Cancer Risks Among Workers Exposed to Metalworking Fluids: A Systematic Review

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Metalworking fluids (MWFs) are commonly used in a variety of industrial machining and grinding operations. The National Institute for Occupational Safety and Health (NIOSH) estimates that more than one million workers are exposed to MWFs. NIOSH conducted a comprehensive and systematic review of the epidemiologic studies that examined the association between MWF exposure and cancer. Substantial evidence was found for an increased risk of cancer at several sites (larynx, rectum, pancreas, skin, scrotum, and bladder) associated with at least some MWFs used prior to the mid-1970s. This paper provides the evidence pertaining to cancer at these sites. Cancer at those sites found to have more limited or less consistent evidence for an association with MWF (stomach, esophagus, lung, prostate, brain, colon, and hematopoietic system) will not be discussed in this paper but are discussed in the recent NIOSH Criteria for a Recommended Standard-Occupational Exposure to MWFs. Because the changes in MWF composition that have occurred over the last several decades may not be sufficient to eliminate the cancer risks associated with MWF exposure, reductions in airborne MWF exposures are recommended. Am. J. Ind. Med. 33:282–292, 1998. *© 1998 Wiley-Liss, Inc.*†

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INTRODUCTION

Metalworking fluids (MWFs) are commonly used in a variety of industrial machining and grinding operations. MWFs (i.e., cutting oils, machining fluids, lubricants, and coolants) are primarily used to cool and lubricate both the tool and the working surface. MWFs are also useful for providing corrosion protection, and removal of metal chips and swarf. There are four major classes of MWF: straight oil MWFs (also called insoluble oils), which are made from naphthenic or paraffinic oils and contain no water; soluble oil MWFs, which are naphthenic or paraffinic oils emulsified in water; synthetic MWFs, which are chemical fluids containing no petroleum base oils; and semisynthetic MWFs, which are emulsions containing small amounts of oil, sometimes distinguished from soluble oil MWFs by the degree of emulsification. The National Institute for Occupational Safety and Health (NIOSH) estimates that more than one million workers are exposed to MWFs (NIOSH, unpublished data).

In recent years, MWF exposures have been the subject of study in several epidemiologic investigations. However, we are not aware of any published comprehensive reviews of the cancer findings from these studies. As such, NIOSH conducted a comprehensive and systematic review of the epidemiologic studies that examined the association between MWF exposure and cancer. The findings of this review can be found in the recent NIOSH Criteria for a Recommended Standard-Occupational Exposure to MWFs [NIOSH, 1998]. The purpose of this paper is to summarize the evidence for cancer of the skin, scrotum, larynx, rectum, pancreas, and bladder.

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METHODS

In order to be included in this review, an article had to be published in a peer-reviewed journal. Articles were identified from computerized database searches, from recommendations made by reviewers of earlier drafts and from references cited in relevant articles. Studies providing data on the association between MWF exposure and cancer were grouped into three categories based on their study design: (1) retrospective cohort mortality and cancer incidence studies of MWF-exposed cohorts and associated nested case-control studies; (2) proportionate mortality ratio (PMR) studies of occupational groups exposed to MWF and associated case-control studies; and (3) population-based studies (primarily case-control interview studies of specific cancer sites which examined cancer risks associated with MWF exposure, or with occupations likely to have MWF exposure, i.e., metal machinists, grinders, turners, or toolmakers).

Of the cohort and PMR studies designed to assess the mortality and/or morbidity of MWF-exposed workers, the Eisen et al. [1992] and Tolbert et al. [1992] studies have the most statistical power because the number of subjects with malignant neoplasms in these studies is an order of magnitude larger than in any of the other cohort studies. The two auto parts manufacturing plants studied by Tolbert et al. were also included in the study conducted by Eisen et al. [1992](Plants I and II). To avoid reporting the results for workers from Plants I and II twice, the findings from these plants are summarized from the report by Tolbert et al. [1992] only, and only the findings from the third plant (Plant III) are summarized from the report by Eisen et al. [1992]. Tolbert's findings for Plants I and II were used because her analyses examined the cancer risks associated with exposure to specific classes of MWF. For the purpose of tabulating the number of cohort studies reporting site-specific data for each cancer, Plants I and II [Tolbert et al., 1992] are counted as a single study and Plant III is counted as a second study [Eisen et al., 1992].

Tables I–V summarize the data generated to examine the association between MWF exposure and risk of cancer at specific organ sites. In an effort to keep the tables to a reasonable size, all the rate ratio estimates reported by these studies are not included. The Tolbert study provides the risk among those ever exposed to each of the specific classes of MWFs, and the remaining studies provide the risk for all workers with potential MWF exposure and, when available, the risk among those workers with the highest duration of employment. All of the rate ratios are for males, except for the studies by Acquavella et al. [1993], Wortley et al. [1992], and Schifflers et al. [1987] in which the reported rate ratios for males and females were combined.

Not included in this paper are hypothesis-generating studies, which examined broad occupational categories based on census or death certificate data. The results of such studies are summarized elsewhere [NIOSH, 1998].

RESULTS

Skin and Scrotal Cancer

Case reports.

Since the 1940s, evidence has accumulated to support an association between skin (including scrotal) cancer and occupational exposure to MWFs. Several case reports have identified skin cancer among MWF-exposed workers [summarized in NIOSH, 1998; Kipling and Waldron, 1976].

Cohort studies.

A cohort study of turners employed between 1960 and 1980 at a Swedish company producing bearing rings found that the straight oil MWF-exposed turners had an increased risk of squamous cell carcinoma of the skin (obs = 5 [four scrotal, and one facial], exp = 0.3, $P < 0.001$) [Jarvholm et al., 1985] (Table I). Three additional scrotal cancer cases were identified among turners in the 1987 update of this cohort [Jarvholm and Lavenius, 1987]. The authors suggest that use of soluble oil MWFs is not associated with scrotal cancer because no cases were observed among the grinders who primarily use soluble oil MWFs [Jarvholm and Lavenius, 1987]. Furthermore, it should be noted that changes in refinery methods since the 1950s have reduced the straight oil MWF content of polycyclic aromatic hydrocarbons (PAHs), which have been suggested as the causative agent for MWF-associated skin cancer [Jarvholm and Easton, 1990; McKee et al., 1990]. As would be expected because of the high survival rate for nonmelanoma skin cancer, a significantly elevated risk was not observed in the one cohort mortality study that reported skin cancer mortality (Table I).

PMR studies.

A significantly elevated risk was not observed in any of the three PMR studies (Table I).

Population-based studies.

In a population-based case-control study in Connecticut involving 45 cases of squamous cell carcinoma of the scrotum, those ever employed in an occupation with potential MWF exposure (toolmaker, setter, setup man, hardener, polisher, automatic screw operator, machinist, and machine operator) had an increased risk of this cancer (odds ratio [OR] = 10.5, 95% confidence interval [95%CI] = 4.0–36.9) [Roush et al., 1982].

Conclusion for Skin Cancer

The large number of case reports, the cancer incidence study, and the case-control study suggest that MWF expo-

TABLE I. Results for Skin/Scrotal Cancer from Epidemiologic Studies of Populations Exposed to Metalworking Fluids

Investigators	Location	Type of study/analysis	No. with cancer or no. of exposed cases	Rate ratio	95%CI (or *P*-value)	Study population/cancer site
Cohort studies						
Jarvholm et al. [1985]	Sweden	SIR	5	16.6	<0.001	Turners employed between 1960 and 1980/ squamous cell cancer of the skin
Jarvholm and Lavenius [1987]	Sweden	SIR	7	—[a]	—	Turners only/scrotal cancer
Eisen et al. [1992]	Michigan	SMR	10	0.61	0.29, 1.13	White autoworker, Plant I/skin cancer
			11	1.06	0.53, 1.89	White autoworkers, Plant II/skin cancer
			7	1.27	0.51, 2.62	White autoworkers, Plant III/skin cancer
Proportionate mortality studies						
Silverstein et al. [1988]	Connecticut	PMR	4	0.92	0.25, 2.34	Ball-bearing plant workers, white/skin cancer
Park et al. [1988]	Connecticut	PMR	4	1.88	0.51, 4.80	Ball-bearing plant workers, white/skin cancer
Vena et al. [1985]	New York	PMR	1	0.60	NS	Based on U.S. mortality, engine plant workers, white/skin cancer
Population-based studies						
Rousch et al. [1982]	Connecticut	Case/control	26	10.5	4.0, 36.9	Ever employed as toolmaker, setter, set-up man, hardener, polisher, automatic screw operator, machinist, or machine operator/ squamous cell cancer of the scrotum

CI, confidence interval; PMR, proportionate mortality ratio; SMR, standardized mortality ratio; SIR, standardized incidence ratio; NS = not statistically significant.
[a]There were too few expected cases of scrotal cancer to make a reliable estimate of risk.

sure, primarily straight oil MWF exposure, has been associated with an increased risk of skin and scrotal cancer. As a result of the changes in MWF composition and reduction of impurities over the last several decades, current straight oil MWF exposures may be associated with a substantially reduced risk of these cancers.

Laryngeal Cancer

Cohort studies.

Only the studies of the three automobile manufacturing plants conducted by Tolbert et al. [1992] and Eisen et al. [1992] reported site-specific data for laryngeal cancer (Table II). Tolbert et al. [1992] reported a statistically significant standardized mortality ratio (SMR) of 1.98 for laryngeal cancer among whites ever exposed to straight oil MWF and a nearly significant SMR of 1.41 for soluble oil MWF exposure. In a case-control analysis including all three plants, and incident as well as deceased cases, a categorized exposure analysis found an OR of 2.23 (95%CI = 1.25, 3.98) among individuals with > 0.5 mg/m^3-years straight oil MWF particulate exposure [Eisen et al., 1994]. The authors also examined the association between laryngeal cancer and specific components or contaminants of MWFs (biocides, steel, iron, aluminum, sulfur, and chlorine). There was some evidence for confounding by sulfur, but models containing sulfur still had a significantly elevated OR in the highest straight oil MWF exposure category (OR = 1.91, 95%CI = 1.01–3.62). Although unable to adjust for smoking and alcohol, two important risk factors for laryngeal cancer [Austin and Reynolds, 1996], these investigators did not think that these risk factors confounded their results because the risk of lung cancer and cirrhosis did not increase with increasing exposure to straight oil MWFs.

PMR studies.

Among the three PMR studies, the overall PMRs ranged from 1.7-1.8, and were not statistically significant [Park and Mirer, 1996; Vena et al., 1985; Mallin et al., 1986]. In the study conducted by Vena et al. [1985], a significantly elevated PMR was found for workers employed less than 20 years and those who were employed after 1950 (PMR = 3.95, $P < 0.05$ for both subgroups).

Population-based studies.

Among six studies that defined occupational categories in sufficient detail to examine risk associated with exposure to MWF, and that controlled for smoking and alcohol, one

TABLE II. Results for Laryngeal Cancer from Epidemiologic Studies of Populations Exposed to Metalworking Fluids

Investigators	Location	Type of study/analysis	No. with cancer or no. of exposed cases	Rate ratio	95%CI (or *P*-value)	Study population
Cohort studies						
Tolbert et al. [1992]	Michigan	SMR	23	1.98	1.26, 2.98	Ever straight oil MWF exposure, white
			30	1.41	0.95, 2.01	Ever soluble oil MWF exposure, white
			8	1.57	0.68, 3.09	Ever synthetic MWF exposure, white
			1	0.50	0.01, 2.78	Ever straight oil MWF exposure, black
			6	0.91	0.70, 1.17	Ever soluble oil MWF exposure, black
Eisen et al. [1992]	Michigan	SMR	2	0.77	0.09, 2.79	White autoworkers, Plant III
Eisen et al. [1994]	Michigan	Nested case/control	28	2.23	1.25, 3.98	Autoworkers with highest exposure to straight oil MWFs
Proportionate mortality studies						
Park and Mirer [1996]	Detroit-area	PMR	1	0.69	0.02, 3.83	Engine plant 1, white
			4	1.67	0.46, 4.28	Engine plant 2, white
Vena et al. [1985]	New York	PMR	3	1.81	NS	Based on US mortality, engine plant workers, white
Mallin et al. [1986]	Illinois	PMR	2	1.76	NS	Equipment manufacturing workers, white
Population-based studies						
Zagraniski et al. [1986]	Connecticut	Case/control	22	2.5	1.2, 5.2	Ever worked as a machinist
			17	2.1	1.0, 4.7	Ever worked as a metal grinder
Wortley et al. [1992]	Washington State	Case/control	NA	1.8	0.5, 6.2	Ever employed as grinding, abrading, or buffing operator
			19	1.0	0.5, 1.9	Ever employed in precision metal working
Zheng et al. [1992]	China	Case/control	12	1.2	0.5, 3.1	Usual occupation of blacksmith, machine-tool operator, electrician, or other related workers
			25	0.8	0.4, 1.6	Self-reported exposure to lubricant fumes
Haguenoer et al. [1990]	France	Case/control	7	1.8	NS	Employed in metal work or as mechanic for at least 15 years
Browne et al. [1988]	Texas	Case/control	5	0.53	0.18, 1.58	Ever machinists
Ahrens et al. [1991]	Germany	Case/control	NA	2.2	0.9, 5.3	Ever mineral oil exposure

Abbreviations: (see Table I.)

found a significant risk of laryngeal cancer. Zagraniski et al. [1986] found an elevated laryngeal cancer risk among those with ''ever employment as a machinist'' (SMR = 2.5, 95%CI: 1.2–5.2) and among those with ''ever employment as a metal grinder'' (SMR = 2.1, 95%CI = 1.0–4.7). Another case-control study of 100 laryngeal cancer cases and 100 controls found a nonsignificantly elevated risk among those who self-reported ever having mineral oil exposure (OR = 2.2, 95%CI = 0.9–5.3) [Ahrens et al., 1991].

Conclusion for Laryngeal Cancer

Several studies suggest that MWF exposure may be associated with laryngeal cancer. In particular, the studies by Eisen et al. [1992, 1994] and Tolbert et al. [1992] suggest that laryngeal cancer is associated with exposure to straight oil MWFs.

Rectal Cancer

Cohort studies.

Only the studies conducted by Tolbert et al. [1992], Eisen et al. [1992], and Decouflé [1978] reported site-specific results for rectal cancer (Table III). Tolbert et al. [1992] reported a significant association between straight oil MWF exposure and rectal cancer among white, but not black, workers. Poisson regression analyses revealed a trend of increasing rectal cancer risk in relation to years of exposure to straight oil MWFs ($P < 0.0001$). The rate ratio for the most highly exposed group was 3.2 (95%CI = 1.6–6.2).

TABLE III. Results for Rectal Cancer from Epidemiologic Studies of Populations Exposed to Metalworking Fluids (MWF)

Investigators	Location	Type of study/analysis	No. with cancer or no. of exposed cases	Rate ratio	95%CI (or *P*-value)	Study population
Cohort studies						
Tolbert et al. [1992]	Michigan	SMR	37	1.47	1.04, 2.03	Ever straight oil MWF exposure, white
			51	1.09	0.81, 1.43	Ever soluble oil MWF exposure, white
			9	0.92	0.42, 1.74	Ever synthetic MWF exposure, white
			1	0.45	0.01, 2.53	Ever straight oil MWF exposure, black
			3	0.68	0.14, 1.99	Ever soluble of MWF exposure, black
Eisen et al. [1992]	Michigan	SMR	7	1.70	0.68, 3.50	White autoworkers, Plant III
Decouflé [1978]	Michigan	SMR	8	1.25	NS	Metal machining plant workers, white
			4	1.29	NS	5+ years of heavy MWF mist exposure, white
Proportionate mortality studies						
Silverstein et al. [1988]	Connecticut	PMR	14	1.36	0.81, 2.29	Ball-bearing plant workers, white
Park et al. [1988]	Connecticut	PMR	11	3.07	1.54, 5.50	Ball-bearing plant workers, white
Vena et al. [1985]	New York	PMR	4	1.38	NS	Based on US mortality, engine plant workers, white
			4	2.76	$P < 0.05$	Employed in engine plant >20 years, white
Mallin et al. [1986]	Illinois	PMR	2	0.80	NS	Equipment manufacturing workers, white
Population-based studies						
Gerhardsson de Verdier et al. [1992]	Sweden	Case/control	25	2.1	1.1, 4.02	Ever exposed to cutting oils
Siemiatycki et al. [1987]	Montreal	Case/control	13	0.7	90%CI; 0.4–1.0	Ever exposed to cutting oils

Abbreviations: (see Table I.)

PMR studies.

Among the four PMR studies reporting data for rectal cancer, the investigation led by Park et al. [1988] found a significant excess in a cohort with potential exposure to straight and soluble oil MWFs (PMR = 3.07, 95%CI = 1.54–5.50). Park et al. [1988] did not report the risk of each specific type of MWF exposure. Another PMR study found a significant excess in a subgroup employed in an engine plant for >20 years (PMR = 2.76, $P < 0.05$) (although three types of MWF [straight, soluble, and synthetic MWF] were used at this plant, their temporal use was not known to the study investigators) [Vena et al., 1985]. Silverstein et al. [1988] found a slight excess of rectal cancer mortality which was not statistically significant; the risk for various processes was not reported. Mallin et al. [1986] found a risk of less than 1; however this finding is based on only two rectal cancer deaths.

Population-based studies.

A population-based case-control study of incident cases of rectal cancer in Sweden found that male workers ever exposed to cutting fluids had an elevated risk of rectal cancer (OR = 2.1, 95%CI = 1.1–4.0)[Gerhardsson de Verdier et al., 1992]. However, several of the cases had other occupational exposures associated with an increased risk of rectal cancer including exposure to asbestos, soot, and coal/coke/wood combustion gases. In an analysis adjusting for these other exposures, the risk of rectal cancer among cutting oil-exposed workers was lower (OR = 1.4, 95%CI = 0.6-3.5). In another population-based case-control study that examined the association between several cancer sites and occupational exposure to several petroleum-derived liquids, ever having cutting oil exposure was found not to be associated with an increased risk of rectal cancer (OR = 0.7, 90%CI = 0.4-1.0) [Siemiatycki et al., 1987].

Conclusions for Rectal Cancer

Several studies suggest that MWF exposure is associated with rectal cancer. In particular, the findings from the study with the most statistical power suggest that straight oil MWF exposure may be associated with an increased risk of rectal cancer [Tolbert et al., 1992].

Pancreatic Cancer

Cohort studies.

Among five cohort studies reporting site-specific data for pancreatic cancer, two found significant excess mortality

TABLE IV. Results for Pancreatic Cancer from Epidemiologic Studies of Populations Exposed to Metalworking Fluids (MWF)

Investigators	Location	Type of study/analysis	No. with cancer or no. of exposed cases	Rate ratio	95%CI (or *P*-value)	Study population
Cohort studies						
Tolbert et al. [1992]	Michigan	SMR	34	0.80	0.55, 1.11	Ever straight oil MWF exposure, white
			61	0.77	0.59, 1.00	Ever soluble oil MWF exposure, white
			19	1.03	0.62, 1.61	Ever synthetic MWF exposure, white
			8	1.40	0.60, 2.77	Ever straight oil MWF exposure, black
			19	1.62	0.98, 2.54	Ever soluble oil MWF exposure, black
Eisen et al. [1992]	Michigan	SMR	8	0.87	0.37, 1.71	White autoworkers, Plant III
Bardin et al. [1991]	Michigan	Nested case/control	9	3.0	1.2, 7.5	Highest exposure to synthetic MWF
Rotini et al. [1993]	Ohio	SMR	8	0.91	0.39, 1.79	Engine plant, white
			7	3.03	1.21, 6.24	Engine plant, black
Acquavella et al. [1993]	Iowa	SMR	11	2.0	0.9, 3.8	Metalworking factory workers
			5	3.6	1.2, 8.3	Factory workers employed>10 years, hired between 1950–1959
Decouflé [1978]	Michigan	SMR	8	1.05	NS	Metal machining plant workers, white
			1	0.27	NS	5+ years of heavy MWF mist exposure, white
Proportionate mortality studies						
Park and Mirer [1996]	Detroit-area	PMR	10	1.82	0.87, 3.34	Engine plant 1, white
			11	1.23	0.62, 2.21	Engine plant 2, white
		MOR	4	3.61	1.04, 12.6	Machining with straight oil MWF
Silverstein et al. [1988]	Connecticut	PMR	24	1.43	0.96, 2.12	Ball-bearing plant workers, white
		MOR	9	3.10	$P = 0.05$	Employed in grinding 10+ years
		MOR	5	3.71	$P = 0.05$	Employed in machinery 10+ years
Park et al. [1988]	Connecticut	PMR	8	1.09	0.55, 2.18	Ball-bearing plant workers, white
Vena et al. [1985]	New York	PMR	11	1.89	<0.05	Based on U.S. mortality, white
			7	2.32	<0.05	Employed in engine plant >20 years
Mallin et al. [1986]	Illinois	PMR	5	1.19	NS	Equipment manufacturing workers, white
			5	3.57	<0.05	Equipment manufacturing workers, black
Population-based studies						
Mack and Paganini-Hill [1981]	Los Angeles	Incidence	21	1.30	NA	Machinists, white males

Abbreviations: MOR = mortality odds ratio (also see Table II).

from this cause of death [Rotimi et al., 1993; Acquavella et al., 1993] Table IV). Rotimi et al. [1993] found that black men employed at two Ohio engine manufacturing plants had an excess pancreatic cancer mortality (SMR = 3.03, 95%CI = 1.21–6.24, based on seven deaths). However, it should be noted that the investigators found no consistent pattern with respect to time since hire or duration of employment, and no pancreatic cancer excess was observed in white workers. Acquavella et al. [1993] reported that factory workers employed at an Iowa metalworking facility, all of whom were white, had an increased risk of pancreatic cancer mortality (SMR = 2.0, 95%CI = 0.9–3.8). The risk appeared to be greatest among factory workers employed 10 or more years who were hired between 1950 and 1959 (SMR = 3.6, 95%CI = 1.2–8.3); however, the authors did not report if workers in a specific occupational group were responsible for this elevation. Among those in the overall cohort, assembly workers, who Acquavella et al. state are unlikely to have MWF exposure, were the occupational group with the highest risk (SMR = 3.0, 95%CI = 1.0–7.5). In contrast, in those departments identified by Acquavella et al. as having potential MWF exposure, there were 2 observed pancreatic cancer deaths while 3.3 deaths were expected. Tolbert et al. [1992] found excess pancreatic cancer mortality among black workers exposed to soluble oil MWFs at Plants I and II in Michigan (SMR = 1.62, 95%CI = 0.98–2.54). In a Poisson regression analysis that controlled for race, age, and gender, an increased risk of pancreatic cancer mortality was observed in those workers with the highest exposures to synthetic MWFs (rate ratio = 2.04, 95%CI: 0.88-4.72) [Tolbert et al., 1992]. In a case-control analysis that included Plants I, II, and III, a categorized exposure analysis found an OR of 2.23 (95%CI = 1.25-3.98) among individuals with >1.4 mg/m^3-years grinding with synthetic MWF [Bardin et al., 1997]. However, neither synthetic MWF, nor any other measured exposure, was found to explain the previously documented excess pancreatic cancer risk among black workers [Bardin et al., 1997]. Although unable to adjust for smoking, an important risk factor for pancreatic cancer [Silverman et al., 1994], the authors did not think that this risk factor confounded their results because the risk of lung cancer did not increase with increasing exposure to synthetic MWFs. One other cohort study found a nonsignificant elevation in pancreatic cancer mortality; however, this study had limited statistical power [Decouflé, 1978].

PMR studies.

Among five studies reporting site-specific data for pancreatic cancer, four found significantly elevated PMRs [Vena et al., 1985; Mallin et al., 1986; Silverstein et al., 1988; Park and Mirer, 1996]. White men employed at an engine plant for at least 10 years had an excess of pancreatic cancer mortality (PMR = 1.89, $P < 0.05$), which was higher for those employed > 20 years (PMR = 2.32, $P < 0.05$) [Vena et al., 1985]. Use of county referent rates resulted in higher PMRs (employed > 10 years, PMR = 2.41, $P <$ 0.05; employed 20 years, PMR = 2.97, $P < 0.05$). Mallin et al. [1986] found a significant excess of pancreatic cancer among black (PMR = 3.57, $P < 0.05$), but not white (1.19, not significant), men employed in the manufacture of diesel engines and construction equipment. The PMR for pancreatic cancer was highest among black men who died after 20 years of service (PMR = 4.79, $P < 0.01$). Another PMR study found an elevation in pancreatic cancer mortality among whites at a ball-bearing manufacturing plant (PMR = 1.43, 95%CI = 0.96–2.12) [Silverstein et al., 1988]. Case-control analyses revealed substantially elevated risks associated with 10 or more years employment in grinding with various MWFs (OR = 3.10, $P = 0.05$) and machining with straight oil MWF (OR = 5.31, $P = 0.05$). The risk associated with grinding was present only for those with early hire dates (during the early 1930s and before) at which time straight oil MWFs were ''almost exclusively used in grinding.'' There were too few deaths among nonwhite men for analysis. A PMR study of workers at two engine plants did not observe significant excesses for pancreatic cancer [Park and Mirer, 1996]. However, a mortality odds ratio (MOR) analysis of these workers found an increased risk among those ever employed in machining with straight oil MWFs (OR = 3.61, 95%CI = 1.04–12.6, based on three cases), but no trend was observed with increasing cumulative exposure. One other PMR study found a nonsignificant elevation in pancreatic cancer mortality; however, an MOR analysis was not reported [Park, 1988].

Conclusion for Pancreatic Cancer

Several studies have found significantly increased risks of pancreatic cancer among MWF-exposed workers. The evidence is strongest for grinding with synthetic MWF [Bardin et al., 1997], and for machining with straight oil MWFs [Silverstein et al., 1988; Park and Mirer, 1996]. Although a number of the studies did not have internally consistent findings (i.e., excesses in black but not white workers, lack of association with duration of MWF exposure), the number of studies with statistically significant findings suggests that exposure to some MWFs may increase the risk of pancreatic cancer.

Bladder Cancer

Cohort studies.

Only two cohort studies reported site-specific data for bladder cancer and neither found a significant excess [Decouflé, 1978; Jarvholm and Lavenius, 1987] (Table V). However, both of these studies are limited by relatively small sample sizes.

PMR studies.

Of the six PMR studies that reported site-specific data for bladder cancer, only one reported a significant excess, which was among white workers employed in an engine plant (PMR = 2.28, $P < 0.05$) [Vena et al., 1985]. The risk was greatest among those first employed during or before 1950 (PMR = 3.37, $P < 0.05$). A study of bearing plant workers found a nonsignificantly elevated risk of bladder cancer [Silverstein, 1988]. A study of workers at two Detroit-area engine manufacturing plants also found nonsignificantly elevated PMRs for bladder cancer [Park and Mirer, 1996]. However, an MOR analysis of these workers found a significant association between risk of bladder cancer and cumulative exposures to grinding with straight oil MWF (MOR for the mean cumulative exposure of exposed cases = 2.99 [95% CI = 1.15-7.77], based on seven deaths), and employment in the machining or heat treat area (MOR for the mean cumulative exposure of exposed cases = 2.86 [95% CI = 1.14–7.18], based on four deaths). Two studies did not find an increased risk of bladder cancer [Park et al., 1988; Mallin et al., 1986]; however, these studies are limited by small sample size.

Population-based studies.

Several case-control studies have also examined the risk of bladder cancer among those whose occupations may

TABLE V. Results for Bladder and Lower Urinary Tract Cancer from Epidemiologic Studies of Populations Exposed to Metalworking Fluids

Investigators	Location	Type of study/analysis	No. with cancer or no. of exposed cases	Rate ratio	95%CI (or *P*-value)	Study population/cancer site
Cohort studies						
Decouflé [1978]	Michigan	SMR	6	1.2	NS	Metal machining plant workers, white/bladder & lower urinary tract
			2	0.8	NS	5+ years heavy MWF mist exposure, white/bladder and lower urinary tract
Jarvholm and Luvenius [1987]	Sweden	SIR	7	1.04	0.4, 2.2	Grinders and turners/bladder
Proportionate mortality studies						
Park and Mirer [1996]	Detroit-area	PMR	6	2.16	0.79, 4.70	Engine plant 1, white/bladder
			5	1.13	0.37, 2.64	Engine plant 2, white/bladder
		MOR	7	2.99	1.15, 7.77	Grinding with straight oil MWF/bladder
		MOR	4	2.86	1.14, 7.18	Machining or heat treat employment/bladder
Silverstein et al. [1988]	Connecticut	PMR	14	1.26	0.75, 2.13	Ball-bearing plant workers, white/bladder
Park et al. [1988]	Connecticut	PMR	1	0.24	0.01, 1.31	Ball-bearing plant workers, white/bladder
Vena et al. [1985]	New York	PMR	7	2.28	<0.05	Engine plant workers, white/bladder
			4	2.76	NS	Employed in engine plant >20 years/bladder
Mallin et al. [1986]	Illinois	PMR	2	0.78	NS	Equipment manufacturing workers, white/bladder
Population-based studies						
Silverman et al. [1989a]	US	Case/control	102	1.3	1.0, 1.7	Ever machinist 6 months or more/bladder
			51	1.4	0.9, 2.1	Ever drill press operator ≥6 months/bladder
Siemiatycki et al. [1987]	Montreal	Case/control	47	1.2	90%CI: 1.0–1.6	Ever exposed to cutting oils/bladder
Claude et al. [1988]	Germany	Case/control	18	2.25	1.0, 5.6	Ever turner/bladder and lower urinary tract
			43	0.84	0.54, 1.3	Ever metal worker/bladder and lower urinary tract
Gonzalez et al. [1989]	Spain	Case/control	31	0.77	0.5, 1.1	Ever toolmaker ≥6 months/bladder
			NA	1.86	1.2, 2.8	Ever machinery adjuster, assembler, or mechanic ≥6 months/bladder
Steenland et al. [1987]	Ohio	Case/control	11	2.00	NS	Ever grinding machine operator/bladder and lower urinary tract
			45	0.69	<0.05	Ever machinist/bladder and lower urinary tract
Vineis and Magnani [1985]	Italy	Case/control	16	1.5	0.7, 3.3	Ever employed in machine tools ≥6 months/bladder
Schifflers et al. [1987]	Belgium	Case/control	34	2.45	1.28, 4.69	All metal workers/bladder
			8	2.57	0.92, 7.16	Turners/bladder
Howe et al. [1980]	Canada	Case/control	NA	2.7	1.1, 7.7	Ever metal machinist/bladder
Silverman et al. [1983]	Detroit	Case/control	137	1.1	0.8, 1.5	All metal machinists/bladder and lower urinary tract
			32	1.5	0.9, 2.7	Tool and die workers/bladder & lower urinary tract
Silverman et al. [1989b]	U.S.	Case/control	26	1.1	0.6, 1.9	Metal machinery worker/bladder

Abbreviations: (see Table I.)

involve MWF exposure. Only those studies that controlled for smoking, a known risk factor for bladder cancer [Matanoski and Elliott, 1981], are included in this review. In a large population-based case-control study from the United States, Silverman et al. [1989a] found an elevated risk of bladder cancer among white men ever employed as machinists (OR = 1.3, 95%CI = 1.0–1.7) or drill press operators (OR = 1.4, 95%CI = 0.9–2.1). Furthermore, among drill press operators, the risk increased with increasing duration of employment (*P* for trend = 0.008). Among drill press operators who worked 5 or more years, the elevated risk was present in both those who began work before 1950 (OR = 1.7; confidence limits not provided) and those who began work in 1950 or later (OR = 2.9; confidence limits not provided). However, among those who were employed as drill press operators for less than 5 years, the risk of bladder cancer was increased only among those who began employment in 1950 or later (OR = 2.8; confidence limits not provided). The same study [Silverman et al., 1989b] examined occupational risk factors for bladder cancer among nonwhite men, and reported an RR of 1.1 (95%CI = 0.6-1.9) for the summary category ''Metal machinery worker,'' with an identical summary category'' Metal machinery worker'' for whites of RR of 1.1 (95%CI = 1.0-1.3)[Silverman et al., 1989a]. The risks for the subcategories ''Machinists'' and ''Drill Press Operators'' was not broken out for nonwhites, nor was duration of employment as a metal machinery worker examined. In a population-based case-control study from Canada, Howe et al. (1980) found that those ever employed as metal machinists had an increased risk of bladder cancer (OR = 2.7, 95%CI = 1.1–7.7). A hospital-based case-control study conducted in Germany found that individuals ever employed as turners had an increased risk of bladder cancer (OR = 2.25, 95%CI = 1.0–5.6), and the risk was consistently elevated with increasing duration of employment (*P* for trend = 0.08) [Claude et al., 1988]. This same study also found no increased risk of bladder cancer for the broad category of metal workers (OR = 0.84, 95% CI = 0.54–1.3). A population-based case-control study from Belgium found that metal workers had a significantly increased risk of bladder cancer (RR = 2.45, 95%CI = 1.28–4.69). Subgroup analyses of these workers found the highest risk among turners (RR = 2.57, 95%CI = 0.92–7.16) [Schifflers et al., 1987]. Another hospital-based case-control study from Italy found that those employed for six months or more in the machine-tool industry had an increased risk of bladder cancer (OR = 1.5, 95%CI = 0.7–3.3)[Vineis and Magnani, 1985]. Within the machine-tool trade, the risk of bladder cancer was elevated among turners, especially among turners hired before 1940 and employed more than 10 years (RR = 3.1, 95%CI = 0.9–10.5). A population-based case-control study conducted in Hamilton County, Ohio, found that grinding machine operators had an increased risk of bladder cancer (OR = 2.00; not significant), whereas machinists were found to have a significantly decreased risk (OR = 0.69, $P < 0.05$) [Steenland et al., 1987]. Another case-control study did not observe an increased risk of bladder cancer among toolmakers (RR = 0.77, 95%CI = 0.5–1.1) but did observe an increased risk among machinery adjusters, assemblers, and mechanics (RR = 1.86, 95%CI = 1.2–2.8) [Gonzalez et al., 1989].

Conclusions for Bladder Cancer

The association between bladder cancer and MWF exposure is well supported by one large and well-designed case-control study [Silverman et al., 1989a,b], as well as several other studies conducted in different geographic locations, all of which controlled for smoking. Although none of the cohort studies found a significantly increased risk of bladder cancer, it has been observed that mortality studies may not be suitable for detecting elevated risks for cancers with high survival rates [Schulte et al., 1985; Steenland et al., 1988].

Route of Exposure

Although the route of exposure to MWFs is generally through dermal contact or through inhalation, the large size of many airborne MWF droplets can lead to gastrointestinal exposure. A significant proportion of airborne MWF particles is in the nonrespirable (extrathoracic) range (i.e., particles with a mass mean diameter >9.8 μm). Eisen et al. [1994] report that in their study approximately 20–33% of the total particulate was in the extrathoracic range. Large particles generally result in gastrointestinal exposures since they are filtered out in the nasopharyngeal region and do not reach the airways. In addition, some of the small particles in the thoracic size fraction are captured by the mucocilliary escalator. The mucocilliary escalator transports the particles to the pharynx, where they are swallowed, thereby permitting gastrointestinal exposure.

DISCUSSION AND CONCLUSIONS

We believe there is substantial evidence for increased risk of cancer at several sites (larynx, rectum, pancreas, skin, scrotum, and bladder) associated with at least some MWFs used prior to the mid-1970s. The inconsistencies between studies with respect to the organ sites that were affected, and the variation in the strength of association between the surrogates of exposure and specific sites are, most likely, related to the diverse nature of MWF mixtures studied, the absence of detailed exposure information, and the limitations of the epidemiologic tools with which MWF exposures have been studied.

As described earlier, there are four major classes of MWF. The types and amounts of chemical constituents can vary across these different classes of MWF. Furthermore, within each class of MWFs there are many different formulations, which vary in composition, and may contain many different additives and impurities. Some MWF constituents are considered carcinogenic in animals, including N-nitrosamines [IARC, 1978], and some PAHs [IARC, 1983]. Efforts to reduce these potential carcinogenic exposures have been ongoing. Removal of PAHs from MWFs began in the 1950s and U.S. Environmental Protection Agency (EPA) regulations during the 1980s were directed at reducing nitrosamine exposures [Code of Federal Regulations, 1984]. Because different epidemiologic study populations may have been exposed to different classes and formulations of cutting fluids, some lack of consistency in site-specific results between studies should be expected when evaluating the carcinogenicity of these substances. Similarly, when comparing studies with limited information on the intensity of exposure, we would expect variation in the strength of association between exposure and the risk of cancer. In our opinion, the consistency among the studies is sufficient to support our conclusions.

Given the small number of epidemiologic studies that have adequate exposure characterization, the specific MWF constituent(s) or contaminant(s) responsible for the various site-specific cancer risks remains to be determined. The study with the most statistical power and detailed exposure information [Tolbert et al., 1992] suggests that specific classes of MWFs are associated with cancer at certain sites. However, within these MWF classes, the specific formulations responsible for the elevated cancer risks remain to be identified. Within the Tolbert et al. study, straight oil MWF exposure was modestly associated with an increased risk of laryngeal cancer and rectal cancer, and there was limited evidence that synthetic MWF exposure was associated with an increased risk of pancreatic cancer. Subsequent case-control studies based on the original cohort have confirmed the laryngeal cancer-straight oil MWF association [Eisen et al., 1994], and the pancreatic cancer-synthetic MWF association [Bardin et al., 1997]. The Tolbert et al. study found less evidence that soluble oil MWF exposure is associated with cancer at any specific site. We believe it is premature to conclude that all members of the soluble class of MWFs were free from any past carcinogenic risks. This is because soluble oil MWFs contain many of the ingredients found in straight oil MWFs, but in different concentrations. Second, many of the epidemiologic studies with positive findings involved exposures to more than one class of MWF.

It is unlikely that non-MWF exposures are responsible for the cancer findings described in this paper. Smoking and alcohol are associated with some of these cancers. However, the case-control studies controlled for these exposures when appropriate or determined that these exposures were unlikely confounders. Although information on these lifestyle factors are not often collected in occupational cohort mortality or PMR studies, it has been demonstrated that smoking is unlikely to account for relative risks >1.3 for smoking related diseases [Siemiatycki et al., 1988]. As for non-MWF occupational exposures, it is unlikely that these exposures explain the majority of findings, as the common exposure across all of the studies was MWF. Although some non-MWF exposures may have interacted synergistically with MWF exposure to produce some of the observed risks, the existence or extent of such synergism remains to be determined.

The studies that provide the bulk of the evidence suggesting an association between MWF exposure and cancer involved workers employed as early as the 1930s and as late as the mid-1980s. Because there is a latency period of 10–20 years, on average, between initial exposure to a carcinogen and the initial appearance of a solid organ cancer caused by that carcinogen, the excess cancer mortality observed in these cohort studies most likely reflects the cancer risk associated with exposure conditions in the mid-1970s and earlier. Over the last several decades, substantial changes have been made in the metalworking industry, including changes in MWF composition, reduction of impurities, and reduction of exposure concentrations. These changes have likely reduced the cancer risks. However, since the epidemiologic studies are unable to identify the MWF composition and impurities associated with the cancer risks observed in earlier cohorts, there are insufficient data to conclude that these changes will have eliminated all carcinogenic risks. The risk of cancer from MWF exposures in the mid-1970's and later remains to be determined because a definitive study has not yet been conducted of workers entering MWF-exposed jobs during this time. The substantial evidence that some MWFs used prior to the mid-1970s are associated with cancer at several sites, and the possible potential for current MWF to pose a similar carcinogenic hazard, support the lowered recommended exposure limit (REL) of 0.5 mg/m^3 total particulate mass. This new REL is based primarily on evidence for an association between nonmalignant respiratory effects and MWF exposure [NIOSH, 1998].

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