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Oils and cancer

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Epidemiologic evidence on the relationship between mineral oil exposure and cancer is reviewed. The review is restricted to occupations involving substantial dermal and inhalational exposure and for which an epidemiologic literature exists: metal machining, print press operating, and cotton and jute spinning. Mineral oils are complex mixtures of aliphatic hydrocarbons, naphthenics, and aromatics, the relative distribution of which depends on the source of the oil and the method of refinement. End-use products contain a variety of additives, and contamination by other agents generally occurs during use. Suspect agents include polycyclic aromatic hydrocarbons (PAH) (particularly benz[a]pyrene), nitrosamines, chlorinated paraffins, long-chain aliphatics, sulfur, N-phenyl-2-naphthylamine, and formaldehyde. The heterogeneity of this exposure makes epidemiologic study difficult and meta-analysis inappropriate. Nonetheless, several associations emerge from the literature with varying degrees of support. There is clear evidence that early formulations of mineral oils used in cotton and jute spinning and in metal machining were carcinogenic to the skin. Associations of mineral oil exposure with laryngeal and rectal cancer have received some support in the literature, particularly with respect to straight oils. Evidence is suggestive that grinding operations (which can entail either mineral oil-based or ethanolamine-based fluids) are associated with excess risk of cancer of the esophagus, stomach, and pancreas. A number of bladder cancer case-control studies have noted an association with work as a machinist. There is limited evidence of an association with cancer of the colon, prostate, and sinonasal region. Several studies of printers have yielded positive findings for lung cancer, whereas studies in metal machinists have been generally negative. The PAH and nitrosamine content of current formulations is lower than in the past and the implications of these changes in composition to the carcinogenicity of the formulations are not yet known. *Cancer Causes and Control* 1997, 8, 386-405

Key words: Cutting oils, cutting fluids, metalworking, mineral oil, nitrosamines, polycyclic aromatic hydrocarbons.

Introduction

Oils derived from petroleum or shale have been used in a wide variety of occupational settings and applications. Many of these involve enclosed systems with little opportunity for human exposure. There are several occupational environments, however, in which an oil mist is generated and in these situations the opportunities for dermal exposure or inhalation exposure, with concomitant ingestion, are substantial. Such occupations include metalworking, print press operating, and cotton and jute spinning. Workers in these occupations, particularly metalworkers, have been the focus of a number of epidemiologic investigations. Evidence regarding carcinogenic effects in these worker populations has been the subject of several reviews," including a comprehensive review conducted by a panel convened by the International Agency for Research on Cancer (IARC) in 1984.' The purpose of this paper, therefore, is to briefly summarize the findings presented in the IARC review and to present findings

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reported in the last decade since publication of the IARC review.

The IARC review concluded that:

> "there is sufficient evidence from studies in humans that mineral oils (containing various additives and impurities) that have been used in occupations such as mulespinning, metal machining and jute processing are carcinogenic to humans."[1]

This conclusion was based on evidence of a strong association of mineral oil exposure with squamous cell carcinoma of the skin, primarily scrotal cancer, from early studies of workers involved in these occupations.[1]

Mineral oil processing and production

In the latter half of the 19th century, oils from oil-bearing shale largely displaced animal and vegetable oils as lubricants. Shale oil was processed primarily in Scotland and to a lesser extent in Romania.[2] The subsequent discovery of petroleum and the competition from this source led to the decline of the shale industry and since the 1930s, almost all of the worldwide production of lubricating oils has been from petroleum. A small amount of shale oil processing continues to occur in China, the United States, and the former Soviet republics.[3]

Petroleum refining processes have changed dramatically during this century, with a trend toward increasingly refined oils containing reduced levels of polycyclic aromatic hydrocarbons (PAH) and other impurities.[2] Initially, acid treatment was widely used. Treatment with acid removes unstable hydrocarbons, resins, asphalts, and sulphur-, nitrogen-, and oxygen-containing compounds, improving the color, odor, and stability of the base oil. Over the past several decades, acid treatment has been largely replaced by solvent refining and/or hydrotreating. Solvent extraction removes olefins, naphthenes, and paraffins. Mild solvent extraction removes less of the aromatic content (including PAHs) than severe solvent extraction. Hydrotreating, often performed in conjunction with solvent extraction, entails catalytic hydrogenation of base oils to saturate olefins and render the oil more paraffinic. Severe hydrotreating converts more of the aromatic compounds to naphthenes.

The resulting base oil is then formulated into an end-use product by the addition of various additives, described below.

Exposure circumstances

Metalworking

In metalworking operations, fluids are directed at the working surface in a spray or stream, for the purpose of cooling and lubricating the metals being worked. Large quantities are used and generally they are collected and reused. Metalworking fluids are variously referred to as cutting oils or fluids, machining fluids, lubrication fluids, cooling emulsions or oils, grinding or drilling fluids or oils, and – as the multitude of names suggest – they comprise a group of fluids defined more by function than by chemical composition.

A wide variety of formulations has been developed for metalworking, most but not all of which contain mineral oil. Metalworking formulations can be broadly categorized into four classes[4]:

(i) Straight oils, also called neat oils, are naphthenic or paraffinic mineral oils, with additives such as sulfurized or chlorinated fats and corrosion inhibitors, and sometimes containing animal or vegetable oils. Straight oils contain no water, although small quantities of water can become entrained in the oils in the course of their reuse; entrained water can allow the growth of microorganisms, sometimes necessitating addition of biocides to the fluid. Of the various classes of metalworking fluids, straight oils have the greatest lubricity and lowest cooling capability, and therefore are preferred for use in operations that do not generate very much heat;

(ii) Soluble oils, also referred to as emulsifiable, water-miscible or suds oils, are aqueous emulsions of mineral oil (generally from a more viscous stock than that used in straight oils), with added emulsifiers (*e.g.*, petroleum sulfonates, amine soaps, sodium naphthenates), biocides (*e.g.*, formaldehyde-releasing triazines, chlorophenols, hexachlorophene, quaternary ammonium compounds), corrosion inhibitors (*e.g.*, amines, fatty oils, sodium nitrite, sulfurized fatty oils), antifoaming agents, dyes, and high pressure stabilizers. Soluble fluids generally are purchased in concentrated form, and diluted in water five- to 50-fold. After dilution, the fluid appears milky and opaque. Soluble fluids are cheaper to use than straight oils, and have better cooling properties but lesser lubricating qualities;

(iii) Synthetic fluids, also called chemical fluids, are generally alkanolamines (most often, ethanolamines) in aqueous solution, devoid of mineral oil. Additives include nitrites, nitrates, phosphates and borates for corrosion inhibition, surfactants (*e.g.*, complex alcohols and esters), biocides, silicone as a lubricant and antifoaming agent, and frequently dyes. They are more stable than soluble oils, and have excellent cooling properties. Synthetic fluids are obtained in concentrated form and diluted 20- to 100-fold. Although not the subject of this review because they

contain no mineral oil, synthetic fluids are mentioned because in many studies of metalworkers it is difficult to distinguish among the types of fluids to which the workers were exposed and in interpreting those studies, it should be kept in mind that synthetic fluids may be responsible for any associations observed with machining fluids rather than a mineral oilbased formulation;

(iv) Semi-synthetic fluids are a hybrid of soluble and synthetic fluids. They are 15 to 40 percent oil-based (pre-dilution), with glycols, polyols, and ester lubricants.

Straight oils have been in use since the nineteenth century, whereas soluble and synthetic fluids were introduced in the 1940s when high-speed machnery made necessary the superior cooling capabilities of water-based fluids. In 1984, it was estimated that 50 percent of metalworking fluids in use were soluble oils, 45 percent were straight oils, and five percent were synthetic and semi-synthetic.'

Hallock *et al*[4] conducted an exposure reconstruction to estimate historic levels of metalworking fluids in the vicinity of machining and grinding operations at several automotive manufacturing plants. Total particulate levels were estimated to be 5.4 mg/m^3 in the 1960s and levels declined to approximately 1.8 mg/m^3 in the 1980s. More recent measurements by other investigators suggest that typical levels have declined further to less than 1 mg/m^3.[5,6] More detailed presentations of results of monitoring machining fluid exposures in different settings are presented elsewhere."'

Printing

Over the last two decades, offset letterpresses have largely replaced rotary letterpresses, but for most of this century, large-scale newspaper production made use of rotary letterpress printing machines.' The high speed rotation of rotary presses generated a mist of ink droplets. Later rotary press models were less open than earlier models, but operated at higher speeds and thus tended to generate levels of respirable particulate at least as high as the earlier models.[10]

Rotary letterpresses made use of ink composed of an emulsion of carbon black in mineral oil, with additives and pigments. The carbon black is amorphous elemental carbon created by a furnace process, the diameter of the dispersed aggregate particles ranging from 0.1-0.2 microns." Carbon black adsorbs benz[*a*]pyrene and other PAHs and, therefore, these agents are present as contaminants of carbon black.' Typical composition of printing ink by weight is 85 percent mineral oil, 12 percent carbon black, and three percent induline dye toner (to impart a blue hue).[9]

A review of ambient levels of oil mist in newspaper press rooms indicated a range of levels from 2.0 to 16.6 mg/m^3.[11] In a detailed investigation of the *New York Times* pressroom, the average concentration in the vicinity of modern presses was determined to be 12.2 mg/m^3.[10] The respirable fraction was estimated to be about 15 percent.

Cotton spinning

Historically, the job of mule-spinning entailed substantial exposure to mineral oil through the operation of an apparatus for spinning cotton. A mechanized rack carried the spindles back and forth to receive the cotton as it was spun. A lubricating oil was applied to the cotton and was dispersed into the air by the spindles as they revolved. In addition, a bar approximately three feet high and extending the length of the machine, became moist with the oil. As mule-spinners leaned over the apparatus to tend to the machine, the groin area of their clothing became drenched with the oil that had collected on the bar. Spindle oils were composed of shale oil until the 1870s when petroleum-derived oils came into use. The petroleum-derived spindle oils were paraffinic, similar to the base oil used in metalworking formulations but usually a distillate of a somewhat lighter 'cut,' *i.e.*, having a lower boiling point.

In the past 40 years, the cotton industry has become increasingly automated and the opportunity for occupational exposure to mineral oil has greatly diminished. Mineral oil still is used occasionally as an overspray in early steps of processing (at a rate of 1 lb/100,000 lbs cotton), but its use is minimized because oil interferes with the ring spinning, air jet spinning, and open-end spinning technologies that have replaced mule-spinning (personal communication, L. Howard Olson, School of Textile and Fiber Engineering, Georgia Institute of Technology, April 1996).

Jute processing

Jute is treated with an emulsion of oil and water prior to spinning. Until the 1920s, whale oil was used for this purpose, but since then, mineral oil has been used. Oil is added during 'batching,' the first step of processing in which the jute is softened between rollers. The ribbon then goes through 'drawing,' during which it is thinned and twisted onto bobbins. Jute spindles revolve at approximately 4,000 RPM.[12] Jute processing practices have remained essentially unchanged since the 1950s. Overall, the industry has experienced decline due to the introduction of synthetic substitutes and jute processing is now performed primarily in India and Bangladesh (personal communication, William Yaffa, President, Burlap and Jute Association, April 1996).

Methodologic difficulties of studying mineral oils

As an exposure for epidemiologic study, mineral oil formulations present a number of methodologic difficulties.

Forniulations are complex mixtures. A wide variety of formulations have been in use, some having no ingredients in common with others. With use, the fluids can undergo chemical changes such as pyrolysis. Recycling and reprocessing of fluids compound this issue. Many of the suspect carcinogens (*e.g.*, PAH and nitrosamines) are unintentional contaminants, and, of course, are not listed in formulation descriptions. Composition of oils also varies as a function of the geographic source of the crude; with, for instance, Venezuelan crude having higher PAH content than Oklahoma crude. There have been secular changes in composition at ill-defined points in time such as the above-described changes in refining processes which have led to a reduction in PAH content in the base oils used in the end products. Finally, the settings in which substantial mineral oil exposure occurs generally entail co-exposure to other agents: in metalworking, for example, there is co-exposure to metals and abrasives, and in printing, there is co-exposure to carbon black and paper dust, making it difficult to distinguish among these agents with regard to their carcinogenic activity.

Given the variability and complexity of the exposure, it is not surprising that there is a lack of consistency across epidemiologic studies of mineral oil-exposed populations. Further, pooling of findings across studies will lead to an underestimation of any effects due to the heterogeneous nature of the exposure.

Case series/descriptive studies

The association of exposure to early lubricating oils formulated from either shale or petroleum with squamous cell carcinoma was so strong that it was apparent through simple case-series observations. Some of the first indications of carcinogenicity came from studies of the British cotton spinning industry. Workers spinning cotton became drenched in lubricants in the course of using spinning mules. A clear clustering of scrotal and other skin cancers was observed in these workers.[13,14] Kinnear *et al*[12] extended these observations to a second textile industry, jute processing. Higher proportions of premalignant and malignant skin changes were noted among jute processers presenting at a dermatologic clinic than among other patients at the clinic. Kinnear *et al*[12] followed this up with a dermatologic survey of workers in the jute industry and found that spinners had the most marked degenerative changes, supporting the hypothesis that mineral oil applied to jute and dispersed during spinning was the responsible agent.

Perhaps the first observation that fluids used specifically for metal working were carcinogenic to the skin was by Cruickshank and Squire.[15] An excess of skin cancer was noted in metalworking fluid-exposed workers in the light engineering industries of the West Midlands area of England. A subsequent study in this region indicated that between 1950 and 1967, 187 cases of scrotal cancer occurred in this geographic area, two-thirds of which appeared to be attributable to machining fluid exposure.[16] The incidence of scrotal cancer among toolsetters and machine operators in the Birmingham Cancer Registry from 1936 to 1972 was estimated to be about 17 times higher than that in the general male population.'' Outside England, an overrepresentation of metal workers exposed to metalworking fluids was noted in a case series of scrotal cancer in the Haute-Savoie area of France.[18] Among 21 men with scrotal cancer, seen 1959-63 at a local hospital, all were found to have been screwcutters for over 10 years. Further investigations in the Haute-Savoie area[19] confirmed this finding for scrotal and other skin cancers.

Population-based and registry-based studies

A number of population-based or registry-based case-control studies have been performed in which potential mineral-oil exposure was assessed using occupational histories. Such studies generally are limited by the fact that specific information on exposures (*e.g.*, type of metalworking fluid) is not available. The studies are presented in Tables 1 through 10, and some of the more informative studies are summarized below. Findings from case-control studies nested in cohorts are presented in the next section, Cohort-Based Studies.

Skin cancer

An excess risk of scrotal cancer was seen in American workers exposed to metalworking fluids in a case-control study using the Connecticut Tumor Registry (United States).[20] The odds ratio (OR) for the association of scrotal cancer with jobs entailing machining fluid exposure was 10, and the risk persisted in the most recent time period of diagnosis, 1966-73. The population attributable risk was estimated to be 57 percent.

Esophageal cancer

No population- or registry-based case-control studies of esophageal cancer assessing mineral oil exposure were identified.

Stomach cancer

Kneller *et al*[21] compared occupational data for 13,489 incident stomach cancer cases reported between 1980 and 1984 to the Shanghai Cancer Registry (China) to 1982 census employment data. The standardized incidence ratio (SIR) for workers in metal grinding, polishing, tool sharpening, and machine tool operation was 1.4 ($P < 0.01$). Other population-based studies assessing exposure to metalworking fluids or printing ink have reported risk estimates near the null.[22,23]

Colon cancer

Case-control studies assessing exposure to metalworking fluids have reported little or no association of exposure with colon cancer risk.[22,24]

Rectal cancer

A population-based case-control study of colon and rectal cancer noted an association of rectal cancer with metalworking fluids.[22] Type of fluid could not be assessed, but a statistically significant OR of two was observed for occupational exposure to metalworking fluids in general. Co-linearity of exposure variables precluded controlling for confounding by other exposures.

Pancreatic cancer

Mack and Paganini-Hill[22] reported a slight, nonsignificant association of employment as a machinist with risk of pancreatic cancer in a study of **3,614** incident pancreatic cancer cases diagnosed **1972-77** compared with all cancers reported to the registry during that time period.

***Larynx** cancer*

After controlling for smoking and alcohol use, Zagraniski *et al*[26] found a statistically significant association of larynx cancer with work as a machinist or metal grinder. In a second case-control study, Ahrens *et al*[27] observed an association of a history of work in jobs with mineral oil exposure and larynx cancer risk that was of borderline statistical significance.

***Lung** cancer*

Several case-control studies have yielded statistically significant associations of lung cancer risk with metalworking[28,29] or with printing.[22]

Bladder cancer

A large number of case-control studies have suggested that bladder cancer cases tend to be more iikely to have been metal machinists or engineers than controls, with ORs ranging from **1.5** to **5.0**.[22,31-40] The informativeness of these studies is limited by the fact that these job groupings are broad and encompass exposure to a variety of agents.

Prostate cancer

No prostate cancer case-control studies evaluating mineral oil exposure were identified.

Sinonasal cancer

Sinonasal cancer is a rare cancer and, therefore, case-control studies are more useful than cohort studies in investigating this outcome. A single case-control study using the Connecticut Tumor Registry supports an association of sinonasal cancer with work entailing machining fluid exposure, with a statistically significant OR of **2.8.**[22]

Cohort-based studies

Findings from cohort and proportional mortality studies are summarized in Tables 1 through 10.

Table 1. Results for skin cancer from epidemiologic studies of mineral oil-exposed populations[a]

Author (ref.) Year	Location	Type of study/ analysis	No. of exposed cases	RR[b]	(CI)[c] or Pvalue	Study population
Cohort-based studies						
Jarvholm et *al*[89] 1985	Sweden	SIR[d]	5	16.6	$P < 0.001$	Turners employed at bearing ring manufacturing plant between 1960 and 1980/squamous cell cancer of the skin
Jarvholm & Lavenius[54] 1987	Sweden	SIR	7	NA (0 expected)	—	Turners employed at bearing ring manufacturing plant/scrotal cancer
Population-based studies						
Roush et *al*[20] 1982	Connecticut (USA)	OR[e]	26	10.5	(4.0-36.9)	Ever employed as toolmaker, setter, set-up man, hardener, polisher, automatic screw operator, machinist, or machine operator/scrotal cancer

[a] Adapted from NIOSH, Draft Criteria for a Recommended Standard: Occupational Exposures to Metalworking Fluids, 1996.[7] Only studies of incident cancer included in this table.
[b] RR = estimated relative risk.
[c] CI = 95% confidence interval.
[d] SIR = standardized incidence ratio.
[e] OR = odds ratio.

Table 2. Results for esophageal cancer from epidemiologic studies of mineral oil-exposed populations[a]

Author (ref.) Year	Location	Type of study/ analysis	No. of exposed cases	RR[b]	(CI)[c]	Study population
Cohort-based studies						
Tolbert et al[43] 1992	Michigan (USA)	SMR[d]	22	1.2	(0.7-1.8)	Autoworkers ever exposed to straight oils, White
			35	1.0	(0.7-1.4)	Autoworkers ever exposed to soluble oils, White
			8	1.0	(0.4-1.9)	Autoworkers ever exposed to synthetic oils, White
			5	0.8	(0.2-1.8)	Autoworkers ever exposed to straight oils, Black
			10	0.7	(0.3-1.3)	Autoworkers ever exposed to soluble oils, Black
		RR	8	1.3	(0.5-3.0)	Autoworkers exposed to straight oils > 7.5 yrs
			9	1.0	(0.4-2.4)	Autoworkers exposed to soluble oils > 20 yrs
			8	1.4	(0.6-3.5)	Autoworkers exposed to synthetic fluids > 8 yrs
Eisen et al[42] 1992	Michigan (USA)	SMR	6	1.4	(0.5-3.0)	Autoworkers, Plant III, White
Sullivan et al[45,e] submitted	Michigan (USA)	OR[f]	8	3.8	(1.1-13.2)	Autoworkers ever exposed to grinding with synthetic fluids, 20-yr lag
			9	2.5	(0.8-7.2)	Autoworkers exposed to grinding with soluble fluids > 12.2 mg/m^3-yrs, 20-yr lag
			6	0.9	(0.3-2.8)	Autoworkers exposed to straight fluids > 2.5 mg/m^3-yrs, 20-yr lag
Delzell et al[57] 1993	Michigan & Ohio (USA)	SMR	82	1.0	(0.8-1.2)	Automotive manufacturing workers, White
			41	0.5	(0.4-0.7)	Automotive manufacturing workers, Black
Population-based studies						
Silverstein et al[59] 1988	Connecticut (USA)	PMR[g]	13	1.8	(1.1-3.1)	Ball bearing manufacturing workers, White
Park et al[90] 1988	Connecticut (USA)	PMR	6	1.9	(0.7-4.0)	Ball bearing manufacturing workers, White
Lloyd et al[6] 1977	USA		5	1.7	NS	Newspaper pressmen

[a] Adapted from NIOSH, Draft Criteria for a Recommended Standard: Occupational Exposures to Metalworking Fluids, 1996.[7]
[b] RR = estimated relative risk.
[c] CI = 95% confidence interval.
[d] SMR = standardized mortality ratio.
[e] Nested case-control analysis of populations studied in Tolbert et al[43] and Eisen et al.[42]
[f] OR = odds ratio.
[g] PMR = proportional mortality ratio.

Metalworkers

The most comprehensive cohort study of machining fluid-exposed workers was a study of approximately 40,000 employees who worked at least three years between 1940 and 1984 at one of three plants in Michigan (US) manufacturing automotive transmission, axle, or chassis components.[42,43] An extensive exposure reconstruction was undertaken, and each subject's exposure to the three types of fluids (in mg/m^3-yrs) as well as various components and contaminants of the fluids (in years) was estimated.* Analysis proceeded from a standardized mortality analysis, using the US population as referent, to an internal analysis using Poisson regression, to nested case-control analyses for specific cancers of interest.

The major positive findings in this study are related to digestive cancers and larynx cancer. For esophageal cancer, statistically significant excesses of two- to fourfold were observed among grinders relative to workers who had never worked in grinding, but a dose-response trend was not evident.[44] This relationship persisted in a case-control

Table 3. Results for stomach cancer from epidemiologic studies of mineral oil-exposed populations[a]

Author (ref.) Year	Location	Type of study/ analysis	No. of exposed cases	RR[b]	(CI)[c]	Study population
Cohort-based studies						
Tolbert *et al*[43] 1992	Michigan (USA)	SMR[d]	49	1.1	(0.8-1.5)	Autoworkers ever exposed to straight oils, White
			99	1.2	(1.0-1.5)	Autoworkers ever exposed to soluble oils, White
			21	1.3	(0.8-2.0)	Autoworkers ever exposed to synthetic oils, White
			9	1.1	(0.5-2.0)	Autoworkers ever exposed to straight oils, Black
			17	1.0	(0.6-1.6)	Autoworkers ever exposed to soluble oils, Black
		RR	25	1.2	(0.7-2.0)	Autoworkers exposed to straight oils > 7.5 yrs
			28	1.2	(0.7-2.1)	Autoworkers exposed to soluble oils > 20 yrs
			10	0.8	(0.4-1.7)	Autoworkers exposed to synthetic fluids > 8 yrs
Rotimi *et al*[56] 1993	Ohio (USA)	SMR	15	2.5	(1.4-4.2)	Engine plant workers, White
Decouflé[51] 1978	Michigan (USA)	SMR	17	1.3	NS	Ball bearing manufacturing workers, White
			11	1.7	NS	5 or more yrs of heavy exposure to oil mist, White
Park *et al*[58] 1994	Ohio (USA)		6	4.4	(1.6-9.6)	Automotive stamping plant
Jarvholm & Lavenius[54] 1987	Sweden	SIR[e]	8	1.1	(0.5-2.1)	Grinders and turners at bearing ring manufacturing plant
Delzell *et al*[57] 1993	Michigan & Ohio (USA)	SMR	123	1.1	(0.9-1.4)	Automotive manufacturing workers, White
		SMR	51	0.9	(0.6-1.1)	Automotive manufacturing workers, Black
Leon *et al*[9] 1994	England (UK)	SMR	10	0.7	(0.3-1.3)	Unskilled rotary press operators
Proportional mortality studies						
Silverstein *et al*[59] 1988	Connecticut (USA)	PMR[f]	36	2.0	(1.4-2.7)	Ball bearing manufacturing workers, White
			13	3.4	$P < 0.001$	Employed in grinding 10 or more yrs
Park *et al*[90] 1988	Connecticut (USA)	PMR	11	2.0	(1.1-3.5)	Ball bearing manufacturing workers, White
		MOR[g]	8	6.2	$P = 0.05$	Nested case-control study – those workers ever exposed to soluble oils
Mallin *et al*[91] 1986	Illinois (USA)	SIR	6	1.9	NS	Diesel engine and equipment manufacturing workers, White
Lloyd *et al*[64] 1977	USA	PMR	11	1.6	NS	Newspaper pressmen
Case-control studies/population-based studies						
Kneller *et al*[21] 1990	China	SIR	191	1.4	$P < 0.01$	Metal grinders, polishers, tool sharpeners, machine-tool operators
		SIR	193	1.1	NS	Toolmakers, metal patternmakers, metal workers
Chow *et al*[23] 1994	Sweden		376	1.1	NS	Toolmakers and machinists
			230	1.0	NS	Printers
Siemiatycki *et al*[22] 1987	Montreal, Canada	OR[h]	24	1.1	90% CI: (0.8-1.4)	Ever exposed to cutting oils

[a] Adapted from NIOSH, Draft Criteria for a Recommended Standard: Occupational Exposures to Metalworking Fluids, 1996.'
[b] RR =estimated relative risk.
[c] CI = 95% confidence interval.
[d] SMR = standardized mortality ratio.
[e] SIR = standardized incidence ratio.
[f] PMR = proportional mortality ratio.
[g] MOR = mortality odds ratio.
[h] OR =odds ratio.

Table 4. Results for colon cancer from epidemiologic studies of mineral oil-exposed populations[a]

Author (ref.) Year	Location	Type of study/ analysis	No. of exposed cases	RR[b]	(CI)[c]	Study population
Cohort-based studies						
Tolbert *et al*[43] 1992	Michigan (USA)	SMR[d]	59	0.8	(0.6-1.0)	Autoworkers ever exposed to straight oils, White
			116	0.9	(0.7-1.0)	Autoworkers ever exposed to soluble oils, White
			26	0.8	(0.5-1.2)	Autoworkers ever exposed to synthetic oils, White
			8	0.6	(0.2-1.1)	Autoworkers ever exposed to soluble oils, Black
		RR	24	0.9	(0.6-1.5)	Autoworkers exposed to straight oils > 7.5 yrs
			32	0.9	(0.4-1.9)	Autoworkers exposed to soluble oils > 20 yrs
			11	1.6	(0.8-3.4)	Autoworkers exposed to synthetic fluids > 8 yrs
Eisen *et al*[42] 1992	Michigan (USA)	SMR	22	1.5	(0.9-2.2)	Autoworkers, Plant III, White
Decouflé[51] 1978	Michigan (USA)	SMR	17	1.3	NS	Workers at metal machining plant w/5+yrs exposure to oil mist, White
			7	1.1	NS	5 or more yrs of heavy exposure to oil mist, White
Leon *et al*[9] 1994	England (UK)	SMR	12	1.6	(0.8-2.8)	Unskilled rotary press operators
Paganini-Hill *et al*[63] 1980	Los Angeles, CA (USA)	SMR	8	0.9	NS	Newspaper pressmen (includes rectal cancer)
Proportional mortality studies						
Silverstein et *al*[59] 1988	Connecticut (USA)	PMR[f]	41	1.4	(1.0-1.9)	Ball bearing manufacturing workers, White
			13	1.9	$P = 0.02$	Employed in grinding 10 or more yrs
Park *et al*[90] 1988	Connecticut (USA)	PMR	15	1.2	(0.7-1.9)	Ball bearing manufacturing workers, White
Vena *et al*[60] 1985	New York (USA)		14	1.4	NS	Engine plant workers, White
			8	1.7	NS	Employed in engine plant > 20 yrs
Mallin *et al*[91] 1986	Illinois (USA)	SIR	10	1.2	NS	Diesel engine and equipment manufacturing workers, White
Greene et *al*[92] 1979	Washington DC (USA)		42	1.4	(1.1-1.8)	US GPO workers
Lloyd *et al*[64] 1977	USA	PMR	12	1.0	NS	Newspaper pressmen
Case-control studies/population-based studies						
Siemiatycki *et al*[22] 1987	Montreal, Canada	OR[g]	32	1.0	90%CI = (0.8-1.4)	Ever exposed to cutting oils
Gerhardsson de Verdier *et al*[24] 1992	Sweden	OR	25	1.5	(0.8-2.8)	Ever exposed to cutting fluids
Brownson *et al*[93] 1989	Missouri (USA)		18	1.9	(1.0-3.3)	Printing machine operators

[a] Adapted from NIOSH, Draft Criteria for a Recommended Standard: Occupational Exposures to Metalworking Fluids, 1996.[7]
[b] RR = estimated relative risk.
[c] CI = 95% confidence interval.
[d] SMR = standardized mortality ratio.
[e] SIR = standardized incidence ratio.
[f] PMR = proportional mortality ratio.
[g] OR = odds ratio.

Table 5. Results for rectal cancer from epidemiologic studies of mineral oil-exposed populations[a]

Author (ref.) Year	Location	Type of study/ analysis	No. of exposed cases	RR[b]	(CI)[c]	Study population
Cohort-based studies						
Tolbert et *al*[43] 1992	Michigan (USA)	SMR[d]	37	1.5	(1.0-2.0)	Autoworkers ever exposed to straight oils, White
			51	1.1	(0.8-1.4)	Autoworkers ever exposed to soluble oils, White
			9	0.9	(0.4-1.7)	Autoworkers ever exposed to synthetic oils, White
		RR	21	3.2	(1.6-6.2)	Autoworkers exposed to straight oils > 7.5 yrs
			14	1.2	(0.5-2.6)	Autoworkers exposed to soluble oils > 20 yrs
			8	0.9	(0.4-2.0)	Autoworkers exposed to synthetic fluids > 8 yrs
Eisen et *al*[42] 1992	Michigan (USA)	SMR	7	1.7	(0.7-3.5)	Autoworkers, Plant III, White
Decouflé[51] 1978	Michigan (USA)	SMR	8	1.3	NS	Workers at metal machining plant w/5+yrs exposure to oil mist, White
Leon et *al*[9] 1994	England (UK)	SMR	9	1.5	(0.7-2.9)	Unskilled rotary press operators
Proportional mortality studies						
Silverstein et *al*[55] 1988	Connecticut (USA)	PMR[e]	14	1.4	(0.8-2.3)	Ball bearing manufacturing workers, White
Park et *al*[90] 1988	Connecticut (USA)	PMR	11	3.1	(1.5-5.5)	Ball bearing plant workers, White
			4	2.8	$P < 0.05$	Employed in engine plant > 20 years
Lloyd et *al*[64] 1977	USA	PMR	7	1.6	NS	Newspaper pressmen
Case-control studies/population-based studies						
Gerhardsson de Verdier et *al*[24] 1992	Sweden	OR[f]	25	2.0	(1.0-4.2)	Ever exposed to cutting oils
Siemiatycki et *al*[22] 1987	Montreal, Canada	OR	13	0.7	90%CI = (0.4-1.0)	Ever exposed to cutting oils

[a] Adapted from NIOSH, Draft Criteria for a Recommended Standard: Occupational Exposures to Metalworking Fluids, 1996.'
[b] RR = estimated relative risk.
[c] CI = 95% confidence interval.
[d] SMR = standardized mortality ratio.
[e] PMR = proportional mortality ratio.
[f] OR = odds ratio.

analysis nested in this cohort that controlled for other exposures, and the association was apparent for grinding with either soluble or synthetic fluids.'' An association of rectal cancer with straight oils also was observed in the cohort, with a monotonically increasing dose-response trend and a statistically significant rate ratio of 3.0 for those who had held jobs entailing straight oil exposure for more than 7.5 years.[43,46] There was a mild, nonsignificant elevation in stomach cancer risk among those who had ever worked in grinding, but no dose-response trend was observed. For pancreatic cancer, Black workers exposed to soluble oils at Plants I and II were observed to have an SMR of **1.6 (95** percent confidence interval [CI] = 1.0-2.5). In a subsequent case-control analysis of pancreatic cancer nested in the cohort,[47] an OR of 3.1 **(CI = 1.3-7.6)** was observed for those exposed to synthetic fluids in grinding operations for more than 1.4 mg/m^3-years. **A** very mild but stable association of exposure to straight oils with risk of prostate cancer was noted in the cohort analysis.'] Lastly, a twofold excess of larynx cancer mortality was observed among those exposed to straight oils.'' This finding was pursued in a case-control study nested çfthin this cohort which, unlike the nested analyses mentioned above, entailed addition of incident cases ascertained through cancer registries and collection of information on possible non-machining fluid confounding exposures (such as solvents, acid mists, and asbestos).[48] The association of straight oil exposure with larynx cancer risk persisted; a dose-response trend was noted, with a statistically significant twofold excess among those exposed to greater than 0.5 mg/m^3-years.

Most noteworthy negative findings of this cohort study were for bladder cancer and for lung cancer. With respect to bladder cancer, the study yielded no evidence of an association of bladder cancer risk with any type of machining fluid. This is of interest in light of the generally positive evidence from case-control studies, mentioned above. Regarding lung cancer, internal mortality analyses of this cohort revealed no dose-response trend for the relationship of lung cancer and straight oil exposure, and

Table 6. Results for pancreatic cancer from epidemiologic studies of mineral oil-exposed populations[a]

Author (ref.) Year	Location	Type of study/ analysis	No. of exposed cases	RR[b]	(CI)[c] or P-value	Study population
Cohort-based studies						
Tolbert *et al*[43] 1992	Michigan (USA)	SMR[d]	34	0.8	(0.6-1.1)	Autoworkers ever exposed to straight oils, White
			61	0.8	(0.6-1.0)	Autoworkers ever exposed to soluble oils, White
			19	1.0	(0.6-1.6)	Autoworkers ever exposed to synthetic oils, White
			8	1.4	(0.6-2.8)	Autoworkers ever exposed to straight oils, Black
			19	1.6	(1.O-2.5)	Autoworkers ever exposed to soluble oils, Black
		RR	15	0.9	(0.5-1.6)	Autoworkers exposed to straight oils > 7.5 yrs
			25	I.4	(0.5-3.7)	Autoworkers exposed to soluble oils > 20 yrs
			9	2.0	(0.9-4.7)	Autoworkers exposed to synthetic fluids > 8 yrs
Eisen *et al*[42] 1992	Michigan (USA)	SMR	*8*	0.9	(0.4-1.7)	Autoworkers, Plant III, White
Bardin *et al*[47,e] 1997	Michigan (USA)	OR[f]	18	0.9	(0.5-1.6)	Autoworkers, exposed to straight oils > 2.1 mg/m^3-yrs
			19	1.4	(0.7-2.7)	Autoworkers, exposed to grinding with soluble fluids
			9	3.0	(1.2-7.5)	Autoworkers, exposed to grinding with synthetic fluids > 1.4 mg/m^3-yrs
Rotimi *et al*[56] 1993	Ohio (USA)	SMR	8	0.9	(0.4-1.8)	Engine plant workers, White
			7	3.0	(1.2-6.2)	Engine plant workers, Black
Decouflé[51] 1978	Michigan (USA)	SMR	8	1.1	**NS**	Workers at metal machining plant w/5+yrs exposure to oil mist, White
			11	0.3	NS	5 or more yrs of heavy oil mist exposure, White
Leon *et al*[9] 1994	England (UK)	SMR	6	1.1	(0.4-2.5)	Unskilled rotary press operators
Paganini-Hill *et al*[63] 1980	Los Angeles, CA (USA)	SMR	5	1.3	NS	Newspaper web pressmen
Delzell *et al*[57] ?993	.Michigan & Ohio (USA)	SMR	145	0.9	(0.8-1.1)	Automotive manufacturing workers, White
		SMR	62	1.1	(0.8-1.4)	Automotive manufacturing workers, Black
Proportional mortality studies						
Silverstein *et al*[59] 1988	Connecticut (USA)	PMR[g]	24	1.4	(1.o-2.1)	Ball bearing manufacturing workers, White
		MOR[h]	9	3.1	P = 0.05	Employed in grinding 10 or more yrs
		MOR	**5**	3.7	P *c* 0.05	Employed in machinery 10 or more yrs
Park *et al*[90] 1988	Connecticut (USA)	PMR	8	1.1	(0.6-2.2)	Ball bearing plant workers, White
Vena *et al*[60] 1985	New York (USA)		11	1.9	P < 0.05	Engine plant workers, White
			7	2.3	*P* < 0.05	Employed in engine plant > 20 years
Mallin *et al*[91] 1986	Illinois (USA)	SIR	5	1.2	NS	Diesel engine and equipment manufacturing workers, White
			55	3.6	P< 0.05	Diesel engine and equipment manufacturing workers, Black
Lloyd *et al*[64] 1977	USA	PMR	9	1.2	NS	Newspaper pressmen
Case-control studies|population-based studies						
Mack and Paganini-Hill[25] 1981	Los Angeles, CA (USA)	Incidence	21	1.3	NA	Machinists, White males

[a] Adapted from NIOSH, Draft Criteria for a Recommended Standard: Occupational Exposures to Metalworking Fluids, 1996.[7]
[b] RR = estimated relative risk.
[c] CI = 95% confidence interval.
[d] SMR = standardized mortality ratio.
[e] Nested case-control analysis of populations studied in Tolbert *et al*[43] and Eisen *et al.*[42]
[f] OR = odds ratio.
[g] PMR = proportional mortality ratio.
[h] OR = mortality odds ratio.

Table 7. Results for laryngeal cancer from epidemiologic studies of mineral oil-exposed populations[a]

Author (ref.) Year	Location	Type of study/ analysis	No. of exposed cases	RR[b]	(CI)[c]	Study population
Cohort-based studies						
Tolbert *et al*[43] 1992	Michigan (USA)	SMR[d]	23	2.0	(1.3-3.0)	Autoworkers ever exposed to straight oils, White
			30	1.4	(1.o-2.0)	Autoworkers ever exposed to soluble oils, White
			8	1.6	(0.7-3.1)	Autoworkers ever exposed to synthetic oils, White
			6	1.5	(0.5-3.2)	Autoworkers ever exposed to soluble oils, Black
		RR	11	2.0	(0.9-4.8)	Autoworkers exposed to straight oils > 7.5 yrs
			6	1.2	(0.4-3.6)	Autoworkers exposed to soluble oils > 20 yrs
			6	0.6	(0.2-1.8)	Autoworkers exposed to synthetic fluids > 8 yrs
Eisen *et al*[42] 1992	Michigan (USA)	OR[e]	28	2.2	(1.3-4.0)	Autoworkers exposed to straight oil > 0.5 mg/m^3-yrs
Delzell *et al*[57] 1993	Michigan & Ohio (USA)	SMR	38	0.8	(0.6-1.1)	Automotive manufacturing workers, White
			17	0.7	(0.4-1.1)	Automotive manufacturing workers, Black
Proportional mortality studies						
Mallin *et al*[91] 1986	Illinois (USA)	PMR[f]	7	1.7	NS	Diesel engine and equipment manufacturing workers, White
Case-control studies/population-based studies						
Zagraniski *et al*[26] 1986	Connecticut (USA)	OR	22	2.5	(1.2-5.2)	Ever worked as a machinist
			17	2.1	(1.0-4.1)	Ever worked as a metal grinder
Wortley *et al*[94] 1992	Washington state (USA)	OR	NA	1.8	(0.5-6.2)	Ever employed as grinding, abrading, or buffing operator
			10	1.0	(0.5-1.9)	Ever employed in precision metal working
Haguenoer *et al*[95] 1990	France	OR	7	1.8	NS	Employed in metal work or as mechanic for at least 15 years
Brown *et al*[96] 1988	Texas (USA)	OR	5	0.5	(0.2-1.6)	Ever machinists
Ahrens *et al*[27] 1981	Germany	OR	NA	2.2	(0.9-5.3)	Ever mineral oil exposure

[a] Adapted from NIOSH, Draft Criteria for a Recommended Standard: Occupational Exposures to Metalworking Fluids, 1996.[7]
[b] RR = estimated relative risk.
[c] CI = 95% confidence interval.
[d] SMR = standardized mortality ratio.
[e] OR = odds ratio.
[f] PMR = proportional mortality ratio.

an inverse trend for both soluble and synthetic fluid exposure.[43] A nested case-control analysis of lung cancer found that only the inverse association with synthetic fluids persisted in models controlling for multiple exposure~. It has been hypothesized that endotoxins may inhibit the growth of malignant cells in the lung by stimulating macrophage activity, by inducing interferon release, by mitogen activity, or by inducing tumor necrosis factor and, thus, endotoxins commonly found in synthetic fluids are a possible basis for the observed inverse association with synthetic fluids.[49,43,50]

Among other major cohort studies of machining-fluid exposed populations is a study by Decouflé.[51] A standardized mortality analysis was conducted of a cohort of 2,485 White men who had worked for at least five years between 1938 and 1967 in jobs entailing machining fluid exposure at a large US engine manufacturing plant. Among those with 20 years of follow-up, a statistically significant twofold excess of cancers of the stomach and large intestine combined was noted, with 15 deaths cf 7.6 expected. (Presumably, results for the two sites were combined due to small numbers of cases of each disease.) Various classes of metalworking fluids were used at the facility studied and no attempt was made to distinguish the different exposures. This study did not support a positive association of machining fluid exposure with lung cancer.

Jarvholm *et al*[52] reported results of a cancer morbidity and mortality study of a cohort of 792 men with at least five years of machining fluid exposure in a Swedish bearing-ring manufacturing plant. Among grinders, a statistically significant twofold excess of digestive cancers was observed (15 *cf* 7.8 expected), after 20 years of follow-up; six stomach cancers were observed *cf* 2.6 expected. Due to the higher temperatures generated by grinding operations, soluble and synthetic fluids are typi-

Table 8. Results for lung/respiratory system cancer from epidemiologic studies of mineral oil-exposed populations[a]

Author (ref.) Year	Location	Type of study/ analysis	No. of exposed cases	RR[b]	(CI)[c]	Study population
Cohort-based studies						
Tolbert et al[43] 1992	Michigan (USA)	SMR[d]	251	1.0	(0.9-1.2)	Autoworkers ever exposed to straight oils, White
			478	1.1	(1.0-1.2)	Autoworkers ever exposed to soluble oils, White
			116	1.0	(0.8-1.2)	Autoworkers ever exposed to synthetic oils, White
			35	1.1	(0.7-1.5)	Autoworkers ever exposed to straight oils, Black
			64	0.9	(0.7-1.2)	Autoworkers ever exposed to soluble oils, Black
		RR	91	0.8	(0.6-10)	Autoworkers exposed to straight oils > 7.5 yrs
			115	0.6	(0.5-0.9)	Autoworkers exposed to soluble oils > 20 yrs
			30	0.6	(0.4-0.8)	Autoworkers exposed to synthetic fluids > 8 yrs
Eisen et al[42] 1992	Michigan (USA)	SMR	60	0.9	(0.7-12)	Autoworkers, Plant III, White
Schroeder et al[49,e] 1997	Michigan (USA)	OR[f]	88	1.0	(0.7-1.3)	Autoworkers, exposed to straight oils > 4.88 mg/m^3-yrs
			122	0.9	(0.7-1.2)	Autoworkers, exposed to grinding with soluble fluids > 15.6 mg/m^3-yrs
			28	0.5	(0.3-0.8)	Autoworkers, exposed to grinding with synthetic fluids > 1.94 mg/m^3-yrs
Rotimi et al[56] 1993	Ohio (USA)	SMR	81	1.2	(1.0-1.5)	Engine plant workers, White
			23	1.4	(0.9-2.0)	Engine plant workers, Black
Acquavella et al[55] 1993	Iowa (USA)	SMR	31	1.8	(1.2-2.6)	Exposed to cutting oils and metal dusts at metalworking plant
			25	2.5	(1.6-3.7)	First exposed to cutting oils and metal dusts between 1950-1959
Jarvholm & Lavenius[54] 1987	Sweden	SIR[g]	5	0.4	(0.1-0.9)	Grinders and turners at bearing ring plant
Park et al[58] 1994	Ohio (USA)	SMR	15	1.3	(0.7-2.2)	Automotive stamping plant
Delzell et al[57] 1993	Michigan & Ohio (USA)	SMR	1,338	1.1	(1.0-1.1)	Automotive manufacturing workers, White
		SMR	435	1.0	(0.9-1.1)	Automotive manufacturing workers, Black
Lynge et al[62] 1995	Denmark	SIR	26	2.0	(1.3-3.0)	Factory workers in newspaper and magazine production
Leon et al[9] 1994	England (UK)	SMR	94	1.8	(1.4-2.2)	Unskilled rotary press operators
Paganini-Hill et al[63] 1980	Los Angeles, CA (USA)	SMR	22	1.5	(0.9-2.2)	Newspaper pressmen
Menck & Henderson[97] 1976	Los Angeles, CA (USA)	SMR	10	2.8	NS	Pressmen
			30	1.0	NS	Newspaper printing
Proportional mortality studies						
Silverstein et al[59] 1988	Connecticut (USA)	PMR[h]	23	0.9	(0.8-1.1)	Ball bearing plant workers, White/both primary and secondary lung cancer
			13	0.6	NS	Employed in grinding 10 or more yrs
Park et al[90] 1988	Connecticut (USA)	PMR	59	1.2	(1.0-1.6)	Ball bearing plant workers, White men/both primary and secondary lung cancer
		MOR[f]	5	19.3	P = 0.008	Females ever employed in grinding
Vena et al[60] 1985	New York (USA)	PMR	48	1.3	NS	Engine plant workers, White
			29	1.4	NS	Employed in engine plant > 20 yrs
Mallin et al[91] 1986	Illinois (USA)	PMR	34	1.3	NS	Diesel engine and equipment manufacturing workers, White
			12	1.3	NS	Diesel engine and equipment manufacturing workers, Black
Lloyd et al[64] 1977	USA	PMR	41	1.1	NS	Newspaper pressmen

Continued

Table 8. *Continued*

Author (ref.) Year	Location	Type of study/ analysis	No. of exposed cases	RR[b]	(CI)[c]	Study population
Case-control studies/population-based studies						
Siemiatycki *et al*[22] 1987	Montreal, Canada	OR	23	1.5	90%CI = (1. 0-2.1)	Ever exposed to cutting oils/oat cell cancer of the lung
Jockel *et al*[29] 1992	Germany	OR	NA	2.2	(1.1-4.8)	Employed 6 months or more as a turner, grinder, driller or cutter
Coggon *et al*[28] 1984	England, UK	OR	113	1.4	(1.1-1.8)	Ever had an occupation with potential metalworking fluids exposure
			26	1.0	(0.6-1.6)	Ever had an occupation with potential high metalworking fluids exposure
			28	1.6	(0.9-2.7)	Ever had occupation with potential printing ink exposure
			9	2.0	(0.8-5.0)	Ever had occupation with potential high printing ink exposure
Malker & Gemne[98] 1987	Sweden	SIR	149	1.6	(1.3-2.9)	Workers in newspaper, journal, bookprinting enterprises

[a] Adapted from NIOSH, Draft Criteria for a Recommended Standard: Occupational Exposures to Metalworking Fluids, 1996.'
[b] RR = estimated relative risk. [c] CI = 95% confidence interval.
[d] SMR = standardized mortality ratio. [e] Nested case-control analysis of populations studied in Tolbert *et al*[43] and Eisen *et al.*[42]
[f] OR = odds ratio. [g] SIR = standardized incidence ratio.
[h] PMR = proportional mortality ratio. [i] MOR = mortality odds ratio.

cally used, not straight oils. Grinders also are exposed to abrasives, hypothesized to be co-carcinogens, potentiating the carcinogenic effect of other agents.[53] Extension of follow-up an additional seven years in a later report[54] did not strengthen the finding of an association of digestive cancer with grinding exposures. Seven scrotal cancers were noted among workers at the plant, whereas less than one was expected."

Acquavella *et al*[55] reported results of a cohort study of 3,630 employees who had worked at least six months at a metal components manufacturing facility. SMRs were generated for subgroups of the workforce categorized according to exposure to specific agents. Among workers exposed to metalworking fluids and metal dusts, the only cancer with sufficient numbers of deaths to be informative was lung cancer, for which an SMR of 1.8 (CI = 1.2-2.6) was observed. The excess of lung cancer was restricted to workers first employed between 1950 and 1959 (SMR = 2.5, CI = 1.6-3.7). No trend in risk with duration of exposure was observed.

Rotimi *et al*[56] studied 21,013 foundry and engine plant workers. For the 6,511 men employed only at the engine plant, an excess of stomach cancer was noted among Whites (SMR = 2.5, CI = 1.4-4.2), of pancreatic cancer among Blacks (SMR = 3.0, CI = 1.2-6.2), and of lung cancer in both races (SMR = 1.2, CI = 1.0-1.5). Nested case-control studies of stomach and lung cancer were undertaken subsequently and results are not yet published.

Delzell *et al*[57] reported the results of the largest standardized mortality study of automotive manufacturing workers (n = 123,232 males) to date. Hourly workers employed at an automotive facility in 1973 were followed-up through 1985. The SMR analyses are null for most cancers, with the exception of a slight excess of lung cancer in White males (SMR = 1.1, CI = 1.0-1.1). This analysis was limited to an external comparison with the US population, and no subgrouping of the workforce according to exposure to metalworking fluids was performed. Nested case-control studies are in progress.

Two proportional mortality studies of workers involved In ball bearing manufacture in Connecticut provided evidence of an association of gastrointestinal cancers with machining fluid exposure. In one of these studies,[58] analyses of 702 deaths occurring among employees who had worked for at least 10 years at a ball bearing plant yielded statistically significant excesses of stomach cancer (twofold) and rectal cancer (threefold). As in the report by Jarvholm *et al*[52] above, the stomach cancer excess appeared to be specific to exposure to water-based fluids in grinding operations. The second study[59] included 1,766 deaths among workers at another ball bearing plant. Excesses of each major digestive cancer were observed, with proportional mortality ratios for cancer of the esophagus, stomach, and large intestine statistically significant. Again, the excess of stomach cancer appeared to be specific to grinding work; there was a statistically significant threefold excess of stomach cancer among those with more than 10 years' exposure to grinding. Because an elevation of stomach cancer risk was not observed among those exposed to straight oils only, the

Table 9. Results for bladder and urinary organ cancer from epidemiologic studies of mineral oil-exposed populations[a]

Author (ref.) Year	Location	Type of study/ analysis	No. of exposed cases	RR[b]	(CI)[c]	Study population
Cohort-based studies						
Decouflé[51] 1978	Michigan (USA)	SMR[d]	6	1.2	NS	Workers at metal machining plant w/5+yrs exposure to oil mist, White
Jarvholm & Lavenius[54] 1987	Sweden	SIR[e]	7	1.0	(0.4-2.2)	Grinders and turners at bearing ring plant
Leon et al[9] 1994	England, UK	SMR	6	1.2	(0.5-2.7)	Unskilled rotary press operators
Coggon et al[28] 1984	England, UK	SMR	5	5.0	(1.0-25.8)	Men w/high exposure to printing inks
Delzell et al[57] 1993	Michigan & Ohio (USA)	SMR	63	1.0	(0.7-1.2)	Automotive manufacturing workers, White
			12	0.8	(0.4-1.4)	Automotive manufacturing workers, Black
Proportional mortality studies						
Silverstein et al[59] 1988	Connecticut (USA)	PMR[f]	14	1.3	(0.8-2.2)	Ball bearing plant workers, White
Vena et al[60] 1985	New York (USA)		7	7.3	$P < 0.05$	Based on U.S. mortality, White
Greene et al[92] 1979	USA	PMR	17	1.4	(0.9-2.2)	Men in general printing
Zoloth et al[99] 1986	USA	PMR	11	1.1	(0.6-2.0)	Men in general printing
Case-control studies/population-based studies						
Silverman et al[38] 1989	USA	OR[g]	102	1.3	(1.0-1.7)	Ever machinist 6 months or more
			51	1.4	(0.9-2.1)	Ever drill press operator 6 months or more
			26	1.1	(0.6-1.9)	Ever metal machinery workers
			37	0.8	(0.5-1.2)	Ever printers
Siemiatycki et al[22] 1987	Montreal, Canada	OR	47	1.2	90%CI= (1.0-1.6)	Ever exposed to cutting oils
Claude et al[100] 1988	Germany	OR	18	2.3	(1.0-5.6)	Ever turner
			43	0.8	(0.5-1.3)	Ever metal worker
Gonzalez et al[101] 1989	Spain	OR	21	0.8	(0.5-1.1)	Ever toolmaker 6 months or more
			NA	1.9	(1.2-2.8)	Ever machinery adjuster, assembler or mechanic 6 months or more
Steenland[102] 1987	Ohio (USA)	OR	11	2.0	NS	Ever grinding machine operator
			45	0.7	$P < 0.05$	Ever machinist
Vineis & Magnani[37] 1985	Italy	OR	16	1.5	(0.7-3.3)	Ever employed in machine tools 6 months or more
Schifflers et al[103] 1987	Belgium	OR	34	2.5	(1.3-4.7)	All metal workers
			8	2.6	(0.9-7.2)	Turners
Howe and Lindsay[104] 1980	Canada	OR	NA	2.7	(1.1-7.7)	Ever metal machinist
Coggon et al[2] 1984	England, UK	OR	52	1.3	(0.9-1.9)	Ever had an occupation with potential cutting oil exposure
			21	1.5	(0.8-2.8)	Ever had an occupation with potential high cutting oil exposure
Malker et al[98] 1987	Sweden		322	1.2	$P < 0.01$	Toolmaker or machinist in 1960
Silverman et al[36] 1983	Detroit, MI (USA)		137	1.1	(0.8-1.5)	All metal machinists
			32	1.5	(0.9-2.7)	Tool & die workers
Brownson et al[93] 1989	Missouri (USA)		7	3.1	(1.1-8.9)	Printing machine operators
Cartwright[35] 1982	England, UK		18	3.1	(1.4-6.8)	Workers exposed to ink from high-speed presses

[a] Adapted from NIOSH, Draft Criteria for a Recommended Standard: Occupational Exposures to Metalworking Fluids, 1996.[7]
[b] RR = estimated relative risk.
[c] CI = 95% confidence interval.
[d] SMR = standardized mortality ratio.
[e] SIR = standardized incidence ratio.
[f] PMR = proportional mortality ratio.
[g] OR = odds ratio.

Table 10. Results for prostate cancer from epidemiologic studies of mineral oil-exposed populations[a]

Author (ref.) Year	Location	Type of study/ analysis	No. of exposed cases	RR[b]	(CI)[c]	Study population
Cohort-based studies						
Tolbert et al[43] 1992	Michigan (USA)	SMR[d]	72	1.2	(0.9-1.5)	Autoworkers ever exposed to straight oils, White
			125	1.1	(0.9-1.3)	Autoworkers ever exposed to soluble oils, White
			26	1.1	(0.7-1.6)	Autoworkers ever exposed to synthetic oils, White
			12	1.0	(0.5-1.7)	Autoworkers ever exposed to soluble oils, Black
			23	1.0	(0.6-15)	Autoworkers ever exposed to soluble oils, Black
		RR	40	1.5	(1.0-2.3)	Autoworkers exposed to straight oils > 7.5 yrs
			54	1.0	(0.5-1.8)	Autoworkers exposed to soluble oils > 20 yrs
			8	1.6	(0.7-3.5)	Autoworkers exposed to synthetic fluids > 8 yrs
Rotimi et al[56] 1993	Ohio (USA)	SMR	8	0.9	(0.4-1.7)	Engine plant workers, White
			5	1.3	(0.4-3.0)	Engine plant workers, Black
Decouflé[51] 1978	Michigan (USA)	SMR	6	0.6	NS	Workers at metal machining plant w/5+yrs exposure to oil mist, White
Jarvholm & Lavenius[54] 1987	Sweden	SIR[e]	6	0.3	(0.1-0.7)	Grinders and turners at bearing ring plant
			NA	0.4	(0.1-0.8)	Grinders and turners, at last 20 years since onset of exposure
Delzell et al[57] 1993	Michigan & Ohio (USA)	SMR	143	1.0	(0.9-1.2)	Automotive manufacturing workers, White
		SMR	89	1.1	(0.9-1.3)	Automotive manufacturing workers, Black
Proportional mortality studies						
Silverstein et al[59] 1988	Connecticut (USA)	PMR[f]	29	1.0	(0.7-1.4)	Ball bearing plant workers, White
Park et al[90] 1988	Connecticut (USA)	PMR	10	0.9	(0.5-1.7)	Ball bearing plant workers, White
Vena et al[60] 1985	New York (USA)		7	1.1	NS	Engine plant workers, White
			7	0.7	NS	
Mallin et al[91] 1986	Illinois (USA)	SIR	10	1.5	NS	Diesel engine and equipment manufacturing workers, White
Case-control studies/population-based studies						
Siemiatycki et al[22] 1987	Montreal, Canada	OR[g]	47	1.2	90%CI = (1.0-1.6)	Ever exposed to cutting oils

[a] Adapted from NIOSH, Draft Criteria for a Recommended Standard: Occupational Exposures to Metalworking Fluids, 1996.[7]
[b] RR = estimated relative risk.
[c] CI = 95% confidence interval.
[d] SMR = standardized mortality ratio.
[e] SIR = standardized incidence ratio.
[f] PMR = proportional mortality ratio.
[g] OR = odds ratio.

excess among grinders was interpreted as implicating exposure to water-based fluids. In addition, an association of exposure to straight oils and pancreatic cancer was observed in this study. For those with 25 years' work in a straight oil-exposed job, there were three- to tenfold excesses of pancreatic cancer.

Most of the cohort and proportional mortality studies done to date were too small to detect a moderate excess of bladder cancer, other than the two large cohort studies of autoworkers,[43,57] which had stable numbers of bladder cancer deaths, and in which no association of bladder cancer with machining fluid exposure was observed. One proportional mortality study observed "an excess of bladder cancer in engine plant workers, particularly among those employed before 1950, when straight and soluble oils were used at the plant.

Printing pressmen

Because the purpose of this review is to attempt to discern carcinogenic effects of mineral oil exposure, in describing the epidemiologic literature for the printing professions studies of newspaper press operators will receive greater emphasis since this group has less heterogeneous exposures than other types of printing which have concomitant exposure to pigments containing benzidines, cadmium, and lead.

Findings from one of the largest cohort studies of printing workers undertaken to date were recently reported.[61] The study followed **9,500** men who were members of one of two printing trade unions in the Manchester (UK) area between **1949** and **1963.** One of the unions included primarily newspaper production workers, while the other comprised primarily non-newspaper printing professions. There were **3,482** deaths occurring through the end of follow-up **(1983).** Compared with the population of England and Wales, men in newspaper letterpress printing had elevated rates of lung cancer (SMR = 1.8, **CI = 1.4-2.2).** When Manchester area rates were used as the referent, the **SMR** diminished to **1.2** and was of borderline statistical significance **(CI = 1.0-1.5**). This finding was followed-up by a case-control study nested within this cohort,' which found that duration of work in newspaper machine rooms was related to lung cancer risk. This finding is unlikely to reflect confounding by smoking because it involved an internal analysis.

A cohort of **15,534** men and **3,593** women in Denmark known to be working in the printing industry based on a **1979** census was followed-up through **1987.**[62] Their cancer incidence was compared with that of individuals in the **1970** census employed in other occupations. **A** lung cancer excess was observed among male factory workers in newspaper and magazine production **(SIR** = 2.0, **CI = 1.3-3.0),** while excesses of bladder, renal, and liver cancer were noted among printers involved in other types of printing. The authors point out that many factory workers in newspaper printing in Denmark operated rotary letterpresses and conclude that their findings support the above-described findings of Leon *et al*[9] and Leon.[61]

Paganini-Hill *et al*[63] followed-up through 1978 a cohort of **1,361** newspaper web pressmen who were members of a pressmen's union for a year or more between **1949** and **1965.** Mortality was compared with the general US population rates. For most cancers, power was low. Significant excesses of renal cancer and lymphatic and hematopoietic cancers other than leukemia were noted, based on five observed cases for each disease group. The **SMR** for lung cancer was **1.5** and of borderline significance.

Lloyd et *al*[64] conducted a proportional mortality study of **2,604** deaths among members of a printing pressmen's union, categorized by commercial and newspaper printing. For newspaper pressmen, a significantly high proportional mortality ratio (PMR) due to cancer of the buccal cavity and pharynx was observed, using US rates for comparison. Slight, nonsignificant excesses of cancers of the esophagus, stomach, rectum, larynx, and lung, and of leukemia were also evident.

Laboratory/mechanistic studies

Regarding animal data, the **IARC'** review concluded that the data are inadequate to evaluate the carcinogenicity to experimental animals of formulated mineral oil products and used products since "the possible carcinogenic activity of individual products is dependent on the severity of processing of the base oils and the nature and concentration of additives and contaminants," and for used products, "the conditions of use." The **IARC** panel found sufficient evidence for carcinogenicity in experimental animals of acid-treated oils, mildly hydro-treated oils, and mildly solvent-refined oils. Data on severely hydrotreated oils were determined to be inadequate to permit evaluation of their carcinogenicity to experimental animals and no evidence was found that severely solvent-refined oils are carcinogenic to experimental animals. All of the above types of base oils have been used in mineral oil formulations such as metalworking fluids, but current formulations generally are composed of the more severely refined oils.

Known or suspected carcinogens in mineral oil formulations include: **PAHs;** long-chain aliphatics; nitrosamines; sulfur; chlorinated paraffins, naphthenics and aromatics; formaldehyde; and N-phenyl-2-naphthylamine.

PAHs

PAHs such as benz[*a*]pyrene are present to varying degrees in crude oil depending on the geographic source and removed to varying degrees by the refining process. Many **PAHs** are known carcinogens (*e.g.*, IARC'). They are thought to be largely responsible for the carcinogenicity of mineral oils. Severe solvent refining is very effective in removing **PAHs** from oil. Whereas acid-refined mineral oils have been found to be highly carcinogenic in animal tests, mildly solvent-refined oils have shown lower carcinogenic activity and severely solvent-refined oils have tested negative in most studies[3,65-68] (exception:[69]).

Generally in the **1970s,** severely solvent-refined oils replaced acid-refined oils in metalworking fluids.' In the case of metalworking fluids, **PAHs** may be reintroduced to varying degrees during the course of use as a result of pyrolytic reactions.[1,70,71] On the other hand, print press inks contain carbon black which has been shown to adsorb benz[*a*]pyrene and other **PAHs** to its surface. Mean content of benz[*a*]pyrene in a random sample of newspaper inks manufactured in England was reported to be **8.3** µg/g.[72] The bioavailability of the **PAHs** adsorbed onto carbon black is unclear, but it has been suggested that the oils in printing inks may elute the **PAHs** from the carbon black, increasing bioavailability of the carbon black **PAHs** in ink formulations.[73]

While an **IARC** expert working group concluded that there was inadequate evidence to evaluate the carcinogenicity to humans of carbon black, the panel found that there was sufficient evidence that solvent extracts of carbon black are carcinogenic to laboratory animals,

presumably due to PAHs.'

Long-chain aliphatics

There is some laboratory evidence that aliphatic hydrocarbons 12 to 14 carbons in length, common in mineral oils, are co-carcinogenic.[74,75]

Nitrosamines

The co-occurrence of nitrites or nitrates and amines in synthetic and soluble fluids can lead to the formation of nitrosamines. N-nitrosoethanolamine, detected in the water-based metalworking fluids, is a potent carcinogen.[76] In **1976,** the National Institute for Occupational Safety and Health in the US issued an alert regarding the possible health threat posed by the presence of nitrosamines in metalworking fluids." The use of nitrites in fluid formulations has decreased since that time,' although nitrosamines continue to be detected at low concentrations in formulations without added nitrites,[78,79] and high levels occasionally are found.[80,81]

Sulfur

Elemental sulfur and some sulfur compounds, commonly added to metalworking fluids, have been found to accelerate tumorigenesis in laboratory studies.[65,82]

Chlorinated paraffins, naphthenics, and aromatics

Chlorination of base oils leads to the formation of chlorinated paraffin, naphthenic and aromatic compounds, some of which have been found to be carcinogenic in animal studies (*e.g.*, National Toxicology Program"). During use, these chlorinated compounds may react to form other potentially carcinogenic chlorinated hydrocarbons, such as dioxins.

Formaldehyde

Some of the biocides used to control microbial growth in mineral oil formulations act by releasing formaldehyde. Formaldehyde is a suspect carcinogen (*e.g.*, Blair *et al* [84]).

N-phenyl-2-naphthylamine

N-phenyl-2-naphthylamine, a suspected bladder carcinogen, is listed as a component of some fluid formulations.[85,54]

Metals

Metal particles are generated in the course of metalworking and can dissolve in metalworking fluids and concentrate with use.[86] The type of metal depends, of course, on the composition of the metal being worked and the tool. These may include nickel, chromium, lead, cobalt, or molybdenum, some of which are known carcinogen~.~'

Carbon black

Carbon black, added to printing inks, is not suspect itself but has benz[*a*]pyrene and other PAHs adsorbed to its surface (see PAHs, above).

Conclusion

There is clear evidence from studies of metalworkers, cotton spinners, and jute processors that early formulations of straight mineral oils were carcinogenic to the skin. The association is strong, has been observed consistently in a large number of studies, and is biologically plausible, in part because the tumors appear on areas that have been in direct contact with the fluids.

Regarding larynx and rectal cancer, several studies have noted associations of these cancers with metalworking in general, and the largest cohort study that included an exposure assessment observed a dose-response trend for each specifically with straight oils. An association with larynx cancer has strong biological plausibility due to the similarity of the squamous epithelium of this tissue with skin and the fact that this organ is directly exposed to aerosolized droplets.

Evidence regarding lung cancer is generally negative from studies of metalworkers but positive from studies of printing pressmen. Several cohort studies, including the largest cohort study of newspaper printers, as well as one case-control study, reported a statistically significant association with printing ink. A case-control study nested in the largest cohort of printers found a duration-response trend. The primary constituent that distinguishes newspaper printing ink from metalworking fluids is carbon black, which is known to be contaminated with benz[*a*]pyrene and other PAHs, plausible etiologic agents for any association of printing ink with lung cancer.

There is suggestive evidence from several studies that workers in grinding operations may be at excess risk of cancer of the esophagus, stomach, and pancreas. Exposure-response relationships generally have not been observed in these studies. If there is indeed an association of grinding with these cancers, it may not reflect mineral oil exposures, since both soluble and synthetic fluids (which contain no mineral oil) are used in grinding. Possible suspect agents within water-based fluids include nitrosamines, detected in both types of water-based fluids and known to be carcinogenic to the stomach, and PAHs which may be higher in fluids used for grinding as a result of pyrolysis occurring at the high temperatures generated in grinding operations. Other exposures unique to grinding work, such as abrasives, also must be considered possible suspect agents.

A number of case-control studies of bladder cancer have noted a positive association with work as a machinist,

but the cohort studies to date offer little corroboration. This observation is perplexing in light of the fact that the case-control studies are likely to entail more heterogeneous exposure than the cohort studies.

There is limited evidence that metalworking fluids are associated with cancer of the colon, prostate, and sinonasal region. Neither strong internal consistency (*e.g.*, an exposure-response trend) nor consistency across studies has been observed for these cancers. It should be kept in mind, however, that given the generally unstable numbers of exposed cases in most of the studies to date, and the variability of exposure within and across work settings, inconsistency across studies would be likely to occur even if there were indeed a causal association.

Data from the US National Occupational Exposure Survey 1981-83 indicate that approximately **1.6** million American workers are exposed occupationally to mineral oils; internationally, the number exposed is many millions.[88] Thus, the potential public health impact of any carcinogenic activity of mineral oil formulations is substantial.

Whether or not mineral oil formulations in current use are carcinogenic is not known. The levels of **two** of the principal suspect carcinogens in mineral oil formulations – PAHs and nitrosamines – have been reduced over the last 20 years. Severe solvent refining of mineral oil has decreased the content of PAHs in straight and soluble oils, and the reduction in use of nitrite additives has led to less nitrosamine formation in soluble and synthetic fluids. Data are not yet available to assess possible carcinogenicity of current formulations allowing for sufficient latency. The composition of fluids in use 20 to 40 years ago, however, is relevant to cancer risk today. Thus, any health risks associated with the formulations containing higher levels of PAHs and nitrosamines will continue to be evident for some time.

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