges varies somewhat by port. For example, ports along the Gulf Coast are major centers for the commercial shipping of petrochemicals, whereas ports in the Northwest are major centers for wood products. Separate analyses were performed by geographic region.

Standardized mortality ratios (SMRs) were used to compare the mortality experience of marine inspectors with that of the total U.S. population and noninspectors. Person-year accumulation in the cohort began on January 1, 1942 (the initial year of cohort identification), when subjects first entered the Coast Guard (if after the cohort identification date), or upon first achieving a specified level or type of exposure, depending upon the particular analysis being undertaken. Person-year accumulation ceased at the closing date of the study (January 1, 1980), last date known alive, date of death, or date of achieving a higher exposure level (whichever was appropriate). Expected numbers for SMRs were calculated by applying 5-y age and calendar-year mortality rates from the appropriate race-sex group of the U.S. population to the person-year distribution of marine inspectors and referents.[3] Ninety-five percent confidence intervals were calculated using the method of Bailar and Ederer.[4] A chi-square test was used to evaluate statistical significance of SMR trends.[5] Mortality rates for inspectors and noninspectors were directly adjusted to the age and calendar-time person-year distribution of the combined cohorts to provide directly adjusted rate ratios (rate among inspectors/rate among noninspectors × 100) so that problems associated with comparison of SMRs were avoided.

Results

Characteristics of marine inspectors and noninspectors are shown in Table 1. Of the 3 681 men included in the study, 1 767 were marine inspectors and 1 914 were Coast Guard officers who had never engaged in marine inspection. The cohort was mostly white men (91%); race was unknown for 326 subjects (8%). In the analysis, those of unknown race were considered to be white. A slightly smaller proportion of marine inspectors entered the Coast Guard before 1945 than did non-

inspectors (38% vs. 44%, respectively). Similarly, more marine inspectors were born after 1930 (28%) than were noninspectors (24%). Tracing was very successful for marine inspectors (97%) and noninspectors (96%): there was a total of 852 deaths—483 among marine inspectors and 369 among noninspectors.

Mortality for nonneoplastic causes of death is shown in Table 2. The SMRs for all causes of death combined were significantly depressed among marine inspectors (SMR = 79) and noninspectors (SMR = 63). This was true for many major causes of death, although the deficits were generally greater among noninspectors. Significant deficits were observed in both groups for mortality from arteriosclerotic heart disease (SMRs of 77 for marine inspectors and 60 for noninspectors), vascular lesions of the central nervous system (SMRs of 71 and

Table 1.—Demographic Characteristics of Marine Inspectors and Noninspectors

Characteristics	Marine inspectors		Noninspectors	
	Number	%	Number	%
Total	1 767	100	1 914	100
Year commissioned				
< 1945	630	38	795	44
1945–1959	551	31	462	24
⩾ 1960	493	28	518	27
Unknown	93	5	139	7
Year of birth				
< 1910	561	32	440	23
1910–1929	712	40	1 020	53
⩾ 1930	494	28	454	24
Vital status				
Alive	1 234	70	1 478	77
Deceased:	483	27	369	19
Death certificates found	451	26	341	18
Death certificates not found	32	2	28	1
Unknown	50	3	67	4

Table 2.—Mortality from Non-neoplastic Diseases among Marine Inspectors and Noninspectors

Cause of death	Marine inspectors				Noninspectors				Directly adjusted rates ratios
	OBS	EXP	SMR	95% CI	OBS	EXP	SMR	95% CI	
All causes	483	608	79*	72–87	369	584	63*	57–70	118
Infective & parasitic diseases	5	10	52	17–120	1	11	9*	1–51	522
Diabetes mellitus	2	9	23*	3–82	3	8	37	8–107	66
Chronic rheumatic heart disease	5	6	90	29–209	2	6	31	4–113	232
Arteriosclerotic heart disease	172	224	77*	66–89	123	204	60*	50–72	123
Vascular lesions of the CNS	34	48	71*	49–99	16	37	44*	25–71	136
All respiratory disease	27	38	71	47–103	19	34	55*	33–86	132
Pneumonia	13	14	90	48–155	8	12	65	28–128	156
Emphysema	6	9	65	23–142	4	8	48	13–124	105
Asthma	2	2	133	16–479	1	1	81	2–451	211
Diseases of the digestive system	25	28	90	59–134	14	30	47*	26–80	173
Cirrhosis of liver	17	13	136	79–217	8	15	53	23–105	190
Disease of genito-urinary system	2	10	20*	2–74	1	9	12*	1–64	188
All accidents	27	30	89	59–130	18	43	42*	25–66	153
Motor vehicle accidents	14	13	107	58–180	9	20	45*	20–86	145
Suicide	5	11	46	15–107	9	14	64	30–122	57
Unknown causes	32				28				
Number of persons		1 767				1 914			
Number of person-years		36 720				55 571			

*$p \leqslant .05$.

44, respectively), and diseases of the genitourinary system (SMRs 20 and 12, respectively). Other causes of death that showed deficits, but were not statistically significant for marine inspectors and noninspectors were, respectively, diabetes (SMR = 23 and 37), infective and parasitic diseases (SMRs = 52 and 9), rheumatic heart disease (SMRs = 90 and 31), all respiratory diseases (SMRs = 71 and 55), pneumonia (SMRs = 90 and 65), emphysema (SMRs = 65 and 48), diseases of the digestive system (SMRs = 90 and 47), all accidents (SMRs = 89 and 42), and suicide (SMRs = 46 and 64). Marine inspectors showed slight excesses for mortality from asthma (SMR = 133), cirrhosis of the liver (SMR = 136), and motor vehicle accidents (SMR = 107), whereas noninspectors showed deficits (SMRs = 81, 53, and 45, respectively).

As with all causes of death, both marine inspectors and noninspectors had deficits for all cancers combined (SMRs = 88 and 75), although the deficit was statistically significant only among the noninspectors (Table 3). No statistically significant excesses occurred for any specific cancer among inspectors or noninspectors. Lung cancer was significantly depressed among marine inspectors (SMR = 52). Marine inspectors had a slight elevation in mortality from cancers of the lymphatic and hematopoietic system (SMR = 157), whereas noninspectors had a deficit (SMR = 60). This excess among marine inspectors was confined primarily to lymphosarcoma and reticulosarcoma (SMR = 175) and leukemia (SMR = 155). According to the death certificates, the histologic types of the leukemias among the marine inspectors were one lymphatic unspecified, three acute myeloids, and three acute unspecified. Among the noninspectors, two leukemias were of the chronic lymphatic type, and one was an acute myeloid. Other cancers, which were slightly elevated among the marine inspectors but not among the noninspectors, were colon (SMRs = 144 and 78, respectively), rectum (SMRs = 121 and 55), liver (SMRs = 112 and 0 deaths), and skin (SMRs = 158 and 95). Cancer of the brain was elevated among marine inspectors (SMR = 170) *and* noninspectors (SMR = 136).

Comparison of directly adjusted mortality rates for inspectors and noninspectors revealed patterns similar to when SMRs were compared. When directly adjusted rates were used, stomach cancer was greater among inspectors and larynx cancer was less frequent than among noninspectors in contrast to the pattern shown when comparing SMRs. Directly adjusted rates for these sites, however, are based on small numbers.

Mortality for selected causes of death by cumulative level of exposure to chemicals is shown in Table 4. Mortality from cirrhosis of the liver, motor vehicle accidents, leukemia, and cancers of the rectum and liver increased as level of cumulative exposue increased, although only the SMR trends for cirrhosis of the liver

Table 3.—Mortality from Cancer among Marine Inspectors and Noninspectors

Cause of death	Marine inspectors				Noninspectors				Directly adjusted rates ratios
	OBS	EXP	SMR	95% CI	OBS	EXP	SMR	95% CI	
All cancer	103	117	88	72–107	66	115	75*	60–92	108
Buccal cavity & pharynx	3	4	83	17–243	0	4	—	0–100	—
Digestive organs	34	35	96	67–134	22	32	68	43–103	171
Esophagus	2	3	72	9–262	2	3	74	9–268	90
Stomach	4	7	54	15–140	4	6	65	18–167	123
Colon	16	11	144	82–234	8	10	78	34–153	218
Rectum	5	4	121	39–282	2	4	55	7–199	273
Liver	3	3	112	23–326	0	2	—	0–156	—
Pancreas	4	6	62	17–158	6	6	96	35–209	64
Respiratory system	19	37	52*	31–81	31	39	79	53–112	58
Larynx	1	2	57	1–317	1	2	58	1–320	35
Lung	18	35	52*	31–82	30	37	81	55–116	60
Skin	3	2	158	33–461	2	2	95	11–344	121
Prostate	10	9	106	51–195	4	7	57	15–145	216
Bladder	2	4	50	6–179	3	3	90	18–262	30
Kidney	3	3	106	22–310	3	3	103	21–301	80
Brain and CNS	5	3	170	55–395	5	4	136	44–317	94
All lymphatic and hematopoietic cancer	17	11	157	91–251	7	12	60	24–126	198
Lymphoma & reticulosarcoma	4	2	175	48–449	1	2	41	1–230	342
Hodgkin's disease	1	1	83	2–464	0	2	—	0–234	—
Leukemia	7	5	155	62–319	3	5	66	14–194	199
Other lymphatic tissues	3	3	115	24–336	2	3	73	9–265	165
Number of persons		1 767				1 914			
Number of person-years		36 720				55 571			

*$p \leq .05$.

Table 4.—Mortality for Selected Causes of Death by Level of Exposure (probability of exposure × months of duration)

Causes	Exposure level: Nonexposed OBS	Nonexposed EXP	Nonexposed SMR	130 mo OBS	130 mo EXP	130 mo SMR	⩾ 130 mo OBS	⩾ 130 mo EXP	⩾ 130 mo SMR	χ^2 trend
All cancer	98	127	77*	35	47	75	56	58	95	1.65
Colon	10	11	87	8	4	182	6	6	108	0.16
Rectum	3	4	74	1	2	60	3	2	149	0.83
Liver	0	3	—	1	1	92	2	1	153	3.47
Lung	31	40	77	10	13	74	7	18	39*	2.64
Skin	3	2	132	1	1	117	1	1	113	0.02
Brain & CNS	5	4	128	3	1	223	2	1	147	0.05
Lymphatic & hematopoietic	11	13	88	4	5	88	9	5	171	2.29
Lymphosarcoma & reticulosarcoma	2	3	76	2	1	214	1	1	88	0.02
Leukemia	4	5	80	2	2	105	4	2	184	1.46
Arteriosclerotic heart disease	144	228	63*	66	88	75*	85	113	76*	1.67
Cirrhosis of liver	8	16	50*	6	6	106	11	6	186	8.99
Motor vehicle accidents	9	21	43*	6	7	81	8	5	170	8.97
Number of persons		2 147			1 660			791		
Number of person-years		58 152			20 665			13 474		

*$p \leqslant .05$.

and motor vehicle accidents were significant. Because the type of cargo varies by port, analyses were also done by location of the duty station of the subjects. Although numbers were small, no clear pattern of risk for any particular cause of death emerged by geographic location of duty stations.

Discussion

When inspecting cargo vessels, marine inspectors may be exposed to many chemicals, including acrylonitrile, carbon tetrachloride, ethylene dibromide, ethylene dichloride, benzene, gasoline, styrene, toluene, tetrachloroethylene, and trichloroethylene.[1,2] Despite such potentially hazardous exposures, the overall mortality experience of marine inspectors is significantly better than the general population. This finding is not surprising given the professional nature of the Coast Guard Marine Inspection Service. The sociodemographic characteristics of the marine inspectors and the "healthy worker effect" seen in most studies of this design almost guarantee that the overall SMR for these subjects will be less than 100. Causes of death typically affected by the healthy worker effect and showing deficits in this study include infective and parasitic diseases, diseases of the circulatory system, arteriosclerotic heart disease, emphysema, and pneumonia. Marine inspectors, however, had larger SMRs for most causes of death than noninspectors, and a similar pattern occurred when directly adjusted rate ratios were used for comparison. The reason for the greater deficit among noninspectors is unknown. Marine inspectors were slightly older than noninspectors, but the difference was small. The socioeconomic standing of the group should be similar because both were comprised primarily of officers.

Marine inspectors had an excess mortality from cirrhosis of the liver, whereas noninspectors had a considerable deficit. It is known that chlorinated solvents and other chemicals—including ethyl alcohol[6]—are metabolized in the liver and may induce liver cirrhosis.[6] Because information on alcohol consumption was not available, it was not possible to directly assess alcohol and solvent effects independently. Cirrhosis of the liver has been induced experimentally in rodents by carbon tetrachloride,[7,8] and cases following exposure have been reported in humans.[9,10] That other chlorinated solvents[11] may have a similar effect is suggested by increased deposits of fat in the liver of rodents following exposure to tetrachloroethylene and chloroform, a feature prevalent in cirrhosis of the liver. Cirrhosis of the liver has been reported in a worker who did not have evidence of excessive alcohol intake but who was exposed to trichloroethylene and tetrachloroethane.[12] Fatty change in the liver has also been reported among persons with occupational exposure to various organic solvents.[13] Mortality studies of cohorts exposed to chlorinated solvents have generally not reported observed and expected deaths from cirrhosis of the liver,[14–18] but a slight excess was noted among Oklahoma dry cleaners.[19] An association between chemical exposure and cirrhosis of the liver is suggested in this study by a significant exposure-response gradient where SMRs rise from 50 (a significant deficit) among the nonexposed, to 106 among those with less than 130 working-level months, to 186 among those with at least 131 working-level months.

Mortality from motor vehicle accidents was slightly elevated (SMR = 107) among inspectors but significantly depressed (SMR = 45) among noninspectors. Mortality from accidents, however, also showed an exposure-response gradient with working-level months. Exposure to organic solvents is known to cause a variety of neurotoxic effects including dizziness, lightheadedness, and incoordination.[20] The effect on reaction

time[21] may be particularly relevant with regard to motor vehicle accidents. Excess mortality resulting from motor vehicle accidents has been noted among workers exposed to methylene chloride.[18]

Deficits for mortality from cancers of the buccal cavity and pharynx, esophagus, and lung; arteriosclerotic heart disease; and emphysema suggest that tobacco use among Coast Guard personnel is less than that among the general U.S. population. The deficit for arteriosclerotic heart disease among marine inspectors contrasts with well known excesses caused by carbon disulfide[22] and a recent report of elevated mortality among rubber workers exposed to solvents, particularly ethanol and phenol.[23] Inspectors, however, had significantly higher risks than noninspectors. The deficit for lung cancer is most striking among inspectors (SMR = 52), whereas among noninspectors the number of deaths from lung cancer is closer to that expected (SMR = 81). Tobacco consumption may be less among inspectors than among noninspectors because the volatile nature of the many chemicals in ships precludes smoking, at least while inspecting vessels. We see no mortality differences between inspectors and noninspectors for emphysema and cancer of the esophagus—causes of death as strongly affected by smoking as lung cancer.

Few cancers showed excesses among either inspectors or noninspectors. Cancers of the colon and rectum were slightly elevated among inspectors, whereas among noninspectors there was a deficit for cancer of the rectum. Cancer of the rectum—but not the colon—showed the highest risk in the highest exposure category. Neither of these cancers has been clearly associated with occupational exposures, although a recent case-control study of colon cancer reported associations with solvents, fuel oils, and abrasives.[24] Solvents and fuels are common cargos for vessels inspected by the Coast Guard.

The slight excess for cancer of the liver among inspectors is based on small numbers. Liver tumors commonly develop in animals exposed to chlorinated solvents such as carbon tetrachloride, trichloroethylene, and tetrachloroethylene.[25] There are a few reports of these cancers among persons with occupational exposures to some of these chemicals.[14,16-28] The risk of liver cancer rose with working-level months of exposure to chemicals to an SMR of 170 among those with a score of ⩾ 131. This excess of liver cancer may be related to alcohol use because it has been reported that this tumor is elevated among persons with alcoholic cirrhosis,[29] and death from cirrhosis of the liver was also elevated among inspectors. The excess mortality from cancer of the skin among inspectors is of interest because of the potential for skin contact during inspection with many organic solvents that pass readily through the skin.[25]

Inspectors and noninspectors showed slightly elevated mortality from brain cancer. Neither excess, however, was statistically significant. Cancer of the brain has developed in rodents exposed to acrylonitrile and has been reported among occupational groups exposed to various chemicals including organic solvents, vinyl chloride, lubricating oils, polycyclic aromatic hydrocarbons, and phenolic compounds.[30] Among Coast Guard personnel the excess did not appear to be exposure-related because it occurred among those not exposed to chemicals as well as among the exposed. The excess could be due to diagnostic sensitivity bias because Coast Guard personnel have access to a comprehensive health care program. Such excesses have been noted among a variety of professional groups where diagnostic sensitivity bias may operate.

Mortality from cancers of the lymphatic and hematopoietic system was elevated among inspectors but not among noninspectors. Although this excess among inspectors was not statistically significant when the U.S. population served as the reference group, SMRs among inspectors were approximately 2.5 times those seen among noninspectors. The risk of cancer of the lymphatic and hematopoietic system increased as level of exposure rose, i.e., SMR of 88 among the nonexposed to an SMR of 171 among those with the most exposure. This trend, however, was not statistically significant. Much of this trend for lymphatic and hematopoietic cancer is accounted for by the mortality pattern for leukemia, where the SMRs rise from 80 to 105 to 184, respectively, across the three exposure categories. Inspectors may contact many chemicals that may affect the lymphatic and hematopoietic system. Benzene is an established human leukemogen,[31] and is one of the major organic solvents transported by ships and barges. Leukemia has also been reported among occupational groups exposed to tetrachloroethylene[14,32] and trichloroethylene.[33]

When interpreting these findings, limitations of the study must be considered. The study population was relatively small (1 767 marine inspectors and 1 914 noninspectors), and information on important potential confounders such as tobacco and alcohol use was not available. Although each subject's likelihood of exposure to chemicals was established, it was not possible to identify specific chemicals.

The study also has several strengths. Complete work histories were available for each subject, which provided detailed information on the tasks and duties for each position held. The use of Coast Guard officers who were never marine inspectors provided a comparison population, which should minimize differences in socioeconommic and lifestyle factors such as tobacco and alcohol use.

Conclusions

Comparison of the mortality experience of marine inspectors with other Coast Guard officers uncovered excess mortality among inspectors from cancers of the colon, liver, skin, and lymphatic and hematopoietic systems (particularly leukemia), which could be related to organic solvents and other chemicals to which they are exposed while inspecting ships and barges. Mortality from cirrhosis of the liver and motor vehicle accidents was also elevated. The risk of motor vehicle accidents, leukemia, and cancer and cirrhosis of the liver increased with level of exposure to chemicals, further

suggesting that occupational exposures may play an important role. These results imply that marine inspectors should take special care to limit exposure to chemicals during inspections.

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Submitted for publication August 15, 1988; revised; accepted for publication November 21, 1988.

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