CABLE: "UAW DETROIT"

Solidarity House

8000 EAST JEFFERSON AVE.
DETROIT, MICHIGAN 48214
PHONE (313) 926-5000

INTERNATIONAL UNION, UNITED AUTOMOBILE, AEROSPACE & AGRICULTURAL IMPLEMENT WORKERS OF AMERICA—UAW

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April 23, 1996

Ms. Diane Manning
Education and Information Division
National Institute of Occupational
Safety and Health (NIOSH)
4676 Columbia Parkway - Mail Stop C-34
Cincinnati, Ohio 45226-1998

Dear Ms. Manning:

At the risk of increasing your burden in preparing the NIOSH criteria document on metalworking fluid hazards, we are enclosing two manuscripts which recently were accepted for publication in the American Journal of Industrial Medicine (copy of acceptance letter also enclosed). One paper presents the general findings of a mortality study of engine plant workers, the other addresses a methodologic issue concerning healthy worker survival bias which arose from that study. Besides identifying a number of specific associations, the study gives some insight into the complexity and diversity of exposures in typical machining plant environments.

Sincerely,

Robert M. Park
Project Epidemiologist
Health and Safety Department
International Union, UAW

Franklin E. Mirer
Director
Health and Safety Department
International Union, UAW

RMP/mkh
opeiu494afl-cio

cc: Jim Howe
Barrie Brooks
Andrea Taylor
Lori Abrams

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THE HEALTHY WORKER SURVIVOR EFFECT AND MORTALITY AT TWO AUTOMOTIVE ENGINE MANUFACTURING PLANTS

March 21, 1996

Robert M. Park, M.S.

From the Health and Safety Department, International Union, United Auto Workers, Detroit, Michigan.

Address reprint requests to: Robert Park, Health and Safety Department, United Auto Workers, 8000 E. Jefferson Avenue, Detroit, MI 48214; telephone 313-926-5563; telefax 313-824-4473.

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Running title: Engine Plant Mortality and the Survivor Effect

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ABSTRACT

Attributes such as time-since-hire or length of followup may be important in occupational mortality due to the "healthy worker survivor effect." In a regression analysis of mortality odds ratios at two automotive engine plants, strong effects of overall employment duration (latency weighted) were observed in addition to effects for (similarly weighted) cumulative exposures. The duration effects were negative for several cancer and non cancer outcomes, and confounded exposure effects. The lung cancer odds ratio declined to 0.68 (95%CI=0.51,0.90) at the mean duration of employment. With control for employment duration, adjusted lung cancer odds ratios for work as millwrights increased from 3.0 to 3.8 and, for work in cylinder head production, from 3.3 to 3.9. Several causes of death with strong duration effects were smoking related, suggesting diminished smoking risk factors with increasing employment duration. Similarly, trends for cirrhosis of the liver mortality suggested the alcohol risk factor is smaller in long duration workers. If personal risk factors are an important component of the healthy worker survivor effect, they could be powerful negative confounders of exposure-response for related outcomes. Including a term for employment duration in regression models appears to partially correct for healthy worker survivor bias.

INTRODUCTION

In occupational mortality studies, analytical methods performing external (indirect) standardization, such as standardized mortality ratios (SMRs), suffer from non comparability of the study and reference populations: the "healthy worker effect" [McMichael et al., 1974; Fox and Collier, 1976; Monson, 1986; Park et al., 1991]. Moreover, this disparity depends on attributes such as employment duration, time-since-hire, active or inactive status, and age-at-hire [Monson, 1986; Goldblatt et al., 1991; Steenland and Stayner, 1991]. Arrighi and Hertz-Picciotto [1994] recently reviewed this "healthy worker survivor effect" in detail. Immediately following hire [Monson, 1986], or at the start of follow-up [Goldblatt et al., 1991; Delzell et al., 1993], there is a substantial deficit of mortality. However, employees terminating after short durations or prior to retirement age have elevated mortality [Delzell et al., 1993; Steenland and Stayner, 1991], implying that health problems are one important reason for early termination in typical industrial populations. Studies in some populations show that over 15-20 years of either employment duration or followup, relative mortality rises to a plateau of about 0.9. However, all these populations (rubber workers, refinery workers [Monson, 1986], and census-identified active employees [Goldblatt et al., 1991]) had potentially confounding exposures which may have obscured downward trends. A survey of 10 industrial cohorts believed to have minimal work-related mortality found downward SMR trends on duration of employment [Steenland and Stayner, 1991].

In their review of analytical options for dealing with healthy worker survivor bias, Arrighi and Hertz-Picciotto [1994] ultimately conclude, with Robins [1987; Robins et al., 1988], that it is not sufficient to control employment attributes as confounders, to lag exposures, or to restrict study populations on employment attributes. The only adequate approach appears to be Robins' rather obtuse G-null method [Robins 1987; Robins et al., 1988]. Arrighi and Hertz-Picciotto, therefore, proposed that "more straightforward but crude" methods be compared with the Robins method to determine how adequate or inadequate they are. The analysis reported here describes a method to control survivor bias using regression models of mortality odds ratios (MOR), and discusses sources of this bias. However, direct comparison to Robins' method was not feasible because sufficient work history detail and demographic information for the surviving cohort were lacking.

Modeling Mortality Odds Ratios with External Standardization

The mortality odds ratio method evaluates exposure effects by internal comparisons [Miettinen and Wang, 1981], which addresses the "healthy hire" component of the healthy worker effect [Arrighi and Hertz-Picciotto, 1994]. With logistic regression procedures, MOR analysis can accomodate variation in expected mortality odds due to employment attributes, as in the "time-since-hire" and "survivor" effects. Furthermore, MOR estimates can be standardized (indirectly), taking advantage of known age, gender and other dependencies from an external population (as do Standard-

ized Mortality Ratios) instead of having to estimate these joint covariate effects [Butler and Park, 1987; Robins and Blevin, 1987, Breslow and Day, 1987]. (This MOR method is a case-control design where controls are all deaths due to selected other causes thought not related to the exposures of interest. There are both disadvantages and advantages to using deceased referents [Gordis, 1982; McLaughlin et al., 1985a,b; Howe, 1991].)

An MOR analysis designed to investigate health effects of machining fluid and other exposures has been reported for two automotive engine manufacturing plants in the Detroit area [Park and Mirer, 1996]. For many causes of death, the engine plant analyses revealed strong and statistically significant effects for overall employment duration at the study plants in addition to specific exposure effects. This report will describe and propose an interpretation of these employment duration effects.

MATERIALS AND METHODS

The population-at-risk was all workers active any time after 1966 with two or more years service since the plants opened (in the 1950s) and with followup from 1970 through 1989. Gaps in employment at the study plants were ignored [as in Steenland and Stayner, 1991] because 1) they were unknown if less that one year in duration or prior to 1967, and 2) most employees (>80%) had no gaps greater than one year after 1966. Construction of the exposure matrix and derivation of exposure measures has been described in detail [Park and Mirer, 1996]. Indicators of ever-exposed and continuous measures of cumulative exposure were derived from work histories consisting of department locations identified annually since 1967. Departments were profiled across twenty exposure categories, several pertaining to machining fluids. In the cumulation of exposures or employment duration, latency-weighting was used to account for the biological delay from the time of exposure until an impact on mortality [Silverstein et al., 1988; Park et al., 1990,1994]. The weighting was a previously specified cumulative logistic function applied to successive 1 month intervals of time. For long latencies (used for most malignancies), the weight took the value 1.0 at times greater than 25 years prior to death, decreasing to 0.5 at 12.5 years, and approaching 0.0 prior to death. For short latency, the weight was 1.0 before 5 years prior to death, and fell below 0.5 within 2.5 years of death. Short or non latency weighted cumulative exposures were used for non malignant causes of death. Smoking history was unavailable.

The MOR method with estimation by logistic regression and external (indirect) standardization has been used in several investigations [Silverstein et al., 1988; Park et al., 1990,1994]. MOR models were fit for the entire study population (all demographic groups at both plants). Unconditional maximum likelihood estimation was performed using EGRET software [SERC, 1985]. Standardization was accomplished using an offset term for the expected mortality odds (specific to age, gender, race and year) assigned to each subject based on U.S. national rates. (Analogous approaches exist for Poisson and Cox regression analyses of follow-up data [Callas et al., 1994], however, race and gender information was unavailable for most of the surviving population-at-risk.) The regression model was as follows:

$$\ln(p/1-p) = A + \ln(r/(1-r_x)) + B*X_1 + C*X_2 + D*X_3$$

where: r = age, gender, race, year, and cause-specific expected proportional mortality rate in U.S.;

r_x = stratum-specific combined expected proportional mortality due to cause of interest and other causes excluded from controls;

X_i = cumulative exposures, employment duration or corresponding indicators (0,1);

A,B,C.. = estimated effect parameters.

Causes of death were excluded from the control group [Miettinen and Wang, 1981] (and expected odds) if they were hypothesized to be work-related or if they appeared to be exposure-related in this or other study populations [Park and Mirer, 1996]. Controls

consisted of all deaths except: cancers of the stomach, pancreas, lung, prostate, bladder and kidney, nonHodgkins lymphoma; cirrhosis of the liver, diabetes, ischemic heart disease, stroke and emphysema. Models were constructed using terms implied by prior hypotheses or suggested by preliminary descriptive analyses using proportional mortality ratios and simple tabulations across exposure strata (non hypothesized effects). Employment duration was included in all final models, with the same latency weighting as selected for cumulative exposures, because it was found to be a predictor of possibly general importance. Findings are presented as odds ratios predicted for the mean exposure (or durations) of the exposed cases. Goodness-of-fit [Hosmer and Lemeshow, 1989] was assessed for final regression models by comparing numbers of observed and predicted deaths across strata of employment duration or cumulative exposure (see Appendix).

RESULTS

Detailed findings are presented elsewhere [Park and Mirer, 1996]. The final model for lung cancer included two cumulative exposures, the employment duration term, and indicators for race, skilled trades, and Plant 2 (Table I). Although not statistically significant, the term for race was retained because it represents the stronger healthy worker effect observed for black workers in this industry [Eisen et al., 1992; Delzell et al., 1993; Beall et al., 1995]; the plant effect was retained because the plant configurations were sufficiently different to plausibly affect air quality (Plant 2 had low ceilings compared to Plant 1). Statistically significant excess lung cancer mortality was observed for work as millwrights (OR=3.8, 95%CI=1.6,9.0; at mean cum. exp. of exposed cases), and in cylinder head production (OR=3.9, 95%CI=1.4,11). With increasing employment duration, there was a significant decline in adjusted lung cancer mortality odds (OR=0.68, 95%CI=0.5,0.9; at mean latency weighted duration). For comparison purposes, models were evaluated with and without employment duration (Table II). Including employment duration increased the lung cancer odds ratio estimate for millwright exposure from 3.0 to 3.8, and for cylinder head exposure, from 3.3 to 3.9 (Table II). Analyses without excluding likely work-related causes of death from controls demonstrated the extent of confounding by other exposure associations (Table II). The resulting exposure effects varied in both directions due to associations of some of the causes included as controls with specific exposures).

In final models for other malignancies (pancreas, bladder, stomach, prostate and nonHodgkins lymphoma/multiple myeloma (NHL/MM)), employment duration effects were also negative. These effects were not statistically significant for stomach cancer or NHL/MM (only 15 deaths) but were striking for cancers of the pancreas (OR=0.52, 95%CI=0.32,0.84), bladder (OR=0.25, 95%CI=0.09,0.66) and prostate (OR=0.37, 95%CI=0.18,0.78) (Table III). Among non malignant causes of death, positive but nonsignificant trends on employment duration (non latency weighted) were observed for diabetes (OR=1.03) and stroke (OR=1.18) (Table IV). There was a modest negative trend for heart disease (OR=0.80, 95%CI=0.65,1.06), a stonger downward trend for cirrhosis of the liver (OR=0.68, 95%CI=0.4,1.15) and a dramatic downward trend for emphysema (OR=0.36, 95%CI=0.14,0.91) (Table IV).

As observed with lung cancer, effect estimates for cumulative exposure measures increased with addition of employment duration to models where the duration effect was negative. For example, the odds ratio for bladder cancer and grinding in straight oil increased from 1.6 to 3.0 (95%CI=1.15,7.8); for prostate cancer and engine assembly/test, it increased from 1.9 to 2.7 (95%CI=1.43,5.0) (Table III). The heart disease odds ratio for for work as electricians increased from 2.3 to 2.5 (95%CI=1.01,6.1), and for cirrhosis of the liver and cylinder head production it increased from 1.95 to 2.3 (95%CI=0.89,6.0) (Table IV). Some exposures were represented as ever-exposed by

indicator variables due to absence of an exposure-response, plausibly the result of misclassification of cumulative exposure, inappropriate latency weighting or non causal association. For these exposures, effect estimates varied in both directions with addition of the employment duration term, for example, in the models for pancreas cancer, NHL/MM and emphysema.

Variation in the interval between employment termination and death was examined across specific causes of death to determine if it could account for some of the employment duration effect in MOR models. Among malignancies, the smallest mean interval was for pancreas cancer, a rapidly fatal disease (mean: 57.6 mos.), and the largest was for prostate cancer (mean: 102.7 mos.) for which death occured at older ages (Table V). Surviving to normal retirement would also introduce delay between employment termination and a subsequent death. Among nonmalignant causes, cirrhosis of the liver deaths occured with the youngest mean age (53.7 yr) and smallest interval (55.9 mos.); emphysema deaths occured with the longest interval between termination and death (94.0 mos.).

DISCUSSION

The models for stomach cancer, stroke and emphysema identified substantial plant-specific effects, some of which were difficult to interpret [Park and Mirer, 1996]. Conceivably, medical restriction practices for workers with hypertension at one plant could explain some of the stroke findings but would have been unusual. The emphysema excess at Plant 2 paralleled that of lung cancer there.

The strong employment duration effects observed for most outcomes represented declining expected mortality odds with increasing duration. That is, the ratio of age-adjusted mortality rates of cases vs. controls, when compared to the national population, deviated downward with increasing duration. This suggests that selection or confounding is occuring with continuing employment that has a larger impact for some causes of death than others, a differential survivor effect. The outcomes studied here were chronic diseases as were many of the control conditions (such as colon cancer, circulatory diseases other than ischemic heart disease and stroke, neurological disorders), but controls also included acute conditions posssibly less effected by survival in employment, such as accidental deaths and infectious disease. Controlling for latency-weighted employment duration resulted in enhancement of most cumulative exposure effects, in some cases identifying statistically significant associations not otherwise apparent.

Many of the exposure-associated causes of death were smoking-related but patterns of exposure association for these causes were distinct, making smoking confounding an unlikely explanation. Odds ratios greater than 4.0 were observed with high exposures for several outcomes in analyses based on internal comparisons, excluding smoking confounding as a plausible cause.

Selection on Host Risk Factors

Almost all smoking related causes of death studied had strong, statistically significant negative duration effects (cancers of lung, pancreas and bladder, and emphysema). Heart disease had a non significant negative effect. In contrast, diabetes and stroke had non negative duration trends and stomach cancer had a weaker negative trend. This suggests that an important component of the healthy worker survivor effect may be a more rapidly diminishing prevalence of smoking-related risk factors in long duration employed or time-since-hire workers than occurs in the general population with age (smoking being a risk factor for mortality). The idea that personal risk factors play a role in healthy worker survival in employment has been proposed previously [Robins, 1987]. The negative duration effect for cirrhosis of the liver (OR=0.68) suggests an analogous selection on alcoholic risk factors (which might explain the modest, negative duration effect for stomach cancer (OR=0.72) [Gordon et al., 1984]. Evidence of employment selection for cirrhosis of the liver was observed in another study of machining fluid mortality where the strongest positive associations were in the lower cumulative expo-

sure strata of soluble oil (but not straight oil or synthetic) machining fluids [Tolbert et al., 1992]. For nonHodgkins lymphoma/multiple myeloma, the negative but uncertain duration effect may be an artifact due to small numbers of cases and absent unexposed cases in that model.

Disability Contributions to Survivor Effects

Explanation for the strong negative duration effect observed for prostate cancer is not obvious. Although smoking and drinking risk factors do not play a large role in prostate cancer [Checkoway et al., 1987], differential patterns of disability following development of disease could contribute to duration effects. The interval between employment termination and subsequent death would then depend not only on age at death (due to normal retirment at age 65) but also on disability intrinsic to the cause of death. Prostate cancer death occured with a mean age of 69, four years after normal retirement and 5 to 8 yrs older than the other cancer deaths studied (Table VII). Nevertheless, the mean number of months of employment averted prior to age 65 for prostate cancer decedents was comparable to other cancers (51 months vs 57 to 76) because of the larger termination-to-death interval for that outcome (102 vs. 65 to 78 mos.). Thus a disability contribution to the duration effect for prostate cancer is plausible. The large post employment interval for emphysema (94 mos.) is also consistent with disability-mediated early termination which, together with smoking selection, would explain the dramatic duration effect observed for emphysema (OR=0.36). Respiratory diseases are highly sensitive to healthy worker selection (Park

et al., 1991].

Employment duration effects have been observed for automotive forge workers [Park and Krebs, 1992]. For lung cancer, the effect (at the mean latency weighted employment duration of the engine plant workers) was 0.77 in the forge, vs. 0.68 in this study. For stroke, the duration trend was weakly positive as in this study, but for diabetes, there was a negative duration effect in the forge population, unlike this study. (The causes of death excluded from controls differed in the forge study.)

There was no reason a priori to expect that latency-weighted employment duration was an appropriately specified variable for addressing survival effects in regression models; this weighting was derived for hypothesized biological exposure effects. However, applying this weighting to employment duration had the attractive feature that, under the null hypothesis, it would preempt biased associations for similarly weighted cumulative exposures. Actually, the fit of the models for employment durations was quite good, notwithstanding some suggestion of over-prediction in the low duration strata for lung cancer (see Appendix).

In the MOR design, where case vs. control death odds are compared on an adjusted basis to expected odds from an external population, systematic non causal exposure differences between cases and controls should be largely eliminated by control for employment duration characteristics. The concern of Flanders et al. [1993] over bias arising from the initially stronger healthy

worker effect at hire does not apply in this study because almost all decedents were hired more than 10 years prior to the start of follow-up (1970) and because, in the MOR design, comparisons are not made to surviving populations. Also, the Flanders simulation assumed a starting population of zero, a constant number of new hires each year, and random exposure reassignments, all inapplicable in this study population (and most others).

The proposed approach does not explicitly treat employment status as an intermediate variable as described by Robins [1987; Robins et al., 1988]. However, if cases of disease caused by exposure have the same disability natural history as the other observed cases, control for employment duration could largely dispose of this intermediate variable problem. Control for employment status has been proposed by Steenland and Stayner [1991] but resisted by others [Arrighi and Hertz-Picciotto, 1994]. Besides theoretical objections, inherent ambiguity of employment status immediately prior to death in this study (active employment cannot be distinguished from medical leave or recent termination) make this approach infeasible.

If a disease preferentially caused exposure termination but not necessarily employment termination, then exposure status would be an intermediate variable in this analysis. This might occur, for example, if persons with the disease were less able to tolerate the exposures on irritancy grounds. The result, however, would be underestimation or reversal of the exposure-response estimate.

When controlling for employment duration in follow-up studies that have detailed work histories, it has been shown that gaps in employmemnt can generate artifactual survivor bias and exposure-response [Robins, 1987]. In this, non follow-up study, gaps in employment at the study plants were ignored, and cause of death was analyzed in relation to total employment history in the study plants. Therefore, the observed duration trends represent real survivor effects (differential with respect to cases and controls). Furthermore, the nature of production was such that major lay-offs or discontinuations of product lines affected all process areas, i.e. all exposures. Thus employment changes did not differentially impact exposure groups which, otherwise, could generate bias in this analysis.

Although the origins of healthy worker survivor bias are complex and probably not generally accessible in a study population, this study offers empirical support for a relatively straight forward method for addressing survivor bias. Validation with the method of Robins [1987] is needed.

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Table I Engine Plant Mortality: Adjusted Mortality Odds Ratios (OR) for Lung Cancer, Final Model[a]

Predictor[b]	n[c]	Effect	(SD)	OR[d]	95% CI	p[e]
Constant		.43680	(.20800)	1.55	1.03-2.33	.036
Empl. Duration	175	-.00382	(.00143)	.68	.51-.90	.008
Ind:Black Men	54	-.32630	(.19400)	.72	.49-1.06	.092
Ind:Plant 2	122	.36880	(.20300)	1.45	.97-2.15	.070
Ind:Skilled Trades	28	-.67220	(.27300)	.51	.30-.87	.014
Millwright/Welder	10	.00234	(.00078)	3.78	1.59-8.99	.003
Cylinder Heads	8	.00271	(.00106)	3.92	1.38-11.2	.010

a Selected causes of death excluded from Controls if judged to be potentially work-related in this population.

b Long latency weighted cumulative exposures (level*months); long latency weighted durations (months); Ind, indicator variable (0,1): Black Men=1, Plant 2=1, Skilled Trades=1.

c No. of lung cancer deaths with duration/predictor/exposure.

d Predicted odds ratio for mean cumulative exposures and employment duration among exposed lung cancer cases.

e Two-sided P-value and 95% confidence interval based on SD of assumed Gaussian effect estimate.

Table II Engine Plant Mortality: Adjusted Lung Cancer Mortality Odds Ratios (OR) Comparing Final Model and Models without Employment Duration or Exclusion of Selected Controls

		without Employment Duration			Final Model[a]			without Exclusions from Controls		
	n	OR	95% CI	p[b]	OR	95% CI	p	OR	95% CI	p
Empl. Duration	175		-		.68	.51-.90	.008	.76	.58-1.00	.046
Ind: Plant 2	127	1.21	.83-1.77	.320	1.45	.97-2.15	.070	1.50	1.03-2.18	.033
Millwright/Welder	10	2.95	1.27-6.87	.012	3.78	1.59-8.99	.003	4.53	2.04-10.1	<.001
Cylinder Heads	8	3.25	1.15-9.17	.026	3.92	1.38-11.2	.010	2.12	.99-4.55	.054

a Only selected terms from models displayed (for full final model, see Table I); Ind: - indicator variable (0,1): Plant 2=1.

b 95% Confidence Interval, P-value calculated assuming Gaussian variance of effect estimate.

Table III Engine Plant Mortality: Selected Adjusted Odds Ratios (OR) for Cancer Outcomes Comparing Final Models and Models without Employment Duration

		Final Model[a] without Employment Duration			Final Model		
	n	OR	95% CI	p[b]	OR	95% CI	p
Pancreas Cancer[c]							
Empl. Duration	28		-		.52	.32-.84	.008
Ind: Inspection	10	5.75	2.27-14.5	<.001	6.42	2.50-16.5	<.001
Ind: Machining (Str Oil)	4	2.92	.87-9.85	.084	3.61	1.04-12.6	.043
Ind: Skilled Trades	10	2.94	1.15-7.53	.024	2.86	1.10-7.45	.031
Bladder Cancer[c]							
Empl. Duration	16		-		.25	.09-.66	.005
Grinding: Straight Oil	7	1.57	.74-3.34	.237	2.99	1.15-7.77	.025
Machining/Heat Treat	4	1.79	.81-3.94	.149	2.86	1.14-7.18	.025
Stomach Cancer[c]							
Empl. Duration	24		-		.72	.34-1.53	.394
Cam-/Crankshaft (Plant 1)	3	4.83	1.50-15.6	.008	5.13	1.56-16.9	.007
Ind: Engine Blocks	4	2.26	.72-7.10	.161	2.32	.74-7.31	.150

continued

Table III, continued (page 2)

		Final Model[a] without Employment Duration			Final Model		
	n	OR	95% CI	p[b]	OR	95% CI	p
Prostate Cancer[c]							
Empl. Duration	36		-		.37	.18-.78	.009
Engine Assembly/Test	15	1.88	1.12-3.16	.017	2.67	1.43-4.96	.002
Tool Grinding	4	2.95	1.02-8.55	.047	4.52	1.43-14.3	.010
Pistons	3	3.27	.93-11.5	.065	4.51	1.22-16.6	.024
NonHodgkins Lymphoma/Multiple Myeloma[c]							
Empl. Duration	15		-		.28	.06-1.34	.111
Machining: Dry	10	2.38	1.16-4.86	.017	3.77	1.42-9.98	.008
Ind: Grinding (Sol MF)	7	3.30	.97-11.2	.056	4.12	1.10-15.4	.036
Ind: Skilled Trades	3	3.30	.66-16.6	.147	4.85	.86-27.5	.074

continued

Table III continued (page 3)

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a Selected terms displayed; for full models, see Park, Mirer [1995].

Additional terms included in final models but not shown:

Pancreas Cancer - Ind: Black Men (n=6), Ind: Tool Room (n=4).

Bladder Cancer - Prior employment duration in plants of same employer for 1) Plant 1, and 2) Plant 2 (n=4,7 resp.).

Stomach Cancer - Tool Room (n=2), Tool Grinding (n=1), Laborers/non skilled maintenance (n=2).

Prostate Cancer - Ind: Black Men (n=9), Ind: Inspection (n=5).

b 95% Confidence Interval, P-value calculated assuming Gaussian variance of effect estimate.

c Cumulative exposures and employment durations long latency weighted except for nonHodgkins lymphoma/multiple myeloma: short latency; Ind, indicator variable (0,1): Ever-Exposed=1, Black Men=1, Skilled Trades=1; Str, Straight Oil machining fluids (MF); Sol, Soluble MF.

Table IV Engine Plant Mortality: Selected Adjusted Odds Ratios (OR) for Nonmalignant Disease Outcomes Comparing Final Models and Models without Employment Duration

		Final Model[a] without Employment Duration			Final Model		
	n	OR	95% CI	p[b]	OR	95% CI	p
Diabetes (ICD-8:250)[c]							
Empl. Duration	33		-		1.03	.45-2.36	.937
Ind: Machining (Str Oil)	7	6.78	1.79-25.7	.005	6.86	1.75-26.9	.006
Machining (Str Oil)	7	.49	.19-1.29	.147	.49	.18-1.31	.155
Heart Disease (ICD-8: 410-414)[c]							
Empl. Duration	518		-		.80	.61-1.06	.125
Ind: ICD-9 Epoch	310	.69	.54-.89	.004	.73	.56-.94	.015
Grinding: Sol MF	178	1.20	.97-1.48	.093	1.25	1.01-1.56	.044
Ind: Tool Grinding	25	4.40	.89-21.6	.069	3.87	.78-19.1	.097
Tool Grinding	25	.44	.11-1.69	.231	.49	.13-1.93	.309
Electricians	16	2.33	.95-5.74	.065	2.49	1.01-6.09	.047

continued

Table IV continued (page 2)

		Final Model[a] without Employment Duration			Final Model		
	n	OR	95% CI	p[b]	OR	95% CI	p
Stroke (ICD-8:430-438)[c]							
Empl. Duration	114		-		1.18	.71-1.95	.519
Ind: Plant 2	78	.78	.40-1.50	.449	.73	.37-1.45	.368
Ind: Combustion Products	56	.44	.19-1.05	.064	.44	.18-1.03	.060
Ind: Comb.Prod. (Plant 2)	47	4.31	1.60-11.7	.004	4.40	1.62-11.9	.004
Ind: Grinding (Sol MF)	39	.75	.44-1.28	.291	.75	.44-1.28	.294
Ind: Grind(Sol) (Plant 1)	15	6.28	1.72-22.9	.005	6.65	1.80-24.5	.004
Grind(Sol) (Plant 1)	15	.43	.18-1.06	.067	.42	.17-1.02	.056
Emphysema[c]							
Empl. Duration	26		-		.36	.14-.91	.031
Ind: Plant 2	16	1.48	.39-5.60	.566	2.09	.53-8.19	.290
Ind: Combustion Products	14	4.24	1.02-17.6	.046	4.20	1.01-17.4	.048
Ind: Comb.Prod. (Plant 2)	7	.29	.05-1.61	.157	.28	.05-1.57	.146

continued

Table IV continued (page 3)

	n	Final Model[a] without Employment Duration OR	95% CI	p[b]	Final Model OR	95% CI	p
Cirrhosis of the Liver[c]							
Empl. Duration	68		-		.68	.40-1.15	.152
Ind: Laborers/Non Skill.	10	3.14	1.45-6.80	.004	3.63	1.62-8.11	.002
Cylinder Heads	4	1.95	.78-4.89	.156	2.30	.89-5.96	.087
Combustion Products	36	1.29	.95-1.77	.106	1.40	1.00-1.97	.051

a Selected terms displayed; for full models, see Park, Mirer [1995].

Additional terms included in final models but not shown:

Diabetes - Ind: Black men (n=8), Pipefitters (Plant 1) (n=2).

Heart Disease - Ind: Black men (n=121), Ind: Skilled Trades (n=108)

Stroke - Ind: Black men (n=46), Ind: Skilled Trades (n=11)

Emphysema - Ind: Skilled Trades (n=3).

Cirrhosis of liver - Ind: Black men (n=26), Ind: Skilled Trades (n=38).

b 95% Confidence Interval, P-value calculated assuming Gaussian variance of effect estimate.

c Cumulative exposures and employment durations non latency weighted except for heart disease: short latency; Ind, indicator variable (0,1): Ever-exposed=1, Black Men=1, Plant 1 or 2=1, Skilled Trades=1; ICD-9 Epoch (year of death 1978 or later)=1; Str, Straight Oil machining fluids (MF); Sol, soluble MF; Comb. Prod., Combustion Products.

Table V Engine Plant Mortality: Interval between Employment Termination and Subsequent Death, by Causes of Death

	No. Deaths	Mean Age at Death (Yrs)	Mean Interval (Mos)
Malignant Causes			
Stomach	24	63.1	76.1
Pancreas	28	60.8	57.6
Lung	175	62.8	71.4
Prostate	36	69.3	102.7
Bladder	16	64.3	78.1
Kidney	14	61.4	65.2
NHL/MM	15	62.8	72.8
Nonmalignant Causes			
Diabetes	33	61.9	86.1
Heart Dis.	518	63.9	79.4
Stroke	114	64.6	91.5
Emphysema	26	64.6	94.0
Cirrhosis of Liver	68	53.7	55.9

Appendix Goodness-of-Fit for Employment Duration and Cumulative Exposures in Final Models of Mortality Odds using Logistic Regression

The goodness-of-fit for the final lung cancer model [Hosmer and Lemeshow, 1989] was good, both for the employment duration term (X_5^2=2.7, p=0.75) (Table A.I) and the two cumulative exposures although for the latter, small numbers prevented a statistical test (Table A.II). The fit for the employment duration predictors of pancreas and prostate cancers appeared adequate and was quite good for diabetes, heart disease (X_5^2=1.06, p=0.96) and cirrhosis of the liver (X_4^2=1.54, p=0.82) (Table A.I). (Duration fit was not examined for other outcomes). Goodness-of-fit for major exposure findings based on continuous exposures also appeared sufficient, although small numbers again limited this assessment (Table A.II).

Table A.I Engine Plant Mortality: Goodness of Fit for Employment Duration in Logistic Regression Models

	Latency Weighted Employment Duration Strata[a]						
	0-14	15-29	30-59	60-119	120-239	240+	All
Lung Cancer (Long Latency) (X_5^2=2.66, p=.75)							
Obs[b]	12	9	29	64	56	5	175
Pred	15.74	13.16	25.48	53.98	61.76	4.79	174.92
Pancreas Cancer (Long Latency)							
Obs	5	6	3	8	5	1	28
Pred	4.39	4.08	4.60	8.41	6.26	.25	27.99
Prostate Cancer (Long Latency)							
Obs	2	1	3	17	12	1	36
Pred	2.32	2.20	4.02	10.84	16.04	.59	36.02
	0-29	30-59	60-119	120-179	180-239	240+	All
Diabetes (Non Latency Weighted)							
Obs	0	2	7	11	7	6	33
Pred	.41	2.82	4.58	10.71	8.60	5.90	33.02

continued

Table A.I continued (page 2)

	0-29	30-59	60-119	120-179	180-239	240+	All
Heart Disease (Short Latency) (X_5^2=1.06, p=.96)							
Obs	8	39	92	167	149	63	518
Pred	10.29	38.56	86.28	174.64	140.64	67.64	518.06
Cirrhosis of the Liver (Non Latency Weighted) (X_4^2=1.54, p=.82)[c]							
Obs	1	7	15	15	22	8	68
Pred	1.75	9.76	12.90	16.20	17.56	9.89	68.07

a Cumulative durations in latency-weighted months.

b Obs, Observed no. of deaths; Pred, Predicted no. of deaths

c Strata with < 5 expected collapsed for chi-squared test.

Table A.II Engine Plant Mortality: Goodness of Fit for Selected Cumulative Exposures in Logistic Regression Models

	Latency Weighted Cumulative Exposure Strata[a]							
	0	1-25	26-50	51-100	101-	201-	401-	801+
Lung Cancer and Millwrights/Welders (Long Latency)								
Obs[b]	165	1	0	0	1	2	2	4
Pred	163.66	1.12	0.25	0.39	1.14	1.80	3.48	3.08
Lung Cancer and Cylinder Head Production (Long Latency)								
Obs	167	0	0	0	1	3	3	1
Pred	163.14	1.44	0.54	1.26	2.62	1.93	2.74	1.26
Bladder Cancer and Grinding: Straight Oil (Long Latency)								
Obs	9	1	1	0	1	0	2	2
Pred	8.72	0.59	0.41	0.48	1.15	1.58	1.85	1.22
Stomach Cancer and Camshaft/Crankshaft (Long Latency)								
Obs	19	0	0	0	0	3	1	1
Pred	17.66	0.56	0.22	0.30	0.94	2.30	1.47	0.53
Prostate Cancer and Engine Assembly/Testing (Long Latency)								
Obs	21	0	0	1	2	2	5	5
Pred	21.73	0.54	0.23	0.69	1.13	2.44	2.72	6.53

(continued)

Table A.II continued (page 2)

	Exposure Strata[a]							
	0	1-50	51-100	101-	201-	401-	801-	1600+
Diabetes and Machining: Straight Oil (Non Latency Weighted)								
Obs	26	0	0	1	1	3	2	0
Pred	26.02	0.16	0.29	1.08	1.87	2.02	1.32	0.26
Heart Disease and Grinding: Sol. MF (Short Latency) (X_5^2=1.21, p=.94)[c]								
Obs	340	1	3	8	16	36	80	34
Pred	342.79	1.33	2.92	4.75	14.72	38.94	76.35	37.07
Stroke and Grinding: Sol. MF (Non Weighted) (X_4^2=.71, p=.95)[c]								
Obs	75	1	0	2	6	12	14	4
Pred	74.91	0.71	0.45	1.95	5.55	11.11	12.85	6.54
Cirrhosis of the Liver: Combustion Products (Non Weighted) (X_5^2=2.33, p=.80)[c]								
Obs	32	2	1	4	13	6	4	6
Pred	30.73	1.87	3.09	5.09	9.16	7.29	6.49	4.36

a Cumulative exposure in latency-weighted exposure-months.

b Obs, Observed no. of deaths; Pred, Predicted no. of deaths

c Strata with < 5 expected collapsed for chi-squared test.

Attachment B

A SURVEY OF MORTALITY AT TWO AUTOMOTIVE ENGINE MANUFACTURING PLANTS

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Robert M. Park, M.S.
Franklin E. Mirer, Ph.D

From the Health and Safety Department, International Union, United Auto Workers, Detroit, Michigan.

Address reprint requests to: Robert Park, Health and Safety Department, United Auto Workers, 8000 E. Jefferson Avenue, Detroit, MI 48214; telephone: 313-926-5563; telefax: 313-824-4473.

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Key Words: chlorinated oils, combustion products, diabetes, lung cancer, machining fluids, mortality odds ratio, nitrosamines, pancreas cancer, stomach cancer.

ABSTRACT

Mortality at two engine plants was analyzed using proportional mortality ratios and logistic regression models of mortality odds ratios to expand previous observations of increased cancers of the stomach, pancreas and bladder, and cirrhosis of the liver among workers exposed to machining fluids. Causes of death and work histories were available for 1870 decedents. There was a significant excess of deaths coded as diabetes for white men in both plants (PMR=25/16.7=1.5, 95% CI=1.02,2.20), and a deficit of respiratory diseases. Black men had fewer than expected diabetes deaths and more emphysema deaths. Elevated PMRs for cancers of the stomach, pancreas, prostate, bladder and kidney were not statistically significant in plant-wide populations. However, stomach cancer mortality increased with duration in camshaft and crankshaft production at Plant 1 (OR=5.1, 95% CI=1.6,17; at mean duration of cases), and among tool room workers (OR=6.3, 95% CI=1.3,31), but these results were based on 5 cases. Nitrosamines were probably present in camshaft and crankshaft grinding at Plant 1. Pancreas cancer risk increased among workers at both plants ever employed in inspection (OR=6.4, 95% CI=2.5,16), in machining with straight oil (OR=3.6, 95% CI=1.04,12) or in skilled trades (OR=2.9, 95% CI=1.1,7.5). Lung cancer increased in cylinder head machining (OR=3.9, 95% CI=1.4,11), millwright work (OR=3.8, 95% CI=1.6,9.0), and in Plant 2 generally (OR=1.45, 95% CI= 0.97,2.2). Potential lung carcinogens included heat treatment emissions, chlorinated oils, and coal tar fumes (millwrights). Bladder cancer increased with duration among workers grinding in straight oil MF (OR=3.0, 95% CI=1.15,7.8) and in machining/heat treat operations (OR=2.9, 95% CI=1.14,7.2).

INTRODUCTION

Following reports from engine and other automotive machining plants associating increased mortality with exposure to machining fluids (MF), two Detroit area engine plants were selected for study. Operations consisted of rough machining of castings or forgings, followed by precision machining and grinding. Some steps were performed dry (e.g. broaching and milling cast iron) but most used soluble oils and, to a lesser extent, straight oils and synthetics. Other processes included heat treatment, usually with induction heating, assembly, painting, engine testing and repair.

Previous Studies

Elevated stomach cancer has been observed in several studies among MF-exposed workers [Decoufle, 1978; Jarvholm et al., 1981; Park et al., 1988; Silverstein et al., 1988; Rotimi et al. 1993] and pancreas cancer excesses have been found in a variety of metalworking plants [Vena et al., 1985; Mallin et al., 1986; Silverstein et al., 1988; Rotimi et al., 1993; Acquavella et al., 1993; Park et al., 1994]. Among engine plant workers, Vena et al. [1985] reported excess lung cancer and Rotimi et al. [1993] observed increasing lung cancer risk with employment duration ($p=0.008$). Lung cancer was elevated in bearing plant forge and heat treat departments combined [Park et al., 1988; Silverstein et al., 1988] and in stamping plants [Silverstein et al., 1985a; Park et al., 1994]. NonHodgkins lymphoma (NHL) was elevated in an engine plant [Mallin et al., 1986] and bearing plant [Silverstein et al., 1988]. A case-control study identified excess bladder cancer among automotive "drill press" operators [Silverman et al., 1989a, 1989b]. Elevated risk for prostate cancer has been observed among machining plant workers [Mallin et al., 1986;

Wolfe, 1986; Tolbert et al. 1992], metal workers [van der Gulden et al., 1992], petroleum products-exposed and combustion product-exposed workers [Siemiatycki et al., 1987, 1988] and rubber preparation workers [Goldsmith et al., 1980].

Excess stroke mortality was observed in bearing plants [Park et al., 1988; Silverstein et al., 1988]. Several studies have observed excess cirrhosis of the liver and disease possibly misattributed to alcohol in MF exposed workers [Park et al., 1988; Silverstein et al., 1988; Mallin et al., 1986; Tolbert et al. 1992].

Prior Hypotheses

Previously reported associations and potential engine plant exposures were the basis for the following prior hypotheses:

1. Stomach cancer associated with MF, particularly soluble grinding fluids;
2. Pancreas cancer associated with straight oil MF;
3. Cirrhosis of the liver associated with soluble MF, particularly in grinding;
4. Lung cancer associated with millwright/maintenance welder activities, heat treat, dry machining, and engine testing;
5. Prostate cancer, bladder cancer and nonHodgkins lymphoma with MF or other plausible carcinogens in metalworking environments.

MATERIALS AND METHODS

Study Population

Plant 1 began operation in 1956, Plant 2 in 1952. Tapes provided semiannually since 1966 identified active employees in the union. Other history came from pension records, life insurance claims, and seniority lists from the mid-1960s. The study population was all those employed at least two years at the study plants, active anytime between 1966 and 1987, and dying between Jan. 1, 1970 and Dec. 31, 1989. Gaps in study plant employment occurring prior to final termination were ignored because 1) they were unknown when less that one year, or prior to 1967, and 2) most employees (>80%) had no gaps greater than one year after 1966. Deaths were identified from computerized records of the Michigan Department of Public Health (1970-1987), life insurance claims (1972-1989), and a union pension file. Ascertainment was incomplete for non Michigan decedents a) who had less than 10 years service, or b) who died prior to becoming pensioners. Fewer than 10% of deaths were estimated to be missed. Underlying cause of death in the ICD revision appropriate for year of death came from the Michigan death registry or death certificates coded by a nosologist at the National Center for Health Statistics.

Environmental Assessment

Seventy-seven industrial hygiene reports since 1954 provided approximately 200 measurements for dust, oil mist or oil smoke, generally in response to complaints. From personal and area samples, MF mist concentrations ranged up to 15 mg/m^3 but more than 75% were less than 5.0 mg/m^3; levels appeared higher before 1975. In the 1950s and '60s, oil/smoke area-samples ranged from 1.0 to 10.0 mg/m^3 in the cylinder head machining department at

Plant 1 where potential exposures included chlorinated oils and emissions from valve seat heat treatment (induction heating, oil quench). In 1954, complaints at Plant 2 were attributed to a coolant containing 10 percent chlorinated and sulfurized oil. A 1967 report from another employer documented residual chlorine or hydrogen chloride in batches of MF causing respiratory and metal corrosion problems. Half of U.S. production of chlorinated paraffins (20,000 tons) was for lubricity agents such as additives to MF [National Toxicology Program, 1986]. Straight oil used in grinding (for honing cylinders, connecting rods and crankshafts) consisted of a light petroleum fraction. Methylene chloride, a suspect pancreas carcinogen, was a component of Magnaflux penetrant used in metal defect testing (inspection). Chlorinated phenol biocides (such as Dowicide) could have been used in early soluble MFs.

The early use of synthetic or semi-synthetic MFs containing nitrites was reported to be largely limited to Plant 1 crankshaft and camshaft grinding. An area sample from 1958 near a Blanchard grinder in the cylinder head department of Plant 1 contained 0.69mg/m^3 sodium nitrite. In 1977, mist from a crankshaft washer using a nitrite/ethanolamine formulation (Alk-Ice) produced a nitrite breathing zone sample of 1 mg/m^3. A 1978 NIOSH survey for nitrosamines identified several coolant systems and a leak testing fluid with measurable nitrosamine at Plant 1 (Plant 2 was not surveyed) [Rounbehler and Fajen, 1983]. Levels of N-nitroso-diethanolamine ranged 1-4 ug/ml in used MF and 6-140 ug/ml in new, undiluted MF; undiluted leak test fluid had 4,900 ug/ml.

Engine testing produced pyrolyzed lubricants, corrosion inhibitors, coatings and paint. Carbon monoxide levels generally ranged from 25 to 100 ppm, and as high as 400 ppm, in engine testing and contiguous areas of both plants prior to 1980, suggesting the presence of other combustion products as well. Two industrial hygiene reports identified deficient ventilation in tool grinding, including occluded exhaust ducts. Total particulate 2-50 per cent of the generic dust standard (1.1-26.8 mppcf) were reported in 1963 at Plant 2.

Work and Exposure History

Workers' department assignments were available semiannually after 1966; prior to that time they were assumed to be the same as in 1966, because assignments tended to be stable. Processes and exposures were characterized from industrial hygiene records, a walkthrough of each plant, and structured group interviews with experienced personnel. Major process changes were described and departments profiled in process and exposure categories (Table I). Rankings across departments were specified for MF and combustion products based on participants' recall of relative oil mist and smoke intensity. Ranks were assigned logarithmic increments ((0),1,2,4,8) because only relative exposure levels could be estimated and exposure distributions typically are lognormal. This exposure matrix was revised after technical review by plant-level, corporate and union personnel. Cumulative exposures and employment duration were calculated as sums across months following hire, weighted to account for the delay between time of exposure and subsequent death (induction period), and ignoring gaps:

$$WCX_j = \sum_i W_L(i,D) \cdot X_j(i), \quad i=\{\text{months following original hire}\}$$

where WCX_j=latency-weighted cumulative exposure or duration

$W_L(i,D)$=latency weighting function (D = date of death)

$X_j(i)$=exposure-level rank (0,1,2,4...)or employment indicator (1 = prior to termination, 0 = after termination)

Previously specified long and short latency weightings were used in addition to unweighted measures [Silverstein et al., 1988; Park, 1996]. Some exposures were correlated because departments could be classified in more than one category, for example, the MF categories, or, engine assembly/testing and combustion products. Smoking histories were unavailable.

Analysis

Only deaths were analyzed because demographic information was incomplete for the surviving cohort. Proportional mortality ratio (PMR) and mortality odds ratio (MOR) analyses were performed with standardization using U.S. reference rates through 1985 [Monson, 1974]. PMR confidence intervals (CI) were from the Mantel-Haenszel chi-squared statistic, or the Poisson distribution when the expected number of deaths was less than 10 [Bailar and Ederer, 1964]. PMRs are presented only for men because numbers of female decedents were small. PMR analyses, however, were potentially confounded by multiple exposures, did not adequately account for latency, exposure duration, healthy worker selection or survivor bias, and underestimated effects when more than one cause of death was associated with an exposure. Mortality odds ratios [Miettinen and Wang, 1981], modeled by logistic regression for the combined gender-race groups of both plants, addressed

these issues. MOR models incorporated the expected age, gender, race and year-specific mortality odds as an offset term [Butler and Park, 1987; Robins and Blevins, 1987; Breslow and Day, 1987]. The regression model used is described in detail elsewhere [Park, 1996]. Unconditional maximum likelihood estimation was performed using EGRET software [SERC, 1985]. Causes of death were excluded from controls and expected odds if hypothesized to be work-related (cancers of the stomach, pancreas, lung, prostate, bladder and kidney, nonHodgkins lymphoma, and cirrhosis of the liver), or if they appeared to be exposure-related in this or other pertinent study populations (diabetes [Vena, 1990; Park and Krebs, 1992], heart disease [Stern et al., 1988], stroke [Park et al., 1988; Park and Krebs, 1992], and emphysema [Wong et al., 1985]. A term for overall employment duration (with the same latency weighting used for exposures) was included to adjust for healthy worker survivor bias [Arrighi and Hertz-Picciotto, 1994] arising from two sources: termination of employment due to disease, and attrition of high risk groups, such as smokers, with increasing duration of employment [Park, 1996]. The constant in the final regression models can be interpreted as the standardized mortality odds ratio predicted for "unexposed" workers whose employment duration (latency weighted)is 0 [Butler and Park, 1987]. Findings are presented as odds ratios predicted for the mean exposure (or durations) of the exposed cases.

RESULTS

Standardized Proportional Mortality Ratios (PMRs)

Out of 2158 decedents, 244 with less than 2 years of employment were excluded as were 44 others lacking cause of death (2.3%). Among the 1870 decedents available for study were 802 qualifying as controls in MOR analyses. Decedents were white men (1170, 63%), black men (613, 33%), white women (53, 3%) and black women (34, 2%). PMR analyses for white men found an excess of deaths coded as diabetes in both plants (Table II) which was significant in the combined plants (PMR=25/16.7=1.5, 95% CI=1.02,2.20) (data not shown). There was a deficit for respiratory diseases. Black men had a deficit in diabetes deaths and more than expected emphysema deaths at both plants. Excess cancers of the stomach, pancreas, prostate, bladder and kidney, were not statistically significant. Suicide was significantly increased among all men and women (data not shown). Compared to Plant 2, Plant 1 had higher PMRs among white men for cancers of the stomach and pancreas, diabetes, heart disease and cirrhosis of the liver, but lower PMRs for lung and prostate cancers (Table II). Among black men, there was a deficit of stroke deaths at Plant 1 but an excess at Plant 2, and a significant excess of deaths coded as drug abuse at Plant 1 (PMR=13/5.0=2.61, 95% CI=1.39,4.46).

Mortality Odds Ratios

Stomach Cancer

Logistic regression identified increased stomach cancer risk with duration in camshaft/crankshaft production only at Plant 1 (OR=5.1, 95% CI=1.6,17 (at mean cumulative exposure of exposed cases); based on three deaths), and with tool room work at both plants (OR=6.3, 95% CI=1.5,19.6; based on two deaths) (Table

III). Adding a term for camshaft/crankshaft at both plants yielded no effect (OR=1.12, 95% CI=0.3,4.0) with almost the same Plant 1 effect (OR=4.8, 95% CI=1.2,19.6). Nonsignificant associations were observed for those ever working in engine block (OR=2.3, 95% CI=0.74,7.3) and with duration in non skilled maintenance (OR=3.9, 95% CI=0.73,20). There was no association with grinding in soluble MF (OR=0.91) or straight oil (OR=0.61), beyond that accounted for by camshaft/crankshaft at Plant 1 (data not shown).

Pancreas Cancer

No trends were observed for pancreas cancer mortality risk with increasing cumulative exposures, but significant effects were found for workers ever-employed in: inspection (OR=6.4, 95% CI=2.5,16), machining with straight oil (OR=3.6, 95% CI=1.04,12), or skilled trades work (OR=2.9, 95% CI=1.1,7.5) (Table III). Skilled tool room activity conferred an additional, non significant risk (OR=2.8, 95% CI=0.81,9.5). In the same model, a significant negative trend was observed for overall employment duration (latency weighted) (OR=0.52, 95% CI=0.31,0.84).

Lung Cancer

There was a significant lung cancer association with duration in millwright work (OR=3.8, 95% CI=1.6,9.0), while (non millwright) skilled trades had less lung cancer than non skilled workers (OR=0.51, 95% CI=0.30,0.87) (Table III). Lung cancer mortality also increased with duration in cylinder head machining, (OR=3.9, 95% CI=1.4,11). There was an overall plant effect for Plant 2 (OR=1.45 95% CI=0.97,2.2), and a significant negative trend on total employment duration (OR=0.68, 95% CI=0.51,0.90). Grinding in soluble MF exhibited a small negative effect (OR=0.89, 95%

CI=0.67,1.2) (data not shown) and dry machining and engine assembly/testing showed small, non significant positive associations.

Other Malignancies

Mortality due to nonHodgkins lymphoma/multiple myeloma (ICD-8: 202-203, combined in Monson's rates) increased with dry machining (OR=3.8, 95% CI=1.4,10) and in those ever grinding with soluble MF (OR=4.1, 95% CI=1.1,15) (Table III). Ten deaths were due to nonHodgkins lymphoma and five due to multiple myeloma. Prostate cancer mortality increased with cumulative exposures in engine assembly/testing (OR=2.7, 95% CI=1.4,5.0), tool grinding (OR=4.5, 95% CI=1.4,14) and piston machining (OR=4.5, 95% CI=1.2,16; based on three deaths). Among black workers, there was a substantial deficit in exposure-adjusted prostate cancer mortality (OR=0.40, 95% CI=0.18,0.90). Bladder cancer mortality increased with cumulative exposures to straight oil in grinding (OR=3.0, 95% CI=1.15,7.8) and machining/heat treat (OR=2.9, 95% CI=1.14,7.2). A non significant doubling of bladder cancer risk was observed at the mean duration of previous employment in other plants of this employer (Table III); the effect was stronger when prior employment for Plant 2 workers was restricted to those who worked in grinding with straight oil at Plant 2 (OR=2.7, 95% CI=0.83,8.8) (data not shown).

Nonmalignant Causes of Death

Diabetes mortality was increased among workers ever employed in machining with straight oil (OR=6.9, 95% CI=1.8,27), although, there was a non significant subsequent decrease in risk with cumulative exposure (non latency weighted) (OR=0.49, 95% CI=0.18,1.3) (Table IV). A complex pattern of stroke mortality was observed. Plant 1 workers ever-employed in grinding with

soluble MF had high risk of stroke death (OR=6.7, 95% CI=1.8,24) but decreasing risk with duration in that exposure (Table IV). Plant 2 workers potentially exposed to combustion products had elevated stroke mortality (OR=4.4, 95% CI=1.6,12) compared to corresponding Plant 1 workers who had a deficit (OR=0.44, 95% CI=0.18,1.03). Less than expected adjusted stroke mortality was observed for black workers (OR=0.69, 95% CI=0.44,1.06) and skilled trades (OR=0.52, 95% CI=0.25,1.08).

Emphysema mortality was associated with combustion products at Plant 1 (OR=4.2, 95% CI=1.01,17); Plant 2 had a non significant overall doubling of emphysema mortality (Table IV). Cirrhosis of the liver mortality was elevated in workers ever employed in non skilled maintenance (OR=3.6, 95% CI=1.62,8.11) and increased with employment in cylinder head production (OR=2.3, 95% CI=0.89,6.0) and with exposure to combustion products (OR=1.40, 95% CI=1.00,1.97) (Table IV).

DISCUSSION

Methodological Issues

Exposure assessment for specific MFs was limited to judgments on historical mixes of operations in departments and relative contributions to air concentrations, producing misclassification. Assignments for MFs as a class were more confident. Classification of process categories was more reliable because departments differentiated production of engine blocks, camshafts/crankshafts, cylinder heads, pistons etc. and distinguished assembly and skilled trades activities. It may be argued that multiple comparisons arising from 20 exposure categories diminish the significance of findings. However, correlations among categories (for example, those MF-related), resulted in far fewer than 20 independent statistical tests. Tests for trend were independent of elevated PMRs. Nevertheless, regression results based on few cases had unreliable variance estimates and could represent chance findings (e.g. some findings for bladder cancer, lymphoma, diabetes and emphysema).

The latency weighting parameters were chosen to conform to generic estimates of induction periods for malignant and other disease. Although goodness-of-fit in the resulting models was adequate in this study [Park, 1996] and previously [Silverstein et al., 1988; Park and Krebs, 1992], there has been no systematic evaluation and optimization of the weighting parameters.

Exclusive use of decedents as controls has both disadvantages and advantages [Gordis, 1982; Howe, 1991; McLaughlin et al., 1985a,b]. Deceased controls would tend to be more comparable to

cases when information on important risk factors such as smoking is lacking. Incomplete death ascertainment (less than 10%) should have minor impact on MOR analyses based on internal comparisons, and would affect mainly the model constant (intercept).

The employment duration effects (and associated intercept constants) that were observed in MOR models are discussed elsewhere in relation to healthy worker survivor bias [Park, 1996]. Both personal risk factors, such as smoking and alcohol, and the employment impact of disability resulting from disease prior to death are considered. Many exposure-associated causes of death in this study were also smoking related but the patterns of exposure association were distinct, and odds ratios greater than 4.0 at high exposures exclude smoking as a plausible explanation.

Specific Work-Related Mortality

Cancer

A significant exposure response relationship for stomach cancer was observed among camshaft/crankshaft in Plant 1, but not at the larger and older Plant 2, or with grinding with soluble MFs generally. The excess at Plant 1 (where semi-synthetics had been used, largely in cam- and crankshaft grinding, and where the presence of nitrosamine was documented) offers modest support for the hypothesis that nitrosamine exposure is a risk factor for stomach cancer [Zingmark and Rappe, 1976; Fan et al., 1977]. Excess stomach cancer in tool room and tool grinding has been observed previously [Silverstein et al., 1988]. Increased stomach cancer was observed in another engine plant (SMR=2.54, 95% CI=1.4,4.2) [Rotimi et al., 1993]. Smaller, inconsistent stomach cancer associations with MF of were observed by Eisen et

al., [1992] and Tolbert et al. [1992], but less grinding was performed in those plants and parts washers, leak testing or skilled trades (tool room) work may not have been accounted for.

Personnel records of pancreas cancer decedents from inspection (OR=6.4) revealed seven out of nine had worked two or more years in engine block inspection. In the mid-1960s, such jobs constituted about a quarter of inspection jobs. Thus, MF, solvents or chemicals used in defect testing may account for the observed pancreatic cancer excess, possibly made worse by inspection tasks (extraction of parts from machines, compressed air blow-off, solvent immersion). Excess pancreas cancer in machining with straight oil had been observed previously [Silverstein et al., 1988]. Eisen et al. [1992], and Tolbert et al. [1992] observed excess pancreas cancer among black workers and a suggestive excess at high cumulative exposures to synthetic MF (OR=2.04, 95% CI=0.88,4.72); inspectors and skilled trades workers in that study may not have been separately classified.

Previously, Silverstein et al. [1985a] found high lung cancer risks among stamping plant millwrights and maintenance welders doing hot work on coal-tar embedded wood block floors, for example, flame-cutting bolts. Polynuclear aromatic hydrocarbons (PAH) were present. This study again observed high lung cancer risk among millwrights and maintenance welders and similar floors were present. At Plant 2, four out of six lung cancer decedents in cylinder head production were in the heavy drill press job in 1967 when 54 out of 149 cylinder head workers were in that classification (OR=3.5, based on a 1967 seniority list). Heavy duty drilling jobs likely had exposure to chlorinated oils.

Emissions from valve seat heat treatment were another plausible carcinogen (PAH) source in these departments but specific exposure measures were unavailable.

Interpretation of increased risk for nonHodgkins lymphoma and multiple myeloma (NHL/MM) is limited by the absence of unexposed cases in the model. Dry machining was correlated with grinding in straight oils (r=0.61) and occurred in areas of heavy duty machining (engine block, cylinder head, and manifold departments) where chlorinated oil may have been used. Early biocides for soluble MFs could have included chlorinated phenols; NHL has been repeatedly associated with chlorinated phenoxy herbicide exposures [Woods et al., 1987]. Among workers in a transmission plant involved in chip-pulling, there was a Hodgkin's disease cluster [Collins et al.,1989].

Excess bladder cancer was observed in honing (engine blocks, crankshafts, connecting rods) with a light petroleum fraction and among other machining or heat treat workers. An NCI bladder cancer study found "drill press" operators had high risk [Silverman et al., 1989]. (Some cases from the present study were probably included in that cancer registry-based study.) Drilling occurred throughout the engine block, head, crankshaft and connecting rod areas. Heat treat emissions contain petroleum fractions, pyrolysis and combustion products (PAH) and possibly additives to retard combustion. The enhanced risk among those with prior employment in similar plants supports an occupational cause.

Assembling and testing engines was associated with a two-fold risk of prostate cancer death, and tool grinding had a 4-fold excess. Siemiatycki et al. found excess prostate cancer among engine exhaust exposed workers [1988]. Tool grinding exposures, besides MFs, could include heat treat emissions, solvent, cobalt/tungsten carbide dust, and cadmium (hypothesized prostate carcinogen) from brazing. Tolbert et al. [1992] observed a significant prostate cancer increase with more than 7.5 years of exposure to straight oils (RR=1.5, 95% CI=1.0,2.3) and a non significant excess for synthetic MF (strongly correlated with straight oils, r=0.67 [Schroeder, 1994]), but no excess for soluble oils.

Diabetes and Stroke

Both diabetes and pancreas cancer were significantly elevated in machining in straight oil in this study. There was a slight diabetes excess among inspection workers (OR=1.25, 95% CI=0.52,3.1), who had high pancreas cancer mortality (OR=6.4). In previous related studies, diabetes mortality was elevated among forge workers exposed to oil smoke and noise [Park and Krebs, 1992] and was associated with exposures to chlorinated [Ott et al., 1985] and brominated [Wong et al., 1984] hydrocarbons. A common etiologic pathway for diabetes and pancreas cancer has been proposed [Lin and Kessler, 1981; Gullo et al., 1994]. Vena found a deficit of diabetes mortality with less that 20 yrs engine plant employment (Obs=0, Exp=4.2) but an excess with more than 20 yrs (Obs=5, Exp=3.3) [Vena et al., 1985; Vena, 1990]. Diabetes present at death is usually not assigned as the underlying cause. Studies of diabetes morbidity or contributing mortality in relation to metalworking exposures would be more informative.

The complex exposure association of stroke mortality is difficult to interpret. The significant association with grinding in Plant 1 (OR=6.7) was consistent with two bearing plant studies [Park et al., 1988; Silverstein et al., 1988]. The deficit of adjusted stroke mortality among black workers (OR=0.69) is consistent with observations in other automotive industry populations [Silverstein et al., 1985b; Delzell, 1991] and suggests favorable socioeconomic or other risk factors.

Other Nonmalignant Causes of Death

Increased emphysema mortality was found among workers exposed to combustion products in Plant 1, and generally in Plant 2. "Combustion products" were exposures attributed to engine testing, heat treat and shipping assignments and included engine exhaust, burn-off, and oil smoke from machining and heat treat. Engine exhaust, both from testing and industrial trucks (initially gasoline powered) is a plausible causative agent [Wong et al., 1985].

Previous studies have identified associations between MF and cirrhosis of the liver [Silverstein et al., 1988; Tolbert et al., 1992], or alcohol-related mortality [Mallin et al., 1986; Park et al., 1988]. Tolbert et al. [1992] observed elevated cirrhosis of the liver deaths in soluble oils (RR=2.4, 95% CI=1.08,5.2) (with a downward trend) but not in straight or synthetic MF. Chlorinated oils in cylinder head machining are a plausible liver toxin but airborne concentrations or degree of skin contact was unknown. Diverse exposures cause fatty liver disease [Hodgson et

al., 1991], which can be misdiagnosed as alcoholism [Park et al., 1988].

Conclusions

Associations were observed between machining fluid exposures and specific causes of death. The study provides equivocal evidence for a work related excess of stomach cancer from exposure to semi-synthetic machining fluids. Risk rates were elevated in the plantwide PMR analyses and a partial exposure response relationship was observed with mortality odds ratios. Some evidence was found for a work related excess of pancreas cancer, however, exposure response was lacking. The study provides clear evidence for a work related excess of lung cancer associated with employment as millwrights and welders. A highly significant increased risk was observed for a substantial number of deaths among employees in a defined exposure group plausibly related to the effect.

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Table I Engine Plant Mortality: Exposure Categories

	Exposures[a]
1. Machining/Grinding: Cylinder Heads	MF,Oil Smoke
2. Machining/Grinding: Engine Blocks	MF,Oil Smoke
3. Machining/Grinding: Pistons (alum.)	MF
4. Machining/Grinding: Cam-,Crankshaft, Water Pump	MF
5. Machining: Dry (broaches, saws)	Oil Smoke
6. Machining: Straight Oils	MF
7. Machining: Soluble,Semi-Synth.,Synth.	MF
8. Grinding: Straight Oils (incl. honing)	MF
9. Grinding: Soluble, Semi-Synth.,Synth.	MF
10. Machining/Heat Treat (cam shafts, rocker arms, valve seats)	Oil Smoke,MF
11. Inspection (floor and process)	MF,Solvent
12. Engine Assembly and Testing	Exhaust,Burn-off
13. Combustion Products (incl. eng.test, heat treat, shipping)	Exhaust,Burn-off, Oil Smoke
14. Millwright/Welder (skilled trade)	Mixed,Coal Tar
15. Machine Repair (skilled trade)	Solvent,MF,Mixed
16. Electricians (skiskilled trade)	Solvent,Mixed
17. Pipefitters (skilled trade)	MF,Mixed
18. Tool Room (skilled trade)	MF,Solvent
19. Tool Grinding (skilled trade)	Cobalt,MF,Solvent
20. Laborers/Non Skilled Maintenance	Mixed

a MF - machining fluids

Table II Engine Plant Mortality: PMRs for Selected Causes of Death among Men at Two Automotive Engine Plants

	Plant 1			Plant 2		
Cause of Death	Obs[a]	PMR	95% CI[b]	Obs	PMR	95% CI
White Men	451			719		
All Cancer	107	0.98	0.83, 1.15	199	1.12	1.00, 1.27
Stomach	8	2.09	0.90, 4.11	8	1.30	0.56, 2.57
Pancreas	10	1.82	0.87, 3.34	11	1.23	0.62, 2.21
Larynx	1	0.69	0.02, 3.83	4	1.67	0.46, 4.28
Lung	33	0.83	0.60, 1.15	81	1.23	1.00, 1.52
Prostate	8	1.08	0.47, 2.13	19	1.61	1.03, 2.50
Bladder	6	2.16	0.79, 4.70	5	1.13	0.37, 2.64
Kidney	3	1.10	0.23, 3.22	6	1.37	0.50, 2.98
All Lymphopoietic	10	0.98	0.53, 1.81	15	0.92	0.56, 1.51
NHL/MM[c]	4	1.03	0.28, 2.63	6	0.95	0.35, 2.08
Diabetes Mellitus	12	1.85	0.95, 3.23	13	1.27	0.74, 2.18
Mental,..Personality[d]	3	0.93	0.19, 2.71	3	0.61	0.12, 1.77
Heart Disease	161	1.06	0.94, 1.20	223	0.92	0.83, 1.02
Stroke	25	1.08	0.74, 1.59	39	1.09	0.81, 1.48

continued

Table II continued, page 2

Cause of Death	Plant 1 Obs[a]	PMR	95% CI[b]	Plant 2 Obs	PMR	95% CI
Respiratory	16	0.52	0.33, 0.83	45	0.92	0.70, 1.33
Emphysema	6	1.08	0.40, 2.35	13	1.47	0.78, 2.51
Cirrhosis of Liver	19	1.64	1.06, 2.53	18	1.00	0.63, 1.57
Suicide	18	1.55	1.00, 2.41	27	1.52	1.06, 2.18
Black Men	180			433		
All Cancer	35	1.06	0.79, 1.42	111	1.01	0.86, 1.19
Stomach	2	1.22	0.15, 4.43	5	0.85	0.28, 1.99
Pancreas	0	0.00	0.00, 1.92	6	1.08	0.40, 2.36
Larynx	1	1.52	0.04, 8.42	1	0.51	0.01, 2.85
Lung	13	1.12	0.67, 1.89	41	1.07	0.80, 1.43
Prostate	1	0.47	0.01, 2.63	8	0.63	0.32, 1.24
Bladder	0	0.00	0.00, 7.88	5	2.80	0.90, 6.53
Kidney	2	3.44	0.42,12.45	3	1.74	0.36, 5.10
All Lymphopoietic	4	1.54	0.42, 3.92	7	1.02	0.41, 2.11
NHL/MM[c]	2	1.83	0.22, 6.56	3	0.86	0.18, 2.53

continued

Table II continued, page 3

Cause of Death	Plant 1 Obs[a]	PMR	95% CI[b]	Plant 2 Obs	PMR	95% CI
Diabetes Mellitus	1	0.34	0.01, 1.87	7	0.83	0.33, 1.70
Mental,..Personality[d]	13	2.61	1.39, 4.46	3	0.53	0.11, 1.56
Heart Disease	24	0.77	0.54, 1.09	97	0.90	0.76, 1.07
Stroke	8	0.81	0.35, 1.60	38	1.14	0.84, 1.55
Respiratory	10	1.11	0.53, 2.04	26	0.99	0.68, 1.43
Emphysema	3	4.69	0.97,13.71	3	1.20	0.25, 3.51
Cirrhosis of Liver	10	1.21	0.58, 2.22	16	1.47	0.91, 2.37
Suicide	9	2.77	1.27, 5.25	5	1.94	0.63, 4.53

a Obs - observed no. of death; PMR - standardized proportional mortality ratio; 95% CI - 95% confidence interval

b Confidence intervals based on M-H chi-squared for expected no. of deaths > 10.0; otherwise based on Poisson; P-values are 2-tailed and not shown if > 0.1.

c NHL/MM - NonHodgkins lymphoma and multiple myeloma (ICD-9:202-203)

d Mental,..Personality Disorders (ICD-9: 290-317); includes drug abuse.

Table III Engine Plant Mortality: Adjusted Mortality Odds Ratios (OR) in All Workers for Selected Cancers - Final Logistic Regression Models

Predictor[a]	n[b]	OR[c]	95% CI	p[d]
Stomach Cancer				
Constant		1.22	.54-2.73	.635
Empl.Duration	24	.72	.34-1.53	.394
Cam-/Crankshaft (Plant 1)	3	5.13	1.56-16.9	.007
Ind:Engine Blocks	4	2.32	.74-7.31	.150
Laborers/Non Skill Maint	2	3.89	.73-20.6	.109
Tool Room	2	6.31	1.29-31.0	.023
Tool Grinding	1	9.98	.82-121	.071
Pancreas Cancer				
Constant		1.10	.43-2.84	.838
Empl.Duration	28	.52	.32-.84	.008
Ind:Black Men	6	.88	.31-2.49	.808
Ind:Inspection	10	6.42	2.50-16.5	<.001
Ind:Machining (Str Oil)	4	3.61	1.04-12.6	.043
Ind:Skilled Trades	10	2.86	1.10-7.45	.031
Ind:Tool Room	4	2.76	.81-9.45	.105

continued

Table III continued, page 2

Predictor[a]	n[b]	OR[c]	95% CI	p[d]
Lung Cancer				
Constant		1.55	1.03-2.33	.036
Empl.Duration	175	.68	.51-.90	.008
Ind:Black Men	54	.72	.49-1.06	.092
Ind:Plant 2	122	1.45	.97-2.15	.070
Ind:Skilled Trades	28	.51	.30-.87	.014
Millwright/Welder	10	3.78	1.59-8.99	.003
Cylinder Heads	8	3.92	1.38-11.2	.010
NonHodgkins Lymphoma (n=10)/Multiple Myeloma (n=5)				
Constant		.53	.11-2.59	.437
Empl.Duration	15	.28	.06-1.34	.111
Machining (Dry)	10	3.77	1.42-9.98	.008
Ind:Grinding (Sol MF)	7	4.12	1.10-15.4	.036
Ind:Skilled Trades	3	4.85	.86-27.5	.074
Laborers/Non Skill Maint	2	40.41	3.47-470	.003
Prostate Cancer				
Constant		2.42	1.14-5.13	.021
Empl.Duration	36	.37	.18-.78	.009
Ind:Black Men	9	.40	.18-.90	.027
Engine Assembly/Test	15	2.67	1.43-4.96	.002
Tool Grinding	4	4.52	1.43-14.3	.010
Pistons (Aluminum)	3	4.51	1.22-16.6	.024
Ind:Inspection	5	1.81	.63-5.26	.273

continued

Predictor[a]	n[b]	OR[c]	95% CI	p[d]
Bladder Cancer				
Constant		3.23	1.16-9.03	.025
Empl.Duration	16	.25	.09-.66	.005
Grinding (Str Oil)	7	2.99	1.15-7.77	.025
Machining/Heat Treat	4	2.86	1.14-7.18	.025
Prior Empl. (Plant 1)	4	2.30	.63-8.41	.209
Prior Empl. (Plant 2)	7	2.18	.80-5.93	.127

a Cumulative exposures and employment durations long latency weighted except for nonHodgkins lymphoma/multiple myeloma: short latency weighted; Ind, indicator variable (0,1): Ever-Exposed=1, Black Men=1, Skilled Trades=1; Str, Straight Oil machining fluids (MF); Sol, Soluble MF.

b n - cause-specific deaths in exposure group.

c OR - predicted for mean exposure/duration of exposed cases.

d 95% Confidence Interval and P-value calculated assuming Gaussian variance of effect estimate.

Table IV Engine Plant Mortality: Adjusted Mortality Odds Ratios (OR) in All Workers for Selected Nonmalignant Causes of Death - Final Logistic Regression Models

Predictor[a]	n[b]	OR[c]	95% CI	p[d]
Diabetes				
Constant		1.11	.43-2.85	.830
Empl.Duration	33	1.03	.45-2.36	.937
Ind:Black Men	8	.47	.20-1.07	.073
Ind:Machining (Str Oil)	7	6.86	1.75-26.9	.006
Machining (Str Oil)	7	.49	.18-1.31	.155
Pipefitters (Plant 1)	2	56.65	3.36-955	.005
Heart Disease				
Constant		1.57	1.13-2.19	.007
Empl.Duration	518	.80	.61-1.06	.125
Ind:ICD-9	310	.73	.56-.94	.015
Ind:Black Men	121	.75	.57-.98	.034
Ind:Skilled Trades	108	.77	.55-1.10	.150
Grinding (Sol MF)	178	1.25	1.01-1.56	.044
Ind:Tool Grinding	25	3.87	.78-19.1	.097
Tool Grinding	25	.49	.13-1.93	.309
Electricians	16	2.49	1.01-6.09	.047

continued

Table IV continued, page 2

Predictor[a]	n[b]	OR[c]	95% CI	p[d]
Stroke				
Constant		1.26	.63-2.51	.519
Empl.Duration	114	1.18	.71-1.95	.519
Ind:Black Men	46	.69	.44-1.06	.091
Ind:Skilled Trades	11	.52	.25-1.08	.079
Ind:Plant 2	78	.73	.37-1.45	.368
Ind:Combustion Products	56	.44	.18-1.03	.060
Ind:Comb.Prod. (Plant 2)	47	4.40	1.62-11.9	.004
Ind:Grinding (Sol)	39	.75	.44-1.28	.294
Ind:Grinding (Sol) (Plant 1)	15	6.65	1.80-24.5	.004
Grinding (Sol) (Plant 1)	15	.42	.17-1.02	.056
Emphysema				
Constant		2.58	.62-10.8	.194
Empl.Duration	26	.36	.14-.91	.031
Ind:Skilled Trades	3	.50	.14-1.83	.299
Ind:Plant 2	16	2.09	.53-8.19	.290
Ind:Combustion Products	14	4.20	1.01-17.4	.048
Ind:Comb.Prod. (Plant 2)	7	.28	.05-1.57	.146

continued

Table IV continued, page 3

Predictor[a]	n[b]	OR[c]	95% CI	p[d]
Cirrhosis of Liver				
Constant		1.84	.99-3.40	.053
Empl.Duration	68	.68	.40-1.15	.152
Ind:Black Men	26	.75	.43-1.29	.302
Ind:Skilled Trades	8	.74	.32-1.70	.482
Ind:Laborer/Non Skill Maint	10	3.63	1.62-8.11	.002
Cylinder Heads	4	2.30	.89-5.96	.087
Combustion Products	36	1.40	1.00-1.97	.051

a Cumulative exposures and employment durations non latency weighted except for heart disease: short latency weighted; Ind, indicator variable (0,1): Ever-exposed=1, Black Men=1, Plant 1 or 2=1, Skilled Trades=1, ICD-9 Epoch (year of death 1978 or later)=1; Str, Straight Oil machining fluids (MF); Sol, soluble MF; Comb. Prod., Combustion Products.

b n - cause-specific deaths in exposure group.

c OR - predicted for mean exposure/duration of exposed cases.

d 95% Confidence Interval and P-value calculated assuming Gaussian variance of effect estimate.