

EPIDEMIOLOGY PLENARY SESSION

Session Arranger / Moderator:

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Discussants:

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GEOFFREY M. CALVERT, MD, MPH, Medical Officer, NIOSH

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Technical Presenters:

ELLEN A. EISEN, ScD, Professor, University of Massachusetts, Lowell

CASE-CONTROL STUDIES of FIVE DIGESTIVE CANCERS and EXPOSURE to METALWORKING FLUIDS

FRANKLIN E. MIRER, PhD, CIH, Director of Health & Safety, UAW

MORTALITY STUDIES in UAW REPRESENTED PLANTS

ELIZABETH DELZELL, PhD, Professor of Epidemiology, University of Alabama, Birmingham

MORTALITY STUDIES of WORKERS at a FOUNDRY and TWO ENGINE PLANTS

TONG-MAN ONG, PhD, CIH, Chief, Microbiology Section, NIOSH

CARCINOGENICITY and MUTAGENICITY of PAHs / NITROSAMINES as POTENTIAL CONTAMINANTS of METALWORKING FLUIDS

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METALWORKING FLUIDS: BASE OIL SAFETY

EPIDEMIOLOGY PLENARY SESSION

Session Arranger / Moderator:

LAWRENCE J. FINE, MD, DrPH, NIOSH

Mr. DAVID FELINSKI, AAMA: Okay, we are going to get started in a minute here. Just a couple of quick announcements. I've had several requests for the ability to get copies of the slides that Dr. Howell showed in his presentation. We will have a basket set up out in the foyer during the break. If you would like a copy of the slides, drop your business card into the basket and Dr. Howell will send you a copy of those slides. There is a lot of information on them. The other announcement is that Dr. Chan, the Session Arranger for Wednesday, would like to meet with all of his Discussants and Presenters in front of the Registration Desk during the break.

And now I'll introduce the Session Arranger for this afternoon's epidemiology session. Lawrence J. Fine has been the Director of the Division of Surveillance, Hazard Evaluations and Field Studies of the Centers for Disease Control's National Institute for Occupational Safety and Health since January of 1988. Dr. Fine was Director of the Occupational Health Program in the Department of Environmental and Industrial Health at the University of Michigan School of Public Health

from 1985 to 1988. Prior to that, he was Assistant Professor of Occupational Medicine at the Harvard School of Public Health from 1976 to 1980 and a lecturer on Neurology and Occupational Medicine at Boston University School of Medicine from 1978 to 1980.

The author of numerous scholarly publications, Dr. Fine received his medical degree from the University of Illinois and his Master's and Doctorate Degrees in Public Health and Occupational Medicine from the Harvard University School of Public Health. He is Board Certified in both Internal Medicine and Occupational Medicine. His major research interests include detection and prevention of musculoskeletal and neurotoxic disorders. Please welcome Dr. Fine.

Dr. LAWRENCE FINE, NIOSH: It's great to be here and I think we are going to have a very interesting and informative afternoon, and I would like to introduce the first speaker, Dr. Ellen Eisen from the University of Massachusetts at Lowell and her topic is case control studies of five digestive cancers and exposure to metalworking fluids. Ellen.

CASE-CONTROL STUDIES OF FIVE DIGESTIVE CANCERS AND EXPOSURE TO METALWORKING FLUIDS

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ABSTRACT

This report summarizes the results of five case-control studies of digestive cancer nested within a cohort of autoworkers exposed to metalworking fluids (MWF). Results have already been reported from the cohort mortality study suggesting that lifetime exposures to specific types of MWF (straight, soluble, and synthetic) are associated with several digestive cancers. Case-control studies were designed to further examine the exposure-response associations for cancer of the esophagus, stomach, pancreas, colon, and rectum. Unlike the cohort analysis, the present analysis includes an examination of latency as well as confounding by constituents and other concomitant MWF related exposures. The findings reported here provide strong evidence that duration of exposure to MWF in grinding operations (using either soluble or synthetic fluid) is associated with elevated risk of esophageal and pancreatic cancer, that straight fluids are associated with rectal cancer, and that exposure to synthetic MWF is associated with increased risk of pancreatic cancer and possibly colon cancer. The magnitude of the risks range from 2.2 for colon cancer and synthetics up to 5.3 for esophageal cancer and grinding with soluble MWF.

INTRODUCTION

In response to growing concern regarding the carcinogenic effects of metal working fluids, a mortality study of a cohort of autoworkers was initiated by the United Automobile Workers Union and General Motors in 1984. In order to permit more detailed examination of the risks associated with these complex fluids, a large population from three automobile manufacturing plants in Michigan was studied and a great deal of effort devoted to the characterization of exposure.

Results from this mortality study, based on

a cohort of more than 46,000 workers, have been reported by the authors.⁽¹⁻⁶⁾ To summarize, exposure-response associations were observed for several cancers of *a priori* interest; cancer of the larynx,⁽¹⁾ and several digestive cancers, including esophagus,⁽⁴⁾ pancreas,^(1,4) and rectal^(4,5) cancer. These analyses, however, did not take account of potential confounding by other MWF-related exposures. Based on these positive findings, a series of nested case-control studies were initiated to further examine the risks for selected causes of death. These studies were designed to examine confounding by other MWF related exposures. A case-control study of larynx cancer has already been reported.⁽⁶⁾ The case-control studies of esophagus, stomach, pancreas, colon and rectum are largely completed and are presented here in summarized form.

METHODS

Cohort

The study population includes 46,384 hourly workers at three automobile manufacturing plants in Michigan. All hourly employees who had worked at least three years (prior to January 1, 1985) were eligible to be included in the study. Follow-up extends from 1940 to 1984 and includes over 1 million person-years. On average there are more than 20 years from the date of hire to the end of follow-up for each subject. By the end of follow-up, 10,159 (22%) were deceased. Cause of death was ascertained for 92% of these subjects based on death certificate information. Although the cohort is predominantly white male, it also includes 7,750 blacks and 4,680 females.

Cases: Cases for the five case-control studies were defined as subjects in the cohort who had died from cancer of the esophagus, stomach, pancreas, colon or rectum prior to January 1, 1985,

the end of follow-up. A subject was considered to be a case if the death certificate listed the cancer as either *underlying cause* or as an *other significant condition*.

Controls: Controls were selected by incidence density sampling. Risk sets were defined for each case including all subjects at risk of the disease at the age of the death of the case. Within the risk set for each case, controls were matched on date of birth (+ or - 5 years), plant, gender, and race. To minimize sampling variability, a 20:1 sampling ratio was used in each of the case-control studies to select controls randomly.

Exposure

The exposure variables in the case-control analyses presented here were defined as years of exposure to specific agents. Exposure tables were developed for each type of MWF and operation, as well as for contaminants and additives present in the machining fluids. In each unique combination of plant/department/job, type of MWF, type of operation (grinding or machining), the presence of ethanalamines, sulfur, chlorine, biocides and metals, including aluminum, steel, and iron was determined on the basis of interviews with plant personnel, material safety data sheets and historical records of lubricant specifications. The co-presence of ethanalamines and nitrites was used to provide a qualitative measure of exposure to nitrosamine. By combining this information with employment records, years of exposure to each agent was determined for each subject.

Latency: An attempt was made to take account of the latency period for these cancers, generally defined as the time between the biologically relevant exposure and diagnosis of disease. For all the cancers of interest, latency for initiators is believed to be 10 to 20 years, i.e., exposures in the 10 to 20 years prior to diagnosis are considered to be irrelevant to the disease outcome, whereas promoters may exert an effect more rapidly. To compute an exposure variable

with a 10 (or 20) year lag, zero weight was assigned to exposures in the 10 (or 20) years prior to risk date, i.e. date of death for the cases and that same year for the matched controls.

Statistical Methods

The same statistical methods were used to analyze the data in each of the separate case-control studies. Adjusted odds ratios for each of the primary exposure variables were estimated in conditional logistic regression models. Continuous exposure variables were examined first. Confounding by other exposures were evaluated by looking for a change in estimated regression coefficient for the primary variable with the addition of a second exposure variable to the model. Categorized exposure variables, rather than continuous ones, were included in the final models to allow for non-exponential exposure-response relationships.

The results presented in this summary report are based on years of exposure as the measure of lifetime exposure to each of the specific exposures under study. Year since hire was included in each model along with the exposure variables in order to adjust for the decrease in the healthy worker effect expected to occur as the number of years since hire increases. No other co-variables were included since the controls had been matched to the cases on all other potential confounders (age at risk, race, gender, plant, and year of birth) and conditional logistic regression accounts for all matching factors. The likelihood ratio statistic (LRS) was used to assess the overall fit of each logistic model.

RESULTS

Esophageal Cancer: The esophageal cancer case control study was based on 54 deceased cases and 1008 matched controls. Results suggest that grinding is significantly associated with esophageal cancer. The odds ratio (OR) increased as years of grinding exposure increased, up to a risk of 7.4 for those with more than 17.7 years of exposure. The increasing trend in the risk estimates was significant in a test for linearity ($p=0.02$). When

grinding was lagged 10 years, the association with grinding increased up to 12.7 (95% CI: 2.1-77.6) in the highest exposure group and the model fit the data slightly better (LRS=18.8, p=0.06).

Metal grinding is generally performed with one of the water based fluids, i.e., soluble or synthetic fluids. The fit of the model improved still further when a specific type of MWF used in grinding was included in the exposure term and when exposure variables were lagged by 20 years. Dose response trends were observed for years exposed to grinding with both soluble and grinding. The risk estimates were statistically significant in the highest categories, 5.4 for grinding with solubles and 3.4 for grinding with synthetics.

Stomach Cancer: There were 125 cases of stomach cancer and 2,212 controls. There was little evidence of an association between stomach cancer and any MWF related exposure. The highest odds ratios were found for soluble MWF. When this exposure variable was included alone in the model, however, there was no exposure-response trend. The risk estimates changed slightly when grinding was added to the model suggesting slight confounding. Because of the higher survival rates for stomach cancer, we expected that if an association existed, lagging exposure would emphasize the risk. However, both the 10 and 20 year lags were found to diminish the associations with soluble MWF and grinding.

Pancreatic Cancer: Based on death certificate information, 98 cases of pancreatic cancer were identified, and 1,880 controls were selected. Synthetic years appeared to be the strongest predictor of risk, i.e., the odds ratio as highest and the fit of the model was better than that of any other model with a single exposure variable. Additionally, when added to any model as a second exposure variable it consistently caused the largest change in deviance. When grinding was added to the model the risk estimates for synthetic exposure decreased. The model that best predicted pancreatic cancer included years grinding and

years exposed to synthetics, both lagged by ten years.

Colon Cancer: The 162 cases of colon cancer were matched to 2,917 controls. Colon cancer was most strongly related to synthetics. The OR increased up to 2.2 with increasing exposure to synthetics. The trend was significant in a test for linearity (p=0.02). More specific exposure variables were also created which combined information on operation and fluid type. There appeared to be some evidence for an association between colon cancer and grinding specifically with synthetics. The OR rose to 4.6 (1.8-11.8), however the risk then declined to 2.1 in the highest exposure category.

Rectal Cancer: All 67 cases of rectal cancer were male. In the series of conditional logistic regression models that included a single exposure variable, an increasing trend was observed between rectal cancer and straight MF. The OR for straight MWF increased to 3.3 in the highest category (95%CI: 1.6-6.9). The significance level in a test for linear trend was 0.07. When all three types of fluid were included together in one model none of the ORs changed from models in which only the single exposure variable had been included, suggesting no confounding among fluid types. A trend was also observed for increasing categories of grinding, with a maximum OR of 2.1 that did not quite reach statistical significance. When both grinding and straights are included together the OR for both are slightly decreased although both remain associated with rectal cancer, suggesting minor confounding. When lagged exposure variables were examined, none were more strongly associated with the outcome than the un-lagged variables.

CONCLUSIONS

The major results of these case-control studies of digestive cancers are presented in Table 1. These analyses go beyond those based on the full cohort in that they address confounding by other exposures and account for latency. The findings provide further evidence, beyond that

already suggested by these data, that grinding operations are associated with elevated risk of esophageal and pancreatic cancer, that straight fluids are associated with rectal cancer, and that exposure to synthetic MWF is related to increased risk of pancreatic cancer and possibly colon cancer. Grinding was sometimes done with straight mineral oils, however, most of the grinding operations in this study involved the water based fluids - either solubles or synthetics. Thus digestive cancer risk was found to be associated with all three types of fluids.

REFERENCES

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Table 1: Summary of major findings from logistic regression models in case-control studies

Cancer	Metalworking Fluid Risk Factor	N Cases*	Odds Ratio*	95 % CI*
Esophagus	Grinding with Solubles (lag 20)	9	5.4	1.6-17.1
	Grinding with Synthetics (lag 20)	8	3.4	1.0-11.7
Stomach	Soluble (lag 0)	29	1.3	0.5-2.3
Pancreas	Synthetics (lag 10)	11	2.9	1.3-6.4
	Grinding (lag 10)	19	1.9	0.9-3.8
Colon	Synthetics (lag 10)	10	2.2	1.8-11.8
	Grinding with Synthetics (lag 10)	6	2.1	0.8-5.8
Rectum	Straight (lag 0)	13	3.0	1.3-6.6
	Grinding (lag 0)	15	1.2	0.5-2.8

* In the highest category of exposure

MORTALITY STUDIES IN UAW REPRESENTED MACHINING PLANTS

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ABSTRACT

Mortality studies were conducted at two UAW-represented bearing plants. Standardized proportional mortality (SPMR) and mortality odds ratio (SMOR) methods were employed. In Plant 1, cause of death and work histories were obtained for 702 of 768 hourly employees with 10 or more years of service who died between 1969 and 1982. Union and company records were used to define exposure measures. The major findings were significant excess in proportional mortality ratios for stomach cancer (PMR = 2.0, based on 11 deaths) and rectal cancer (PMR = 3.1, based on 11 deaths) among white men. After control for age at death, there was a significant association between stomach cancer and precision grinding exposures, primarily direct contact with water based cutting fluids (usually soluble oil) and their aerosols. Some straight oils and synthetic cutting fluids were used as well. In Plant 2, cause of death and work histories were obtained for 1,766 workers who died between 1950 and 1982. The proportional mortality excess for stomach cancer among white men was greatest among those with more than 10 years exposure in the major grinding group (PMR = 13/3.8 = 3.39; $P < 0.001$). The SMOR by logistic regression for stomach cancer among white men was 2.3 ($P = 0.02$) for 25 years grinding experience. For cancer of the pancreas among white men, there were significant associations with both machining and grinding jobs in straight oil (SMOR = 9.6 and 3.2 respectively for 25 years duration). These findings could not be explained by confounding due to the ethnic background of the decedents. There were indications that non-malignant liver disease is associated with machining fluid exposures and that lung cancer is associated with oil smoke from forging and heat treat. Each study provided clear evidence for work related mortality

from exposure to machining fluids, in that each found a significant excess and an exposure response relationship in the studied population. Bearing plants are likely to have higher levels of machining fluid exposure than other machining plants, because of manual grinding operations and hand placement of small parts.

INTRODUCTION

This paper presents in detail the combined results of two studies of machining workers previously published by the UAW Health and Safety Department and places these findings in context. The UAW formally launched its own program of epidemiology research in April, 1980, as part of a comprehensive occupational cancer response program. This initiative was spurred by local union concerns which had led to confirmed findings of excess cancer mortality in pattern and model makers on the design staffs of the car companies and among workers in a hardware plant. Concern for metalworking fluid (MWF) hazards was triggered by the then known carcinogens in the materials used, and by literature reports of excess cancer. Results of research projects following the 1980 UAW Occupational Cancer response initiative lead to the UAW petition to OSHA for a new standard for machining fluids.

Nine completed mortality studies in 13 UAW represented plants support the UAW petition. The study populations were drawn from two bearing plants, six engine plants, three transmission plants and a parts manufacturing plant (Fig. 1). Four were SMR studies, the rest PMR and MOR studies. In addition to the reported studies, a study in two engine plants is completed but not reported, and a larger study is ongoing in transmission and chassis operations (equivalent to Eisen). This report will focus on

two bearing plant studies.

LOCATIONS AND STUDY TYPES

STUDY PLANT	LOCATION	DATE	TYPE
CADILLAC ENGINE	DETROIT, MI	1978	SMR
CHEVROLET ENGINE	TONAWANDA, NY	1985	PMR
INT'L HARVESTER	CHICAGO, IL	1986	PMR
CATERPILLAR	YORK, PA	1986	SMR
FAFNIR-BEARING	NEW BRITAIN, CT	1988	SMR, MOR
GM-BEARING	BRISTOL, CT	1988	PMR, LGR
FORD ENGINE	CLEVELAND	1990	SMR, CLR
GM MACH. FLUID	MICHIGAN	1992	SMR, PRG
FORD T&C	MICH, OHIO	1992	SMR

Figure 1

The investigation at Fafnir (UAW Local 133) was spurred by observations among the bargaining committee of recent deaths among local union officers. The study was negotiated as part of the settlement of a multiple week strike. The investigation at the GM New Departure-Hyatt Bearing Plant (UAW Local 626) was launched after university researchers had approached the union and management with a proposal based on evidence of exposure derived from a large number of dermatitis cases reported to the state labor department. In each case, UAW Health and Safety Department staff collaborated with external investigators.

These two studies relied on work histories derived from old seniority lists, dues cards, or periodic soluble oils. The production processes for each department were identified, distinguishing grinding, machining, and other categories. Material categories distinguished straight oil, water based fluids and other exposures, notably smoke from heat-treat and inorganic dusts. Industrial hygiene data were sparse, so only a quantitative job exposure matrix could be constructed.

At the Fafnir plant, cause of death and work histories were obtained for 702 of 768 hourly employees with 10 or more years of service who died between 1969 and 1982. Exposure classification was based on the worker's assignment 15 years prior to death. At the GM Bearing plant, cause of death and work histories

were obtained for 1,766 workers who died between 1950 and 1982. Cumulative exposures, weighted for latency before death so that older exposures weighed more heavily, were calculated based on seniority lists dating from 1986. Thus, the number of deaths from the GM Bearing study alone exceeds the number of deaths for the Ford SMR study. The results presented in the summary table are for white male decedents only (Fig. 2).

PMR's FROM SELECTED CAUSES Plantwide Results

	FAFNIR - LU 133 n=610 decedents		GM BEARING-LU 626 n=1532 decedents	
	O/E	PMR	O/E	PMR
ALL GI CANCERS	55/35.6	1.54 P<.001	137/90.1	1.52 p=.001
STOMACH	11/5.5	1.99 p=.02	35/17.8	1.97 p<.001
ESOPHAGUS	6/3.25	1.85	13/7.1	1.83 p<.03
COLON	15/12.7	1.18	41/29.6	1.39 p=.04
PANCREAS	8/7.31	1.09	24/16.8	1.43
RECTUM	11/3.58	3.07 P=.002	14/10.3	1.35

Figure 2

For Fafnir, the major findings were significant excess in proportional mortality ratios for stomach cancer (PMR = 2.0, based on 11 deaths) and rectal cancer (PMR - 3.1, based on 11 deaths). Deaths from stroke were significantly elevated, as were deaths from diagnoses associated with alcoholism. The stomach cancer excess was most prominent in grinding (PMR=3.8, p=0.008), compared to machining and tool and die. Small non-significant excesses were observed for cancers of the esophagus, rectum and prostate in various grinding, machining or tool and die groups. Mortality attributed to alcohol consumption was significantly elevated in grinding (PMR=6.4, p<0.001). (In almost all cases, the alcohol attributions were made by medical examiners, not attending physicians, and may be chemically induced liver disease). Stroke mortality was elevated in grinding (PMR-1.48, p=0.08) but not in machining or tool and die (Fig. 3).

**PMR's FROM SELECTED CAUSES
FAFNIR BEARING -- UAW LOCAL 133**

	GRINDING n=199		MACHINING n=78		TOOL & DIE n=68	
	O/E	PMR	O/E	PMR	O/E	PMR
ALL GI CANCERS	23/12.1	1.90 p=.002	5/4.6	1.1	8/3.8	2.1 p=.08
STOMACH	7/1.9	3.8 p=.006	1/0.7	1.4	0/0.6	0
ESOPHAGUS	2/1.2	1.7	0/0.45	0	0/0.31	0
COLON	6/4.3	1.4	2/1.6	1.2	2/1.4	1.4
RECTUM	2/1.2	1.7	2/1.1	1.8	2/4.0	5

Figure 3

For GM Bearing, stomach cancer was also elevated two-fold, based on a larger number of deaths. Esophageal cancer was nearly 2-fold elevated. Colon cancer was significantly elevated as well. The GM Bearing study observed an exposure association for stomach cancer and grinding (PMR=3.4, $p<0.001$). Tool grinders also showed a large relative risk (PMR=5.1, $p=0.04$) but no excess was found for machining workers (PMR=1.1). Pancreas cancer was elevated in both grinding and machining metalworking groups. Small nonsignificant excesses for rectum and prostate cancer were seen in all groups. As observed for alcohol related disease in the first bearing plant study, cirrhosis of the liver was elevated among grinders at the second plant, particularly among production operators who could have used both straight and soluble oil Machining Fluids (MF) (PMR=3.3, $p=0.04$), but not among machining workers (PMR=1/2.4=0.4). (Fig. 4). Internal exposure comparisons were also calculated in order to address possibly important confounding (healthy worker effect, ethnicity). In the Fafnir study, mortality odds ratios for stomach cancer and grinding or water-based MF were significantly elevated (OR=6.5, 6.6 respectively) (Fig.5). There was no confounding evident by location of birth.

In the GM Bearing study, mortality odds ratios were modeled using logistic regression with external standardization for age and year of death. Statistically significant excess stomach cancer was observed with grinding (OR=2.3, $p=0.024$, for 25 years exposure (latency weighted)). These two

highly significant correlations with duration of exposure constitute exposure response relationships for machining fluid exposures.

**PMR's FROM SELECTED CAUSES
GM BEARING-- UAW LOCAL 626**

	GRINDING: all n=350		GRINDING: water/oil n=105		MACHINING: all n=158	
	O/E	PMR	O/E	PMR	O/E	PMR
ALL GI CANCERS	40/20	1.96 $p<.001$	14/6.2	2.28 $p=.002$	18/9.4	1.92 $p=.005$
STOMACH	13.3.8	3.4 $p<.001$	5/1.2	4.2 $p=.02$	2/1.9	1.1
ESOPHAGUS	2/1.6	1.3	0/.47	0	1/7.2	1.4
COLON	13/6.9	1.9 $p=.02$	4/2.0	2.0	6/3.1	2.0
RECTUM	3/2.3	1.3	1/7.1	1.4	2/1.1	1.9

Figure 4

MORTALITY ODDS RATIOS FOR CANCER

Cancer Site	Exposure Group	# Deaths from Cause	Odds Ratio	p value
<i>Fafnir Bearing -- UAW Local 133</i>				
Stomach	Grinding	7	6.5	.008
	Water Based MWF	8	6.6	0.02
<i>GM New Departure Bearing -- UAW Local 626</i>				
Stomach	Grinding	18	2.3	0.024
	Tool Grinding	3	3.4	0.10
Pancreas	Machining, oil	6	9.6	.007
	Grinding	11	7.2	.009
Lung	Forge/Heat Treat	19	2.0	.035

Figure 5

As observed with PMRs at GM Bearing, internal comparisons revealed pancreas cancer to be elevated both in machining with straight oil (OR=9.6, $p=0.007$ at 25 years exposure (latency weighted)), and in grinding (Fig. 6). The grinding association showed a significant downward trend in calendar time.

Lung cancer was elevated in heat treat or forging operations at the second bearing plant (OR=2.0, $p=0.035$). Exposures there include oil mist derived from quenching hot metal in oil baths and from aerosolized lubricants in hot forging and upsetting operations (Fig. 7).

**PANCREAS CANCER MORTALITY RELATIVE RISKS
in UAW machining plants**

by SMR,PMR,logistic/Poisson regression methods

STUDY PLANT	ALL WORKERS	EXPOSED GROUP
CADILLAC ENGINE	1.05 (8)	1.06 (5)
CHEVROLET ENGINE	1.89 (11)	--
INT'L HARVESTER	1.78 (10)	3.57# (5)
CATERPILLAR	1.59 (3)	--
FAFNIR-BEARING	1.09 (8)	2.52 (4)
GM-BEARING	1.43 (24)	2.33 (9)
FORD ENGINE	1.35 (15)	3.03# (7)
GM MACH. FLUID	0.90 (98)	1.62 (19)
FORD T&C	0.85 (23)	--

Figure 6

* p < 0.05
among Black Workers only

**LUNG CANCER MORTALITY RELATIVE RISKS
in UAW machining plants**

by SMR,PMR,logistic/Poisson regression methods

STUDY PLANT	ALL WORKERS	EXPOSED GROUP
CADILLAC ENGINE	1.12 (38)	1.26 (22)
CHEVROLET ENGINE	1.25 (48)	--
INT'L HARVESTER	1.28 (46)	--
CATERPILLAR	0.42 (6)	--
FAFNIR-BEARING	1.23 (59)	19.0 (5)
GM-BEARING	0.92 (83)	2.4 (4)
FORD ENGINE	1.23* (104)	--
GM MACH. FLUID	1.06 (593)	--
FORD T&C	1.21 (252)	--

Figure 7

* p < 0.05
among Black Workers only

These studies separately provide clear evidence for occupational cancer among workers exposed to machining fluids in bearing plants, in that excess mortality and exposure response were observed.

Comparison to Other Studies

The UAW Bearing studies should be given heavy weight in hazard identification and qualitative risk assessment. The quality of the studies overcomes the main objection to PMR studies which is bias in ascertainment of the cohort. The strength of association (risk ratios) are high and highly significant and therefore unlikely to arise from overestimation bias which is a concern for PMR studies. The number of deaths observed was larger than all but the GM Machining Fluids study. Exposure assessment

was superior in quality to all but the GM Machining Fluids study, which is the only one to employ quantitative methods. The GM study however did not take into account non-MF exposures, which may have obscured existing exposure response relationships.

The observations from the two bearing studies are comparable to those from other studies. All but one study found elevated stomach cancer, with the bearing plants showing the largest overall excesses (PMR=1.97, 1.99). No deficits were observed. In the GM MF cohort, stomach cancer was elevated in an SMR study to a small degree. A possibly important difference between these populations is the high concentration of grinding in bearing and engine plants, particularly cast iron grinding (Fig. 8).

**STOMACH CANCER MORTALITY RELATIVE RISKS
in UAW machining plants**

by SMR,PMR,logistic/Poisson regression methods

STUDY PLANT	ALL WORKERS	EXPOSED GROUP
CADILLAC ENGINE	1.25 (17)	1.97* (15)
CHEVROLET ENGINE	0.91 (4)	--
INT'L HARVESTER	1.85 (6)	--
CATERPILLAR	2.34 (3)	--
FAFNIR-BEARING	1.99* (11)	6.9* (8)
GM-BEARING	1.97* (35)	2.35* (18)
FORD ENGINE	2.05* (17)	2.51* (13)
GM MACH. FLUID	1.12 (109)	1.57 (20)
FORD T&C	0.99 (18)	--

Figure 8

* p < 0.05

Larynx cancer was elevated in three and deficit in three plants, but based on few expected cases (Fig. 9).

**LARYNX CANCER MORTALITY RELATIVE RISKS
in UAW machining plants**

by SMR,PMR,logistic/Poisson regression methods

STUDY PLANT	ALL WORKERS	EXPOSED GROUP
CADILLAC ENGINE	--	--
CHEVROLET ENGINE	1.70 (3)	--
INT'L HARVESTER	1.76 (2)	--
CATERPILLAR	0.0	--
FAFNIR-BEARING	0.0	--
GM-BEARING	0.68 (3)	1.01 (1)
FORD ENGINE	--	--
GM MACH. FLUID	1.25 (33)	2.1* (11)
FORD T&C	0.38 (3)	--

Figure 9

* p < 0.05

Esophagus cancer was elevated in five of seven studies with the bearing plants again having the highest excesses (PMR=1.85, 1.88) (Fig. 10).

ESOPHAGUS CANCER MORTALITY RELATIVE RISKS in UAW machining plants

by SMR,PMR,logistic/Poisson regression methods

STUDY PLANT	ALL WORKERS	EXPOSED GROUP
CADILLAC ENGINE	1.14 (4)	0.91 (2)
CHEVROLET ENGINE	1.16 (3)	--
INT'L HARVESTER	1.01 (2)	--
CATERPILLAR	0.0	--
FAFNIR-BEARING	1.85 (6)	1.74 (2)
GM-BEARING	1.83* (13)	1.25 (2)
FORD ENGINE	--	--
GM MACH. FLUID	1.15 (48)	3.5* (15)
FORD T&C	0.95 (13)	--

* p < 0.05

Figure 10

Overall pancreas cancer mortality was elevated in all seven studies, with relative risks ranging from 1.05 - 1.89. Cancer of the rectum was elevated in all but two plants with a threefold excess observed in one of the bearing plant studies (Fig. 11).

RECTUM CANCER MORTALITY RELATIVE RISKS in UAW machining plants

by SMR,PMR,logistic/Poisson regression methods

STUDY PLANT	ALL WORKERS	EXPOSED GROUP
CADILLAC ENGINE	1.25 (8)	1.3 (4)
CHEVROLET ENGINE	1.4 (4)	--
INT'L HARVESTER	0.8 (2)	--
CATERPILLAR	2.7 (2)	--
FAFNIR-BEARING	3.1 * (11)	1.6 (2)
GM-BEARING	1.36 (14)	1.3 (3)
FORD ENGINE	--	--
GM MACH. FLUID	1.08 (61)	2.57* (21)
FORD T&C	--	--

* p < 0.05

Figure 11

among Black Workers only

Prostate cancer mortality was elevated in four plants and was highest at the one non-bearing and non-engine plant (SMR=4.9). Among non-malignant causes of death, stroke was elevated in one bearing and one engine plant. Due to healthy worker confounding and because circulatory disease constitutes a large proportion of all mortality, circulatory disease excesses of less than 20% are difficult to discern in PMR analyses. Similarly, in SMR analysis, healthy worker

confounding makes excess disease at that level unlikely to be detected absent an appropriate reference population.

Risk Assessment Based on Mortality Studies

The GM machining fluids study is the only one of the group with quantitative exposure assessment, and provides insights into specific effects of MF exposures. However, an actual exposure response relationship is difficult to observe in this environment because of misclassification of exposures, particularly for those with major process and material changes over time.

Assessments of overall mortality from SMR analyses underestimate potential work related mortality because of the healthy worker effect (Park *et al.*, 1991) and are therefore strongly biased against hazard identification; (the negative bias of SMR studies is less of a problem in quantitative risk assessment once hazard identification has been accomplished). Increased 'all causes' and 'respiratory mortality' above that expected for industrial populations in the Ford and GM SMR studies is a significant cause for concern.

Probably the most appropriate comparison population available for use in auto industry studies is the set of rubber industry cohorts previously analyzed by Delzell and others. As observed in large industrial populations from the oil and chemical industries, rubber workers, even with some work-related mortality, have SMRs that are substantially below 1.0 for both nonmalignant (SMR=0.805) and malignant (SMR= 0.900) outcomes (Fig. 10). Rubber and auto workers likely had similar demographics and locations. From this comparison, we can estimate the potential excess mortality in the machining plants studied by Eisen (Fig. 12). Combining men of all races, the two GM plants with complete data had all-cancer SMRs of 1.01 and 1.02, and all non-cancer SMRs of 0.96 and 0.99 (Fig. 10).

Compared to an expected SMR of 0.9 for cancer, there could be as much as 11% more cancer deaths than expected in these two plants. Compared to an expected SMR of 0.8 for non-

malignant disease, there could be as many as 18% excess non cancer deaths. Nonmalignant causes of death have been little studied in machining plant populations.

COMPARISON OF SMR's IN MAJOR INDUSTRIES

INDUSTRY (# Studies)	All Cause	All Cancer	Non Cancer	Resp. Disease
Oil Refining (15)	0.76	0.81	0.75	0.55
Chemical (12)	0.79	0.93	0.74	0.64
Rubber (9)	0.82	0.90	0.81	0.71
GM (G&A)	0.97	1.01	0.96	0.83

Figure 12

Exposures In the UAW Study Plants

The historical levels of MF exposures are difficult to estimate because measurements are almost entirely limited to non representative air samples. Most sampling done pre-1980 was complaint-driven or worst case sampling. The documented levels are higher than what would be intuitively reasonable as population averages. Therefore, risk estimates based on those levels will underestimate present risks.

Chemical composition of past exposures is also obscure. Identified carcinogenic components of machining fluids include polynuclear aromatic hydrocarbons, nitrosamines, alkanolamines, formaldehyde generated from biocides, and chlorinated paraffins. Weight of particulate, particularly fine particles, regardless of composition may play a role in carcinogenesis (Fig. 13).

Interpreting health effects in machining plant studies requires that other non MF exposure risk factors be accounted for. Failure to take these other exposures into account underestimates MF exposure-response in internal comparisons. Also, the exposures of supposedly unexposed internal comparison populations need to be considered. In several studies assembly areas had average oil mist levels about one tenth of the machining

areas, small particles are not collected by recirculating control systems, and vapor phase contaminants including oil vapor are likely circulated through the entire facility.

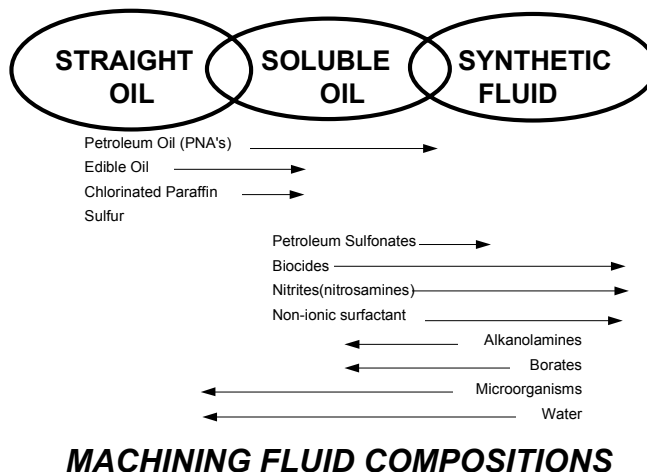


Figure 13

Interpretations of Health Effects

The studies reported to date have clearly identified a cancer hazard to MF-exposed workers. Additional work may expand the number of cancer sites identified and confirm mortality other than cancer. The only study with quantitative exposure assessment was limited to two plants in a narrow sector of metalworking activity (transmission, gear/axle). Similar scrutiny awaits engine, stamping and other specialty parts operations, not to mention non automotive industrial settings. Grinding activities and synthetic MFs also received relatively less attention in the GM machining study.

The more fundamental limitation, however, concerns historical exposure assessment at the level of specific MF ingredients. Although the types of MF in use can be catalogued retrospectively in some situations, specific ingredients generally cannot. Identical processes in similar plants may use the same type of MF but can have very different composition. Not only do specific parts bring specialized requirements, the plant engineering culture itself can settle on a set of product and vendor choices that represent individual engineering, financial, marketing and

personal preferences. Different housekeeping and other plant management practices including coolant system design and management can restrict the range of successful MF applications. These considerations suggest it is unlikely that additional retrospective exposure-response studies can rebut current findings or exclude concern for any particular ingredients.

Nevertheless, some clear patterns have emerged. A full spectrum of gastrointestinal cancers has now been observed. Grinding operations in the bearing plants generally had higher associated mortality risk but such comparisons may be confounded by MF type. The clearest exposure response is with straight oils, many of the same components are present in soluble oils. Stomach cancer appears to follow a pattern different from several other sites (larynx, esophagus, pancreas, rectum, prostate) possibly responding to different MF components.

The SMR results suggest non malignant disease mortality in MF exposed populations. Suggestive evidence for this was found in the bearing plant studies where respiratory, stroke and liver mortality was elevated among grinding workers, the majority in those plants.

Recent observations of increased mortality associated with fine particulates in the air pollution context suggest that fine particulates evolving from coolant mists, particularly water-based or synthetics containing little or no oil phase, may pose a hazard. Such particulates would be expected to spread widely in the plant and immediate extra-plant environment, and therefore confound exposure response studies. This suggests that studies of these effects will require comparison populations from non machining plant environments.

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Mortality Studies of Workers at a Foundry and Two Engine Plants

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ABSTRACT

We conducted a retrospective follow-up study and two nested case-control studies of workers at a manufacturing complex consisting of a large iron foundry and two engine plants. The purpose was to evaluate relationships between various aspects of employment at the complex and death from lung cancer, stomach cancer and other diseases. The follow-up study examined cause-specific mortality patterns among 21,013 hourly workers actively employed from 1973 through 1986 or retired before 1973 and alive as of 1970. Vital status tracing for the period 1970-1987 identified 2,235 deaths. Male employees had overall and all-cancer mortality rates similar to those of men in the United States (US) general population. Their rate of stomach cancer (28 observed deaths) was 35% higher than that of US men and 9% higher than that of men from the county where the complex is located. The stomach cancer excess was restricted to white men with 20 or more years since hire and was concentrated in engine plant workers. Male subjects had 13% more than expected lung cancer deaths (224 observed) compared to US men and 7% more than expected compared to the county male population. The lung cancer excess (relative to the county population) was restricted to white men, was present in both foundry and engine plant workers and was limited to subjects with long duration of employment. The stomach cancer case-control study of 30 cases and 116 controls found an odds ratio (OR) of 1.1 for ever having worked in the engine plants, compared to having worked only in the foundry. Subjects in engine plant machining areas had an OR of 1.8 (95%

confidence interval, CI=0.8-4.1). There was no trend in risk with years spent in machining, and the positive association was limited to one of the engine plants, despite the fact that machining fluid use was similar at the two facilities. Stomach cancer was not meaningfully associated with any foundry work area or job. The lung cancer case-control study, which included 231 cases and 408 controls selected from the cohort, found no association with plant (foundry or engine plants). The OR was 0.9 (CI=0.6-1.5) for 20+ years of work in the foundry, compared to no foundry work. Statistically significant positive associations were found for work in foundry material handling and foundry quality control areas, but length of employment in these areas was not related to lung cancer risk. There was no association between work in high silica or other foundry areas and lung cancer. Cases were less frequently employed than were controls in engine plant machining areas. In summary, the small increases in stomach and lung cancer deaths found in the follow-up study are not clearly attributable to foundry or engine plant exposures.

INTRODUCTION

We conducted a series of mortality studies at a motor vehicle industry manufacturing complex consisting of an iron foundry and two engine plants. Concerns about employees' health had arisen because a previous investigation of decedents from the complex had found elevated proportional mortality ratios for lung cancer, stomach cancer and arteriosclerotic heart disease. Also, foundry and engine plant workers are known to have potential exposure to a number of toxic

substances. Polycyclic aromatic hydrocarbons, formaldehyde, metal fumes and dusts, carbon monoxide, sulfur and nitrogen oxides and free silica are present in foundries; machining fluids, which may contain nitrosamines and other carcinogens, and metal dust are common in engine plants. Toxicologic and epidemiologic research has indicated that exposure to these substances may cause lung, stomach and other cancers, as well as nonmalignant respiratory disease.

The objectives of our research were to evaluate further the overall and cause-specific mortality patterns of workers at the complex and to determine if specific work areas and jobs were associated with lung cancer or stomach cancer. Our investigation included a retrospective follow-up study and two nested case-control studies, one of lung cancer, and one of stomach cancer. In the aggregate, these studies provide indirect information on the health hazards of machining fluids and other exposures found in engine plants and iron foundries. The principal limitations of the studies were the relatively small number of stomach cancer decedents; the lack of quantitative exposure estimates and of data on types of machining fluids; for the case-control studies, the lack of a control group completely unexposed to foundry and engine plant workplace contaminants; and the incompleteness of information on potential confounders, such as tobacco use and place of birth.

METHODS AND RESULTS

The foundry under investigation began operating in 1952. It produces cylinder blocks and heads, intake and exhaust manifolds, crankshafts, flywheels and a number of other automotive parts. The engine plants opened in 1951 (engine plant 1) and in 1954 (engine plant 2), and their operations consist of machining and assembly of various iron, steel and aluminum automotive engine components. The retrospective follow-up study included 21,013 subjects (18,770 men and 2,243 women) who worked at the plant from 1973 through 1986 or who had retired before 1973 and were still living as of 1970. We

compiled the cohort and obtained identifying and work history information from the computerized personnel data files of the company that owned the complex. Detailed computerized work histories were available for the time period 1973-1986. We determined the vital status of 87% of the cohort, identified a total of 2,235 deaths and compared the cohort's mortality experience with that of the US general population and the population in the county where the complex is located, computing standardized mortality ratios (SMRs) as measures of association.

Forty-six per cent of the cohort had 15+ years of follow-up; 59% had worked at the complex for 10+ years. Since 1973, 35% had worked only in the engine plants, 28% had worked only in the foundry, and 33% had worked in both operations. Comparisons with the US general population indicated that male subjects had SMRs of 93 (95% CI=89-97) for all causes of death, 102 (CI=94-111, 555 observed) for all cancers, 135 (CI=90-196, 28 observed) for stomach cancer, 113 (CI=99-129, 224 observed) for lung cancer, 126 (93-167, 48 observed) for prostate cancer, 95 (803 observed) for heart disease and 71 (CI=58-86, 105 observed) for nonmalignant respiratory disease. SMRs based on comparisons with the county general population were lower than US-based SMRs for each of these causes of death and were 93 for all cancers, 109 for stomach cancer and 107 for lung cancer. The slight increase in stomach cancer was limited to white men (county-based SMR=115, CI=74-171), to subjects employed for 20+ years (county-based SMR=140, CI=84-218, white and black men, combined) and to men employed only in the engine plants since 1973. Black men, including those with 20+ years work and those employed in the engine plants, did not have an excess of stomach cancer. An excess of lung cancer was found in white (county-based SMR=110), but not black (county-based SMR=97), male subjects and was restricted to men with 20+ years of employment at the complex (county-based SMR=122; white and black men, combined). Small increases in lung cancer deaths were found both in foundry and in engine plant workers.

Other results of the study include an excess of prostate cancer among black men in the foundry (US-based SMR=234, CI=112-430, 10 observed) and an excess of pancreas cancer among black men in the engine plants (US-based SMR=303, CI=121-624). Other studies have reported results indicating that machining fluids may cause larynx cancer and several forms of gastrointestinal cancer in addition to stomach and pancreas cancer. We found no increases in these cancers in the overall cohort or in engine plant workers.

We conducted the nested case-control studies to evaluate in more detail relationships between employment factors and stomach and lung cancer. Data for these two investigations included complete, rather than partial, work histories and information on potential confounders, such as smoking habits and place of birth, obtained from interviews conducted with subjects or their next-of-kin. Odds ratios (ORs) were computed using conditional logistic regression procedures.

The stomach cancer case-control study included 30 cases and 116 controls selected from among cohort members. We completed interviews for 77% of cases and 68% of controls. Stomach cancer risk was positively but imprecisely related to duration of employment at the complex. Stomach cancer ORs were 1.1 (CI=0.4-3.1) for ever having worked in one of the engine plants, compared to foundry work only, 1.3 (CI=0.5-3.6) for 10+ versus zero years of employment in an engine plant and 1.8 (CI=0.8-4.1) for ever, versus never having worked in engine plant machining areas. There was no trend of increasing ORs with increasing years worked in machining (<5 years: OR=2.3, CI=0.8-6.3; 5+ years: OR=1.5, CI=0.6-4.0). The OR for machining was elevated at only one of the two engine plants. There was no relationship between foundry work areas or jobs and stomach cancer. Stomach cancer was associated strongly with foreign place of birth of the subjects' parents and weakly with birth of the subject in Eastern Europe. Place of birth did not confound associations between employment factors and

stomach cancer.

The lung cancer case-control study included 231 cases and 408 controls. Information on smoking and other potential nonoccupational confounders was available for 72% and 80% of these two subject groups, respectively. Smoking was strongly and positively associated with lung cancer risk, independent of occupational factors. Duration of employment at the complex was inversely related to lung cancer, with an OR of 0.7 (CI=0.4-1.2) for subjects with 25+ years, compared to those with <15 years, of employment. The smoking-adjusted lung cancer OR was 0.9 (CI=0.6-1.5) for 20+ years of work in the foundry, compared to work only in the engine plants. An elevated OR was observed for ever having worked in foundry quality control departments (OR=5.5, CI=1.1-27) and for usual employment in foundry material handling departments (OR=5.1, CI=1.5-17), but there was no consistent trend of increasing ORs with increasing amount of time spent in either department group. Further, although one material handling department involved potentially high silica exposure, there was no association, overall, between work in foundry areas with potential for relatively high silica exposure and lung cancer (OR=0.9, CI=0.6-1.2). An elevated OR was found for work in two engine plant cutting and grinding departments and in several engine plant maintenance departments. However, these results were based on small numbers of exposed cases, and lung cancer was inversely associated with all machining operations combined (including all cutting and grinding departments) and was unassociated with all maintenance departments combined.

CONCLUSIONS

The results of this series of studies are consistent with the absence of potent, widespread carcinogenic exposures in the work environment of the foundry and engine plants. White men in the overall cohort, compared to the local general white male population, had a small excess of stomach cancer deaths, but there was no

consistent evidence that this excess was due to work in operations which would have entailed high exposure to machining fluids or to work in other operations. It is possible that the increase in stomach cancer seen among white men in the follow-up study was attributable to differences in ethnicity between the cohort and the US and local general populations. White male subjects also had a slightly elevated SMR for lung cancer, and several foundry and engine plant departments, employing few subjects, were associated with an increased risk of lung cancer. The occupational

exposures, if any, responsible for these increases remain unknown, as the case-control study results did not implicate departments where there would have been high exposure to silica, machining fluids, polycyclic aromatic hydrocarbons or other suspected lung carcinogens. The findings of an excess of pancreas cancer among black male engine plant workers and of prostate cancer among black male foundry workers were unanticipated, and the reasons for these excesses remain unknown.

Carcinogenicity and Mutagenicity of PAHs/Nitrosamines as Potential Contaminants of MWFs

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ABSTRACT

Workers have a variety of occupational exposures in the metalworking fluid (MWF) industry. Two possible contaminant sources of exposure are potentially carcinogenic polycyclic aromatic hydrocarbons (PAHs) and N-nitrosamines. Although severe refining processes are required to eliminate or reduce the aromatic hydrocarbons for mineral oils used in MWFs, PAHs may still be present in the oils, or as contaminants of ancillary chemicals, or be generated over time under conditions of use.^(1,2) In addition, the Occupational Safety and Health Administration and the U.S. Environmental Protection Agency have promulgated standards to prevent nitrosamine formation in new MWFs. However, nitrosamine formation may occur under certain work conditions or in the presence of nitrate-reducing microorganisms.^(3,4,5,6) Current exposure concentrations for PAHs and N-nitrosamines in MWFs across the MW industry are not known.

INTRODUCTION

The Metalworking Environment

Metalworking fluid (MWF) lubricant base oils (mineral oils) are refined from petroleum crude oils and are complex mixtures of straight and branched-chain paraffinic, naphthalenic (cycloparaffin), and aromatic hydrocarbons. The chains have carbon numbers ≥ 15 and boiling points in the range of 300° to 600°C. The International Agency for Research on Cancer (IARC) lists 8 classes of lubricant base oils and by-products based on the severity and finishing steps of refining. IARC identifies several of these classes (including solvent refining, and hydrotreating of distillate oils) for use in MWFs.^(7,8,9)

The Occupational Safety and Health

Administration (OSHA) Hazard Communication Standard (HCS)⁽¹⁰⁾ requires that employers report on material safety data sheets that a substance is a carcinogen, or potential carcinogen when 1) OSHA has regulated the substance as a carcinogen; 2) the National Toxicology Program lists the substance on its annual list of carcinogens; or 3) IARC has evaluated the substance, and found sufficient or limited evidence of carcinogenicity. Based on the IARC process parameters of mild hydrotreatment, an oil processed at a pressure of 800 psi or less, at temperatures up to 800°F is subject to the HCS.⁽¹⁰⁾

MWFs, Process Chemicals, and Ancillary Lubricants

In addition to the oil based MWFs, ancillary lubricants and process chemicals can be introduced into the machining processes depending on the type of operations. These substances include hydraulic fluids, bearing and gear lubes, greases, cleaning compounds and degreasers, etc. These ancillary lubricants such as hydraulic fluids do not undergo the same severity of refining steps as do the oils used in MWFs.

Epidemiologic and Toxicologic Data for the Carcinogenicity of Contaminants in MWFs.

The NIOSH draft document *Special Hazard Review of the MWF Industry* describes several known MWF contaminants. Some of these contaminants have been reported to cause cancer in animals. Two examples of contaminants are N-nitrosamines⁽¹¹⁾ and some polynuclear aromatic hydrocarbons.⁽¹⁾

Since the 1940s, evidence has accumulated to support an association of skin (including scrotal) cancer with occupational exposures to mineral oil containing polynuclear aromatic hydrocarbons (PAHs) in MWFs. Several case reports have

identified skin cancer among MWF-exposed workers.^(12 through 21)

Acid-refined oils, which contain higher concentrations of PAHs than solvent-refined oils, have been shown to produce skin cancer in experimental animals.⁽²²⁾ A refined, emulsifiable MWF assayed in the Salmonella/microsome assay after prolonged use as aluminum rolling oils was found to be directly mutagenic. These data suggest that mutagens may form in highly refined MWFs under high temperature conditions of use.⁽²⁾

N-Nitrosamines

In general, the formation and concentration of nitrosamines in MWFs is dependent on: 1) the concentration of amine and nitrosating agent; 2) the type of amine; e.g, mono-, di-, or tri-; 3) the presence of catalysts or inhibitors; 4) the pH of the MWF; 5) temperature of the fluid; and 6) the time of contact between amine(s) and nitrosating agent(s).⁽²³⁾ The degradation of nitrosamines in MWFs is less well understood, but may also depend on the pH of the fluids, the type of machining operation and metal being machined, and length of fluid use.

Certain nitrosamines may be formed in MWFs during the extreme heat and pressure generated by machinery.^(18,24,25) Triethanolamine (TEA) can be readily nitrosated to form N-nitrosodiethanolamine (NDELA); a nitrosamine that IARC considers to be potentially carcinogenic.^(26,27,28,29,30,31)

The EPA prohibitions of the addition of nitrosating agents to MWFs containing the triethanolamine salt of tricarboxylic acid (1984), mixed monoamides and diamides of an organic acid, or a triethanolamine salt of a substituted organic acid (1991) were intended to eliminate or reduce the concentration of contaminating nitrosamines by controlling the precursors.^(32,33) However, several studies as recent as 1986 have reported the presence of n-nitrosamines in MWFs.^(34,35,36)

In MWFs that contain TEA or DEA, nitrosamines may be formed even though nitrites have not been added. Challis *et al.*⁽³⁷⁾ demonstrated the rapid nitrosation of primary and secondary amines by nitrogen oxides; oxygen

accelerates nitrosation by converting NO through NO₂ to either of two nitrosating agents, N₂O₃ or N₂O₄. N-nitrosamine formation from NO and amines is accelerated under specific conditions by formaldehyde, paraformaldehyde, thiocyanate, nitrophenols, and certain metal salts (e.g., ZnI₂, CuCl, AgNO₃, SnCl₂, CoSO₄, and HgCl₂).^(23,37,38,39,40,41) The processes of nitrosamine formation in MWFs at the workplace have not been clearly identified.

CONCLUSIONS and RECOMMENDATIONS

PAHs and N-nitrosamines may still contaminate MWFs. Research is needed to identify any potential cancer or other adverse health risks for workers exposed to metalworking fluids contaminated with PAHs and/or N-nitrosamines. Areas for research include:

- Studies should be conducted to examine the potential worker exposures to microbial growth which may contribute to the development of hazardous contaminants.
- The effectiveness of worker protection and engineering controls in various work situations should be studied to determine the most effective ways to eliminate or reduce exposure to potentially hazardous contaminants in MWFs.
- Research should be conducted to develop sampling and analytical methods for simple on-site detection and monitoring of nitrosamines, PAHs and their precursors.
- Biomonitoring methods should be developed to determine nitrosamine and PAH exposure to workers.
- Use of safe, non-toxic alternative or substitute ingredients and additives which will not contribute to the generation of nitrosamines should be examined.
- Studies should be conducted to determine conditions that enhance nitrosamine formation in MWFs, and methods should be developed to prevent or reverse this process.
- Studies should be conducted to determine whether contaminants are concentrated or

removed during the rerefining and recycling of used MWFs. The safety of recycled and reused MWFs should be examined.

- Dermal exposures to contaminants in MWFs and absorption through normal or damaged skin should be examined.
- The degree of contamination of MWFs by ancillary lubricants and process chemicals should be assessed to determine their contribution to the PAH and nitrosamine content in used MWFs.

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METAL WORKING FLUIDS, BASE OIL SAFETY

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ABSTRACT

This presentation will address an historical perspective on the association of mineral base oils and adverse human health effects, an overview of the manufacturing of base oils used in metalworking fluids (MWF), an update on the regulatory status of base oils, and the methods currently available to screen and test a base oil for its skin tumor potential in mice.

The use of base oils prior to 1900 through 1950 had often resulted in exposure to unrefined or minimally refined products. In many instances airborne and direct exposure had resulted from poor industrial hygienic practices. As a result, epidemiological studies using work histories from this period have demonstrated associations of cancer with prolonged exposure. An increased incidence of skin cancer, mostly scrotal but also hand and arm, has been most often demonstrated. In some studies an association of base oil exposure to cancer of the lung and rectum has been demonstrated.

Studies conducted by academic and petroleum industry investigators have demonstrated that the skin tumor potential in rodents, primarily mice, is due to the polycyclic aromatic content of the base oil. As a result of this finding the manufacturing of base oils for use in MWF now utilizes severe refining processes. Severe solvent extraction and severe hydrotreatment are most often used to manufacture noncarcinogenic base oils. These refining processes completely eliminate the carcinogenic potential of the base oil.

The OSHA Hazard Communication Standard has resulted in a heightened awareness and some confusion over the differences between carcinogenic and noncarcinogenic base oils, particularly those manufactured by hydro-treatment. OSHA's effort to clarify the situation through its 1985 Notice of Interpretation may have, without intent, added to the confusion.

It is now apparent that a process-based definition for severity of treatment has several limitations.

The American Petroleum Institute (API) contends that a variety of screening and testing combinations can be used to demonstrate, in a weight of evidence approach, that a base oil does not represent a carcinogenic risk. Biological test methods currently available are chronic and initiation-promotion skin painting bioassays, and the modified Ames assay. Analytical methods, which essentially measure the polycyclic aromatic content of a base oil, are the Institute of Petroleum IP 346 test, the Food and Drug Administration ultraviolet absorbance test, and various tests for the total polycyclic aromatic content and individual polycyclic aromatic hydrocarbon content.

Historical Perspective

Although the emphasis of this paper will be the carcinogenic potential of mineral base oils currently used to produce MWF, it is important to mention the early use of MWF and their associated human health effects. In the past, MWF had been derived from both shale and petroleum oils. Kerosene weight oils, as well as heavier base oils had been used depending upon the application. Prior to the 1950's, the petroleum and shale oils that had been used were primarily raw distillates, or only mildly refined oils. Little had been done to these oils after primary distillation other than filtration. While these oils had reasonable lubrication properties, they also contained a significant amount of substances that posed some cancer hazard to workers. This, coupled with work practices that often resulted in excessive dermal, inhalation, and ingestion exposures had increased the potential for adverse health effects.

Epidemiological and clinical data have shown an association between exposure to unrefined mineral oils and skin disorders such as dermatitis, oil acne and folliculitis. Skin cancer, especially

scrotal, has also been associated with these unrefined mineral oil lubricants. In some studies, association with cancer other than the skin, such as lung and rectal, has also been reported.

The International Agency for Research on Cancer (IARC) has determined 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 metal machining are carcinogenic to humans. This evaluation was based on the results of studies of manufactured MWF and work practices that are not generally relevant today.

Studies by academic and industrial investigators with animals, particularly the mouse, have confirmed the skin cancer causing potential of these early mineral oil lubricants. Extensive analytical and toxicologic efforts have helped identify certain polycyclic aromatic compounds as the causative agents.

PACs and PAHs

The acronyms PACs (polycyclic aromatic compounds) and PAHs (polycyclic aromatic hydrocarbons) have often been used interchangeably although there are subtle differences. PAHs are comprised of multiple aromatic benzene rings. PAH rings contain only carbon and hydrogen. PACs are very similar to PAHs, but also contain molecules of nitrogen, sulfur and oxygen attached to the ring structures. In other words, all PAHs are PACs but not all PACs are PAHs. Unfortunately, the carcinogenic potential of PAHs and PACs is quite variable, some structures have clearly been associated with cancer, while others have not. The cancer potential of PAHs and PACs has been generalized to include 3-7 ring structures, although again not all 3-7 ring materials have been shown to be carcinogenic in experimental studies.

Overview of Petroleum Refining

The manufacture of MWF base oils involves the distillation of crude oil in a fractionation tower under atmospheric pressure. Products from the atmospheric tower include gasoline, jet fuel, diesel fuel, kerosene and heating oil. The heavier

residual material from the atmospheric tower is further distilled in a fractionation tower under vacuum pressure to produce raw base oils. Raw base oils are then further refined to produce finished base oil products.

Modern refining techniques of solvent extraction selectively remove PACs from base oils, leaving behind relatively few PACs. The process of hydrogen treatment chemically alters or "busts" the PAC ring structures open to produce non-ring structures, rendering them non-carcinogenic in nature.

Dewaxing is necessary to remove the waxy materials from the base oil fractions. Clay filtration improves the color of base oils. Dewaxing and clay filtration do not impact the carcinogenic potential of a base oil.

The carcinogenic potential of petroleum streams used for MWF has routinely been assessed by mouse skin painting studies (Table 1).

Table 1

Refinery Stream	Mouse Skin Cancer Hazard	PAC Content
Crude oil	Fail	> 1 %
Raw vacuum distillate	Fail	> 1 %
Mild solvent extracted	Fail	> 1 %
Severe solvent extracted	Pass	< 1 %
Mild hydrotreatment	Fail	> 1 %
Severe hydrotreatment	Pass	< 1 %
Mild hydrotreatment & mild solvent extraction	Pass	< 1 %
Acid treated	Equivocal	variable

Crude oils, from which base oils are derived, have caused cancer in mouse skin and have been shown to contain high levels of PACs. Raw vacuum distillates, similar in nature to the lubricating oils pre-1950's, are the stream from

which most MWF base oils are derived and these oils typically cause skin cancer in mice. These materials have also been shown to contain high levels of PACs. Experience and experiments have shown that mild refining, or light treatment with solvent and/or hydrogen, may reduce the amount of PACs, but that these materials may still fail the mouse skin painting bioassay due to remaining levels of PACs. On the other hand, if base oils are severely solvent extracted, severely hydrotreated, or sequentially mildly solvent extracted and mildly hydrotreated they are no longer carcinogenic in the mouse skin painting bioassay, and not surprisingly have greatly reduced levels of PACs. The amount of PACs in acid/clay treated base oils alone has not been well documented and mouse skin painting results and analyses from these materials have not been consistent.

Regulatory Status

Mineral oils, specifically lubricant base oils, were first evaluated by IARC in 1982. Their evaluations were summarized and published in IARC Monograph 33. IARC had evaluated the carcinogenic potential in experimental animals to eight different classes of mineral oils. Classes were mostly determined by refining technique, but also included a class for formulated products. IARC had determined that there was sufficient evidence for the carcinogenicity in experimental animals for mildly solvent refined and mildly hydrotreated oils, that there was no evidence for severely solvent refined oils, and that there was inadequate evidence for severely hydrotreated oils. IARC had also determined that there was inadequate evidence for formulated products as a whole, which would include formulated MWF. In addition, IARC had determined that there was sufficient evidence for carcinogenicity from studies in humans that mineral oils (containing various additives and impurities) that have been used in occupations such as metal machining are carcinogenic to humans.

In Supplement 7 (1987), IARC re-evaluated the carcinogenic potential to humans for substances which had been previously evaluated in earlier

IARC monographs. With regard to mineral oils, IARC determined that untreated and mildly treated oils were carcinogenic to humans, and that highly refined oils were not classifiable as to their carcinogenicity to humans.

IARC evaluations became more important in the regulation of base oils with the passage of OSHA's Hazard Communication Standard (HAZ COM) in 1983. According to OSHA, substances considered carcinogenic by IARC must be so designated in compliance with HAZ COM. Unfortunately, IARC did not define what parameters constituted mild and severe treatment. Therefore, on December 20, 1985, OSHA published an interpretative notice in the Federal Register in response to numerous questions about the HAZ COM regulation and the carcinogenic potential of hydrotreated naphthenic base oils.

The notice was written to interpret IARC Monograph 33. OSHA noted that IARC had not explicitly defined the terms mild and severe when used to describe some types of oil processing. Specifically IARC had not defined mild or severe parameters for solvent extraction or hydrotreatment. Moreover, IARC had not explicitly defined the significance of variations in the processes used to produce petroleum streams, such as crude slate, catalysts, solvents utilized, temperature and pressure conditions, space velocity, etc.

OSHA limited the 1985 Notice of Interpretation to hydrotreatment of base oils. Ultimately, OSHA set a process limit to define mild hydrotreatment as an oil that is treated with hydrogen at pressures less than 800 psi and at temperatures up to 800 degrees F. Under this definition, OSHA regarded oils that were hydrotreated under these mild conditions as carcinogenic as discussed in IARC Monograph 33. Such oils were to be labeled as carcinogenic by the supplier in order to comply with HAZ COM. Other process definitions offered in this guidance were that severely solvent extracted and/or hydrotreated oils were not considered carcinogenic. Also, sequential mild solvent extraction and mild hydrotreatment would render

an oil noncarcinogenic. These decisions were made based on data and information from IARC Monograph 33. Finally, OSHA indicated that apart from the IARC review, if any manufacturer/producer of oil had results of credible scientific validity on their oil that indicated carcinogenic activity, that information had to be used in the hazard determination for that product for compliance with HAZ COM.

The current OSHA permissible exposure limit (PEL) is 5 mg/m³ for an 8-hour time weighted average (TWA). The limit is based on a no observable effect level in animals exposed repeatedly to 5 mg/m³ of a white mineral oil mist containing no additives. At 100 mg/m³ slight changes, including lung effects, were observed in exposed animals. OSHA also noted that heat-decomposed oil fumes are irritating to the lungs. The PEL is set at a level intended to protect from eye and respiratory tract irritation.

The ACGIH threshold limit value (TLV) for mineral oils is 5 mg/m³ for an 8 hour TWA, and 10 mg/m³ for a 15-minute short-term exposure limit (STEL). The TLVs are based primarily on the same studies evaluated by OSHA. The TLVs are set to protect against respiratory tract irritation. The ACGIH is currently in the process of changing the mineral oil TLV to account for severely and mildly treated mineral oils. ACGIH has proposed a TLV-TWA of 5 mg/m³ for severely treated oils and 0.2 mg/m³ for mildly treated oils. As with IARC, the ACGIH has not proposed any parameters to define mild and severe treatment

The API has submitted to ACGIH a proposed recommendation for severely and not severely treated oils. API has recommend a weight of evidence, performance-based paradigm using a variety of available testing and screening assays to define degree of treatment. These assays are further discussed later.

Acute and Sub-acute Toxicity

In general, the acute and sub-acute toxicity of mineral base oils is considered low or relatively non-toxic. Data available from animal studies on a number of both light and heavy base oils from a variety of crude slates and processes indicate very

low acute toxicity. These data correlate with industrial experience with base oils.

The primary exposure route to base oils is dermal (skin), and results of high dermal exposures of base oils and commercial lubricating oils show no effects in test animals other than a generalized defatting of the skin on repeated exposure. The skin is a protective barrier and the base oils are generally not absorbed to any extent due to the high molecular weight of base oil molecules. Base oils are not primary skin irritants and do not cause allergic skin reactions when tested in either animals or human volunteers.

When large doses of base oils are given internally by the oral route, the resulting effects are also considered not harmful. The primary response is a laxative effect, and no organ damage or effects are observed in test animals. There is a possibility of lung toxicity and/or chemical pneumonitis if lighter molecular weight oils are introduced into the respiratory system, typically by aspiration of vomit containing light oil, which can occur after accidental ingestion. However, this does not occur with base oils with viscosities greater than 100 SUS, and most MWF base oils exceed 100 SUS. Base oils are also not considered eye irritants, although they can cause discomfort if they are left in contact with the eye for more than a minute or so without flushing the eye with water.

Finally, base oils have relatively low inhalation toxicity and no effects on organs other than slight changes to the lung are observed on high oil mist exposure. Some lung and upper respiratory tract irritation may be observed, but this generally subsides after exposure ceases.

Mouse Skin Cancer Testing and Screening

Early investigators had noted that mineral oils associated with squamous cell carcinoma in human skin also produced the same type of cancer when applied to mouse skin. Interestingly, rats and hamsters were not susceptible to skin cancer development. Based on these findings, the chronic mouse skin painting bioassay was developed for assessing carcinogenic potential of petroleum products. In the chronic mouse skin painting bioassay the test material is applied to the skin for

up to 2 years. The application site is examined for the development of tumors and associated findings. A shorter term skin painting bioassay is the initiation-promotion (I/P) bioassay. The I/P bioassay, also performed in mice, determines if a material initiates cancer - generally thought to occur through genetic cell mutations, promotes the growth of initiated cancer cells or both. The I/P test takes 6-months to complete. Another biological test used to predict base oil carcinogenicity is the modified Ames assay (MAA; - modified to allow for testing of petroleum oil). The MAA is a test tube type of assay that measures the ability of a base oil to cause mutations in bacteria. If a base oil can produce mutations in bacteria, it may have the potential to cause cancer, at least in mouse skin. The MAA has an excellent correlation with mouse painting bioassay results. The MAA is also approved by the ASTM as an accepted test method for determining the carcinogenic potential of MWF base oils containing no additives

In addition to the biological tests, three

analytical tests have been developed for use as predictors of carcinogenic potential. Two of these tests utilize a solvent, dimethyl sulfoxide (DMSO), to extract chemical classes of the oil including PACs. One of these, the IP 346 test is a gravimetric method which measures the weight percent of DMSO extractable material. This test also correlates reasonably well with mouse skin painting data. The IP 346 test is accepted by the European Union as an acceptable way to determine the carcinogenic potential of base oils containing no additives. An oil with a DMSO extractable content of less than 3% is considered noncarcinogenic. The other test, the FDA absorbance test is a spectroscopic procedure based upon the ultraviolet absorbance of the DMSO extractable portion of oil. The FDA test has long been used as a specification for demonstrating the purity of white mineral oils. Finally, several different methods can be used to measure either total or individual 3-7 PACs using specific analytical instrumentation such as liquid and gas chromatography and mass spectrometry.

Table 2

Process History	Skin Painting	MAA	IP 346	FDA	PAC
Raw distillate	Fail	Fail	Fail	Fail	High
Mildly solvent extracted	Fail	Fail	Fail	Fail	Medium
Severely solvent extracted	Pass	Pass	Pass	Pass	Low
Mildly hydrotreated	Fail	Fail	Fail	Fail	High
Severely hydrotreated	Pass	Pass	Pass	Pass	Low
Mildly hydrotreated / mildly solvent extracted	Pass	Pass	Pass	Pass	Low

Table 2 presents data on petroleum derived base oils that generalize results of mouse skin painting bioassays and a battery of short-term predictive tests. The far left column displays the base oils and the variation of processing

employed, while the other five columns display the results of the skin painting bioassay and the predictive tests. The data are all shown as a qualitative pass or fail, with the exception of the PAC column which is expressed as high, medium

and low. However each predictive test can be, and is, quantified with limits set to ensure the highest correlation possible with the lifetime mouse skin painting bioassay. In fairness to the universe of data, all assays do not uniformly agree in every case, but the short-term test correlations are generally quite high with the mouse skin painting bioassay and the data shown in this table represent generalized findings of industry.

Raw distillates fail the chronic skin painting tests, exceed the fail limits in the short-term predictive tests, and have very high PAC values. In a similar fashion, mild solvent extraction or mild hydrotreatment, where mild is either defined by industry practice or the current OSHA scheme, does nothing to reverse the qualitative results in all the tests, except that there is a reduction of PACs, and a reduction in quantitative values of the other tests. However, when a base oil is severely refined by solvent extraction or hydrotreatment, or sequentially extracted by the two processes, the cancer potential in rodents is eliminated and the remaining predictive tests

generally achieve a pass level, which is coincident with a low level of PACs that are found on analysis.

CONCLUSIONS

Early refining processes and misuse by today's standards of mineral base oils had been associated with the potential to produce cancer in humans, particularly skin cancer. It was later discovered, primarily through animal experimentation, that PACs were the causative substances. Subsequent improvements in the refining process, most notably severe solvent extraction and/or severe hydrotreatment, were found to eliminate the cancer hazard by reducing the PAC level. It is now possible to produce completely safe base oils and to demonstrate their safety through a variety of bioassays and screening test. The API recommends that severity of treatment be defined and demonstrated by a weight of evidence approach using a variety of methods, and that customers should request this information from their suppliers.

DISCUSSANT'S COMMENTS and OPEN DISCUSSION

Dr. LAWRENCE FINE, NIOSH: The way we are going to organize the next session is that we will have three Discussants who will speak for about ten to no more than 15 minutes and then I will invite all of the speakers who are not yet up on the platform to come up and then we'll open it for questions, comments and a general discussion and we'll continue until at least five o'clock, if that seems appropriate. Our first Discussant is Dr. Gordon Reeve from Corporate Epidemiology at the Ford Motor Company. Dr. Reeve.

Dr. GORDON REEVE, Ford: Good afternoon. In the next ten to 15 minutes, I'd like to go through the interpretation of some of the epidemiologic findings, but I'd like to do that in a general way as opposed to study by study. And sometimes it's helpful to have a bit of a background of someone who is going to ask you to accept their opinion, so I thought I'd give you a very brief synopsis of my experience.

I started out in 1975 when the only thing going on in occupational epidemiology was occupational cancer with asbestos and benzene and vinyl-chloride coming to the front, and I worked at that for four years at M.D. Anderson Cancer Hospital coordinating medical follow-up of a cohort of asbestos workers. In 1979, I went to NIOSH for five years and studied brain cancer in the petrochemical industry. About 1984 when budget cutting under Reagan took place, I left NIOSH to do "front line public health" in Houston and later in Indianapolis. Six and a half years ago I came to Ford primarily to work on occupational injury epidemiology, but I find myself here today talking about the old standbys of occupational cancer epidemiology. My purpose in pointing this out to you, though, is through my experience I have had a lot of chances to see the people behind the numbers over the years. From my public health background in Houston, especially, I have been involved in a lot of situations where you can't say, "well, we need more studies," but instead come to

some conclusion that can push us forward to decisions, and I think that's probably where we are now with the cutting fluid situation.

Now, in evaluating and interpreting epidemiologic studies, there are two things that I want to highlight. One is the study designs and how they affect outcomes. And there is a lot of work that has been done over the years, but in marching through this, I want to point us towards the types of studies that I think we really ought to focus on and their results regarding the health effects of cutting fluids.

Typically when you start looking at occupational epidemiology problems, there are basically three to four steps you can go through.

PROGRESSION OF OCCUPATIONAL EPIDEMIOLOGY INVESTIGATIONS

- Case Clusters
- Community-Based Surveys and Studies
- Proportionate Mortality Studies
- Plant- or Industry-Based Cohort Studies with/without Nested Case-Control Studies

Figure 1

The initial steps, case cluster investigations, community based surveys or community based studies, are basically your first targeting mechanisms to let you know that there might be a problem. Then you go on to proportionate mortality studies, depending on what your resources are and availability of data are. After these initial studies, then you finally get down to plant-based or industry-based cohort studies, typically with nested case controls, similar to what Dr. Eisen presented this morning.

But the point of all this is that as you move down from the case clusters down through the other studies, you are learning more and more all the time. But it's not a situation where if you have a finding in the more comprehensive studies that

doesn't please you, you can't toss this out and go back to the case clusters of the community based studies because they fit with your way of thinking.

One often begins with a case cluster investigation. Clusters are usually identified by observant clinicians.

PROGRESSION OF INVESTIGATIONS

Case Clusters

- Usually Detected by Clinicians
- Most Production For Rare Diseases
- Usually Prompts Further Investigation

Figure 2

Examples of these would be polyvinyl chloride and angiosarcoma of the liver. Another example would be oat cell carcinoma of the lung and exposure to BCME. Now these are most productive for very, very rare diseases like the two I just mentioned. If clinicians look at a series of lung cancers that are squamous cell or basal cell, they won't be able to put things together very well. But if you have a very rare type of a cancer, they'll be able to identify it as an unusual event a lot more quickly because it will be a unique observation in their experience. But no matter what the outcome of that initial case investigation is, it's going to have to be followed up by some other type of studies, either a PMR studies or a cohort study.

Now, another way that you can hone in on things is that you can look at community based surveys and many of these were presented by NCI in the mid 1970's with their cancer maps.

PROGRESSION OF INVESTIGATIONS

Community-Based Surveys and Studies

- Ecological Surveys of Mortality
- Case-Control Studies Based on General Risk Factors
- Requires Further Investigation More Closely Linked to Occupational Exposures

Figure 3

When I was living on the Texas Gulf Coast in 1975, I remember the glow of the area around Houston with all of its refineries being a high area for cancer and I think the phrase cancer alley in New Jersey came from these types of community based surveys.

We can also look at county-based studies where we can look at death certificates in particular counties and look at the usual occupation of those people who died of certain cancers on those death certificates. This is one tool we used at NIOSH when we looked at brain cancer in the petrochemical industry that targeted at Dow Chemical in Freeport Texas. But still even with these, these aren't definitive and they need to be reinforced by further study.

Which brings us to proportionate mortality studies.

PROGRESSION OF INVESTIGATIONS

Proportionate Mortality Studies

- Percentage Differences Among Worker Groups and U.S. General Population Deaths
- Typically Done When Not Possible To Conduct Full Vital Status Follow-Up
- Study Design Subject To Several Biases
- Findings Typically Subjected to Further Study

Figure 4

And with these, you are essentially taking a series of deaths and looking at the percentage of deaths to a particular cause, For example, 25 percent of these deaths in your population may be due to lung cancer. Then you look at a corresponding percentage of deaths in the U.S. general population, that might be 15 percent and you say, "gee, I have a proportional excess which indicates that there's an occupational association there."

The problem with PMR studies is that they typically are done when you don't have access to full records or you don't have the funds or time to do a full follow-up or cohort study. But you also have some problems with how this study design

impacts the findings because you're comparing percentages. If one particular percentage is higher for one type of cancer, it will shove other things in your other percentage groups lower.

Let me give you one example from a car perspective. Right now Ford is sitting at about 26 percent of the car and truck market. That's pretty good by our way of thinking, but let's say that if we increase our market share to 30 percent, something has to happen to GM or Chrysler or Honda or Toyota because if our market share increases, the other ones have to come down and this is the same kind of phenomenon that affects a PMR study. So typically you can run into problems that way with a PMR study. The best thing that you can do is you can conduct a cohort study that is based on complete follow-up of an entire population.

PROGRESSION OF INVESTIGATIONS

Plant-Based Cohort Studies With or Without Nested Case-Control Studies

- Gives Rate-Based Estimate of Risk for Cohort
- For Mixed Exposures Provides Estimate of Risk AND Finds all Deaths for Nested Case-Control Studies
- Further Productive Research is Study of Larger Cohorts and their Nested Cases With Improved Exposure Assessment

Figure 5

It will give you a population-based death rate, whether it's for a certain type of cancer or a collection of cancer types. You can also use this to do nested case controls as you have heard discussed earlier this morning.

Now, having gone through that, it's my opinion that if you look at all the studies that have been done in this area, you really need to focus in on the two largest cohort studies and their nested case-control studies.

STUDY FINDINGS

The largest one is the UAW-GM study that we have heard discussed earlier this morning and they

found in that cohort study laryngeal cancer excesses and rectal cancer excesses. We also need to look at the UAW-Ford study that shows that we had a 58 percent excess that was statistically significant for stomach cancer in engine and foundry workers. When we looked at engine workers only, we had an SMR of 254, which was basically 2.5 times the risk relevant to the U.S. General population.

UAW - GM		
Straight Oils	SMR	Cases
Larynx	198*	n=23
Rectum	147*	n=37
Stomach	112	n=49
Lung	102	n=251
UAW - Ford		
Engine & Foundry		
Stomach	158*	n=24
Lung	111	n=176
Engine Only		
Stomach	254*	n=15

Table 1

Now as you may have noticed, for particular studies summarized in Table 1, I did not include anything about the esophageal cancer which was discussed earlier. The case-control studies indicated a five-fold risk for one group, and then there was one analysis that produced a 12-fold risk. But I think these analyses need to be evaluated carefully. There were certain things about the graphs presented earlier that should be consistent on all those bar graphs when they go from short times of exposure to long time of exposures, and were not. It's necessary to know how many cases each of those graphs were based on, and we couldn't tell that from the presentation this

morning. So I think that's something we need to examine further.

From the published cohort studies, we have two to three excesses here, so there is some indication of risk, at least with the historic exposures. Now looking at those risks, we have to look at the dose response.

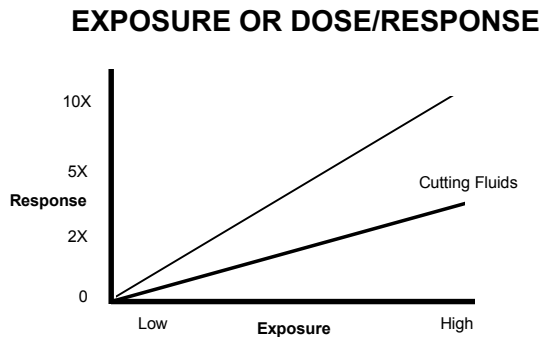


Figure 6.

Now with the cutting fluids, basically you're looking at a maximum of 2.5 for stomach cancer in Ford engine plant workers, and for GM workers, a two-fold risk for laryngeal cancer, and a 50% excess of rectal cancer. What we have to remember, about the exposures with those, is that the exposures were extraordinarily high. These people had exposures much higher than the current standard of five milligrams per cubic meter. They also had operations that they needed to perform where they were actually doing the manual manipulation of the machine and it required that their faces were literally inches from the cutting and grinding surfaces, and they were coated with cutting fluids as they did these operations. And the exposure estimates that we have seen in all of these studies do not consider this type of dermal exposure, or the, I guess you could say, using a popular term in Detroit, the "in your face" exposures, where you breathed it, you ate it and you were it.

Now, a few things have changed as we heard about from some of the other speakers. One is that they have removed or reduced significantly the PNAs and some of the other agents that were

proven in other industrial settings to have carcinogenic effects. Another improvement is the tremendous progress that has been made to reduce airborne levels of cutting fluids in plants. So if this is as bad as it gets, with very high exposures and only two to two and a half fold risk increases for selected cancers, one has to wonder what risks exist for situations where exposures are much, much lower over the last 10 to 15 years. Realistically, how much more benefit can we get by controlling all the airborne exposures from cutting fluids to levels substantially lower than the current standard?

But I don't want to leave you with an impression that we should do nothing. There is this sort of the continuum of things, where we can do from nothing at all, to taking extreme actions.

STRENGTH of ASSOCIATION

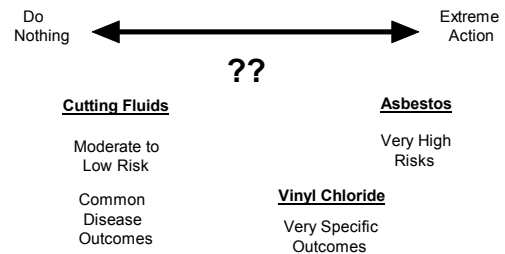


Figure 7.

Now with asbestos we had very, very high risks, even though it was lung cancer types that were fairly common and associated with smoking. We had vinylchloride that was associated with a very specific outcome and a very specific exposure. with cutting fluids, we have a moderate to low risk, and I'll let someone else argue about adjectives, but if you think the risk is low, I would say that that is probably where we are today. If you think the risk is high, then we could say that was historical. But I'll let somebody else argue about those adjectives.

The other thing here is we have very common disease outcomes. We have things that esophageal cancer is strongly associated with alcohol and

tobacco use. So we have a situation here where we're trying to control something where we have common cancers that can be caused by many causes, both occupational and non-occupational.

So the thing is, do we do nothing or do we take extreme action. Actually, most of the information you have heard presented here today was presented at a NIOSH meeting in Cincinnati last year with a much smaller group of people. My recommendation at that time about a year ago, that was BNG, (before Newt Gingrich) was that OSHA was in the process of assembling a list of 132 priorities. Why 132, I don't know. But they were going to go from that 132 priorities and develop a top 20 list. In my recommendation, based on my interpretation of the studies, is that one, we need to do something as opposed to nothing.

Regulation or further regulation of cutting fluids should be on the top 20 list, but not at the top of that list. Furthermore, I think the handwriting is on the wall in terms of how this is going to go in the industry because we have seen the future at least in our Engine Plant 2 in Cleveland, which has just gone through a dramatic change-out where all the old cutting fluid and transfer lines were taken out and disposed of and brand new equipment was brought in. The airborne levels of cutting fluids in that plant are basically nonexistent.

Now the real question for others to answer is how fast that process can take place when you consider that we're talking billions of dollars to refit or update all cutting fluid operations in the U.S. But again, I'm just an epidemiologist. I don't want to over-step my bounds. I stated the case here that we should do something. The speed and cost of that something is left for others to decide. Thank you.

Dr. LAWRENCE FINE, NIOSH:

Thanks very much Gordon. Our next Discussant is a colleague of mine. Dr. Geoff Calvert.

Dr. GEOFFREY CALVERT, NIOSH:

Why the concern over metalworking fluids. Since

the 1970's, there has been concern that metalworking fluids may be associated with cancer. In addition, there are a large number of workers who were exposed to metalworking fluids. I've got a figure of over a million and Dr. Ong presented a figure of about three million. These are estimates from a survey that was done by NIOSH back in the early eighties, *The National Occupational Exposure Survey*. There are probably differences, based on who you define as being exposed to metalworking fluids, but the million probably represents the more highly exposed individuals.

As a result of the concern about cancer and the large number of workers exposed, NIOSH has been in the process of writing a hazard review dealing with metalworking fluids and as part of that, I have been responsible for examining the association between metalworking fluids and cancer.

Based on my review, these are the cancer sites that probably have the strongest association with metalworking fluid exposure. They are stomach, rectal, pancreatic and laryngeal, and also skin cancer should probably be on that list. Skin cancer and scrotal cancer and a few other cancers that I'll be talking about a little bit later.

As part of my review, I looked at a number of different studies, including the cohort mortality studies that were presented earlier in the afternoon, as well as case control studies. Dr. Reeve did not talk much about case control studies. In general, case control studies look at a group of people with the disease of interest and compare them to a group of people without that disease, to determine if the people with disease have exposures to specific factors at a higher rate than people who are not diseased. So there are some problems and limitations with case control studies. They are not as strong as the cohort mortality studies, but again if you see a consistency across many studies, you begin to think that there may be a pattern of an association.

This slide shows the number of studies that I have looked at for stomach, rectal, pancreatic and laryngeal cancer. And as you can see, a number of

studies have been done. This row shows the total number of studies. This row shows the studies with the risk greater than one and as you can see, almost all the studies found an elevated risk and this row shows the number of studies that had a significantly elevated risk above one.

And again, all the sites had more than one study with a significant elevation in risk. And many sites had many more than one; six for stomach cancer, four for rectal, five for pancreatic. So this slide conveys that there is a consistency across studies for an increased risk of cancer at these sites.

This slide deals more with the strength of an association, in that it shows those studies that had a risk of 1.5 or greater. The earlier slide had a risk of just one. This slide shows that half or more of all the studies that examined these sites had risks greater than 1.5 and many of these studies had significantly elevated risks. So based on this evidence, there appears to be an association with metalworking fluids and cancer at these sites. Unfortunately, we do not have time to go through each one of these studies here, but all the details of these studies will be provided in the NIOSH Hazard Review, which should be released soon.

Here are four other sites (esophagus, bladder, brain and lungs) that we investigated for an association with metalworking fluids. Again, we'll show the data in terms of a consistency across the studies. Actually, I just have the strength of an association. Here's the slide looking at consistency across the studies and for esophageal cancer, all eight studies found a risk greater than one. This does not include the studies that were reported by Dr. Eisen earlier this afternoon. Only one of these studies was statistically significant.

For bladder cancer, a lot of the studies are case control studies that looked at workers with potential exposure to metalworking fluids. Many of these studies, almost all of them, found risks greater than one and five found significantly elevated risks. For brain cancer, 12 studies were conducted, six found elevated risks, and one was significant. For lung cancer, many studies were conducted. Many found elevated risks. Four were significant. However, the most powerful study, the

one by Eisen, et al, found that metal working fluid exposure was actually "protective" for lung cancer, in that the risk was significantly less than one. The data from the Eisen study indicates that there may not be an association with lung cancer and metalworking fluids.

Again, this slide examines the strength of the associations, by showing the numbers of studies that found a risk of 1.5 or more. Many studies found risks greater than 1.5 and many found significantly elevated risks greater than 1.5.

The metalworking fluids are complex. We have heard that throughout the day. They consist of many different ingredients, some of which are considered carcinogenic, including some nitrosamines, and some of the PAHs. Actually, only one study has looked at individual metalworking components to determine which individual components might be responsible for the elevated cancer risk. That's the Eisen *et al* study, and to date they have not published any studies where they have identified specific components that are responsible for the elevated cancer risk. So today, we know that there is an association with metalworking fluids and certain cancers, but we don't know what specific ingredients in those complex mixtures are responsible.

This slide shows that it's probably not unusual to have an association between cancer and industry or mixture, instead of a single agent. These are the carcinogens that are recognized by IARC and as you can see, there are individual agents, complex mixtures and industrial processes. So it's not unusual that an individual agent cannot be identified as a human carcinogen, but rather the entire complex mixture is identified as carcinogenic. For example, acid mists, coal tar pitches, shale oils and mineral oils, untreated or mildly treated, and industrial processes are determined to be human carcinogens.

In addition, there is historical precedent for complex mixtures being occupational carcinogens. Percival Pott was the British physician who identified that chimney sweeps had an increased risk for scrotal cancer. That was in 1775. He was not sure what was causing the increase in scrotal

cancer, but he suspected it was soot. However, it wasn't until 1933 when an actual carcinogen was identified in soot, that being benzo[*a*]pyrene. So it was over 150 years from the time that an exposure was found to be associated with cancer to the time when an individual component in that mixture was found to be the cause of cancer.

The other problem with both the cohort mortality studies and the trouble actually with the case control studies are that the exposures experienced by the workers in those studies were much higher than the exposure levels are experienced today. Before 1970, the exposures were often five milligrams per meter cubed or higher and since the seventies and eighties, the exposures have been reduced due to various interventions.

So in conclusion, it appears that metalworking fluids are associated with cancer at various sites, however, more work is needed to identify the specific components responsible for those elevations.

Thank you.

Dr. LAWRENCE FINE, NIOSH: Our last Discussant before you all get your opportunity to ask questions is Dr. Jane Teta, who is the Director of Epidemiology from Union Carbide Corporation.

Dr. JANE TETA, Union Carbide: I have the honor of being the final speaker of the day. I'm absolutely certain I won't have the last word, however. I'm going to limit my comments to the number of health studies that have been conducted of metalworking fluid workers, specifically since the 1970's. There have been a number. I'm not going to try to reconstruct the many studies Dr. Calvert had up there. I'm sure there are some that weren't specifically targeted toward workers involved with metalworking fluids.

In particular, I'm going to focus on the two largest and most recently conducted studies you heard about today the GM-UAW and the Ford studies. They are by far the most sophisticated

studies that have been done. But an overall assessment of the results of these and earlier studies is best conducted in the context of the known changes in metalworking fluid practices and exposures over time and you've heard a great deal about these from the prior presentations today.

You have heard about the major types of fluids, the straight oils which are mostly mineral oil, the water-based soluble oil and the synthetics with little or no mineral oil containing different types of glycols and additives, and the semisynthetics and the differences between them. What's important to recognize is that straight oils have a long history of widespread use. Soluble and synthetic fluids, while introduced in the 1940's, have found wider applications only since the 1970's. As a result, and this is a critical piece of important information for epidemiology, many workers have been exposed to more than one type of fluid.

In addition, refining processes and formulations have changed substantially over time and workplace exposures have been significantly reduced. You have heard all about that today as well.

You heard that Dr. Eisen and her colleagues have completed an extensive retrospective exposure assessment to compliment their evaluation of worker health patterns over time. As part of this phase of their effort, their other colleagues, Hallock, *et al*, quantified from the late 1950's, decreases in workplace exposure levels to all three types of fluids.

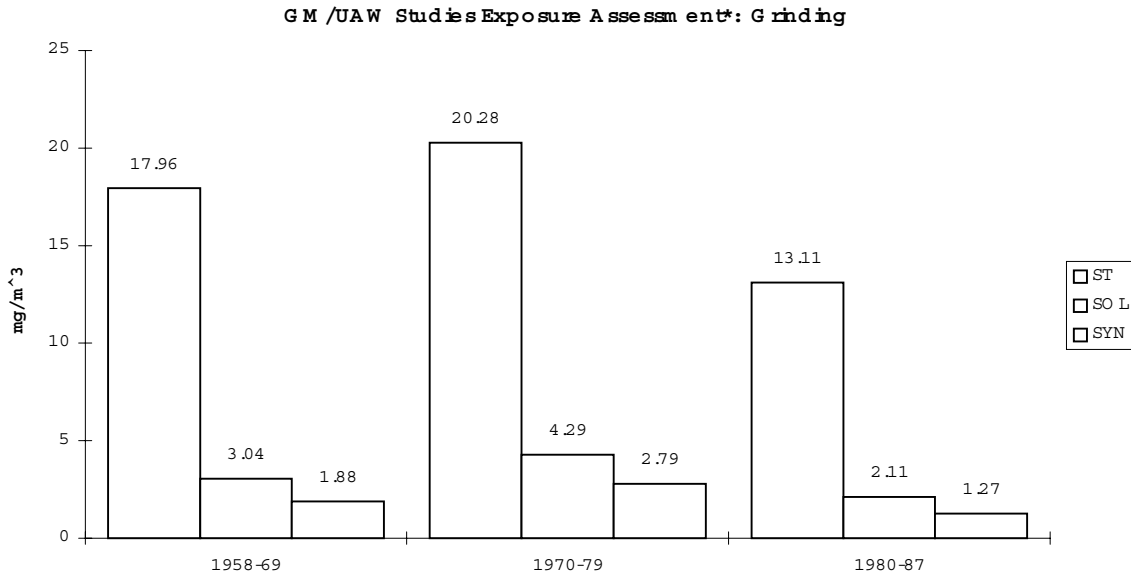
Levels prior to 1970 were reported to be several times higher than later measurements as a result of major plant modifications following the adoption of the five milligram per meter cubed as the OSHA PEL.

For example, up on the slide (Figure 1) you'll see Hallock, *et al*, estimated for the GM-UAW plants, the arithmetic means for grinding, now this is just grinding, for the three fluid types over three time periods. The exposure concentrations range from 13 to 20 milligrams per meter cubed from 1958 to 1969, compared to two to four [mg/m³] in the 1970's, and one to three

[mg/m³] in the 1980's.

Most epidemiology studies conducted have simply examined cancer in groups of workers with widespread exposure to various types of metalworking fluids over working lifetimes

extending back to the pre-1950 era. Several reported associations with various types of cancer, straight oils and grinding.



* Plants 1+3, Table V, Hallock *et al.*, 1994

Figure 1

With the exception of the GM-UAW studies, these investigations did not examine specific types of fluids, separately and jointly, their components, or findings in relation to estimated exposure levels.

Now, this next slide may just look like a whole lot of red dots to you because that's exactly what it is, and that's exactly what I'd like you to see. These are studies with positive associations. Many of them are simply examples of cancers in groups of workers with widespread exposure to

various types of machining fluids over working lifetimes extending back to the pre-1950 era.

And what you can see there, is that there are several reporting associations with various types of cancers, particularly involving straight oils and grinding. Now with the exception of the GM-UAW studies, these investigations did not examine specific type of machining fluids separately and jointly, components, or findings in relation to estimated exposure levels.

Studies With Positive Associations

<u>Site</u>	<u>Straight</u>	<u>Soluble</u>	<u>Synthetic</u>	<u>General</u>	<u>Grinding</u>
Stomach:					
Decoufle (1978)	•	•			
Jarvolm (1987)					•
Silverstein (1988)	•	•			
Park (1988)		•			•
Waterhouse (1971)	•	•			
Esophagus:					
GM/UAW		•	•		•
Colon:					
GM/UAW			•		•
Larynx:					
GM/UAW	•				
Ahrens (1991)	•				
Prostate:					
GM/UAW	•				
Vena (1985)				•	
Rectum:					
GM/UAW	•				
Pancreas:					
GM/UAW				• (Blacks)	•
Silverstein	• (whites)			• (Whites)	
Vena (1985)				• (Blacks)	
FORD					

Figure 2

Now I'd like to look at them separately. Stomach. This is the top part of that chart (Figure 2), just stomach cancer. A number of studies suggested a relationship to stomach cancer, although there was no assessment of important dietary risk factors. The results of the earlier, smaller studies, are not supported by the results of the large, GM-UAW and Ford studies, which were more rigorous in design and analytically thorough.

It is noteworthy that the suggested increase in stomach cancer in the Ford cohort study was not found to be attributable to the workplace in the follow-up nested case control study, in which more detailed information was obtained, including complete work histories and ethnicity, a surrogate for diet and probably genetic influences.

Other findings have been even less consistent across studies. Increased rates of esophageal and colon cancers have been reported only by the GM-UAW investigators and in

relation to grinding with synthetic or soluble fluids. Data relating these results to exposure concentrations or fluid components have not been presented. It would be very interesting if there were more analyses to come from that study on exact exposure level associations and fluid components.

What have been presented are data suggesting excess risk with a ten or 20-year lag. That is, only considering worker exposures to these fluids that may have occurred more than ten or 20 years before the diagnosis of cancer or death. The close of the study was at the end of 1984 and all deaths occurred before that data, so what we're saying is the risks are associated ten or 20 years prior to the deaths, and the deaths occurred between 1940 and 1984.

The hypothesis that there was sufficient exposure to synthetic fluids between 1920 and

1964 with the lag, in other words, excess risk due to exposure during those periods; the hypothesis for such findings is questionable, based on what we know of the types of fluids in use during the relevant time periods of exposure.

This being the case, how might such a relationship appear in the data? One possible explanation derives from the incompleteness of work histories prior to the mid 1970's. Both studies suffered from this limitation. In the follow-up case control study by the Ford group, they obtained complete work histories. But in the GM-UAW studies, various assumptions about exposure and job assignments during the earlier time periods were necessary.

Information on the magnitude of the missing work history data problem would be useful, as well as information on the impact of various assumptions in the absence of data. As epidemiologists, we're all very supportive of doing retrospective exposure assessments. I, for one, am very pleased to see this work being done because it means that epidemiology will have a greater role in the risk assessment process. But we also have to look at the limitations when we begin trying to figure out what happened many years ago based on modeling, interviews, and assumptions. We have uncertainties and we have to describe them and take them into account in our inferences.

So in this case, I don't know what happened, what assumptions were made when data were missing. But if, for example, one assumed that whatever type of fluid a worker was using for grinding in the 1970's, was what they were using in the earlier time period, an artifactual relationship with synthetic fluids could arise. Synthetics were used more in the 1970's.

Interpretations of the significance of the GM-UAW findings related to straight oils and laryngeal, prostate and rectal cancers, is complicated by the impossibility of sorting out changes in base oil refinement practices which began taking place we heard earlier today, around 1950. This, unfortunately, limits their relevance to current workplace exposure assessments.

It is important to recognize that over 60 percent of the deaths in the GM-UAW study came

from the oldest plant, Plant 1, which began operations in the 1920's. In fact, I believe two of the three plants began in the 1920's and Plant 1 used predominantly straight and soluble fluids. The average time from first exposure for study subjects from this location was 29 years. This means that, on average, first exposure occurred prior to 1954. Among those who died, which would be the oldest workers, their average year of first exposure would be even earlier. While inclusion of large numbers of older workers with the potential for high, historical exposures increases the potential to identify workplace-related health effects with long latencies, it is irrelevant to addressing whether the more refined mineral oils, the more recently introduced synthetic fluids and lower exposures to all types of metalworking fluids after 1970 pose carcinogenic risks.

The Ford study population derives from two engine plants which began operations in the early 1950's, and you can see that time period of observation of the studies on this slide (Figure 3).

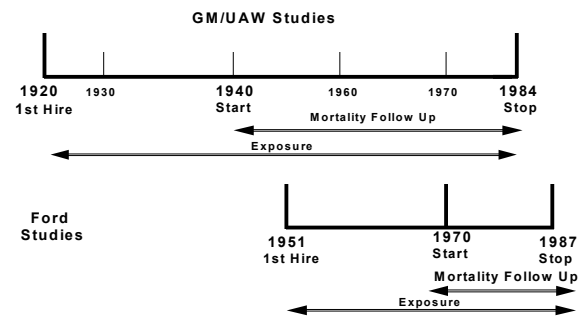


Figure 3

This eliminated some, but not all, of the complicating factors of changes in fluid types and refining of base oils. Work histories prior to the mid-1970's were also missing from the Ford cohort study, however, assumptions were not made since this study did not include analyses by fluid type or estimates of exposure.

Now the ideal study, and we don't live in the world of ideal studies, but the ideal study

would have large numbers of older workers first exposed after 1970, and I suppose, after all we have heard today about additional refinements and removing nitrites, we might even say that wouldn't be perfect, but certainly more ideal than the retrospective work we have here on past exposures.

There was one other issue besides the missing work history that I'd like to raise with regard to the GM-UAW study and it has to do with the sizable proportion of workers with missing race data. You saw some of that earlier in Dr. Eisen's presentation. Incomplete race data is typically not a major problem in studies if the proportion of non-white workers is small. But for Plant 1 in this particular study, one-third of those with known race were black. In their cohort analysis, the investigators made the assumption that all those with missing race data, and that was 14 percent of Plant 1, were white. This would tend to inflate the risk estimates for causes of death that are higher in blacks such as laryngeal and pancreatic cancer. It would tend to decrease risks for causes such as skin cancer, which are lower in blacks. The authors in their publication point out the apparent deficit of skin cancer at Plant 1. But it's unclear, based on the information presented today, what impact missing race data might have had on the case control studies.

I wanted to go back now to the chart on the pancreatic cancer. Both the Ford and the GM-UAW studies observed increases in pancreatic cancer among black, but not white workers in their overall cohort analyses. The excess for one racial group only, and absences of trends with time since first exposure and duration of exposure in the Ford study, led to the inference that the finding was not work related. Now we also have Vena, *et al* and Silverstein, *et al*, also reporting excesses of pancreatic cancer, but among long-term, white workers in engine and ball bearing plants respectively. The excess risk in the Vena, *et al* study occurred in men hired prior to, but not after 1950.

In the GM-UAW case control analyses, there was evidence of a pancreatic cancer

association with grinding and synthetics. Now the impact of incomplete work histories, misclassification of race and the failure to include control for other potential confounders, lifestyle and others on those results is unknown.

Researchers often assert that such errors which we call misclassification, if they are random in nature, produce underestimates of the true risk. I think we know now, as shown in two recent papers in the American Journal of Epidemiology, that this so-called "bias to the null" is rarely guaranteed in practice. What that means is we're not sure where the errors will bring us versus where the true risk really is.

Both these large studies report deficits in lung cancer which were inversely associated with exposure to water-based fluids in the GM-UAW study and with all machining operations combined in the Ford study. Because lung cancer is a relatively common disease, these risk estimates were more stable than the risk estimates for the rarer diseases, such as esophageal cancer. While the hypothesis of a protective effect has not been proven by these studies, they clearly do not implicate metalworking fluids as lung carcinogens.

In conclusion [Figure 4], hypotheses raised by the smaller less rigorous, early studies of workers exposed to metalworking fluids relating to lung and stomach cancer have been tested and not confirmed by the two large studies, which used strong study designs and analytic approaches.

The most suggestive evidence in a number of studies relates to historical grinding operations. The GM-UAW study reported some weak to moderate excesses of a variety of cancers not observed in the Ford investigations. Both studies reported an excess of pancreatic cancer in black, but not white men.

These findings, if not due to chance or assumptions made in the absence of complete data, relate to historical patterns of fluid types, usage and exposure concentrations which are far different from today's workplace. The findings related to synthetic fluids are particularly weak, in my opinion, although reassurance of their safety will require longer follow-up of workers exposed

predominantly to these fluids after 1970. Thank you.

SUMMARY

- Lung and Stomach cancers not confirmed
- Findings on other cancers
 - Not consistent across studies/racial groups
 - Incomplete work histories
 - No data on other risk factors
 - Irrelevant time periods of exposure

Future Research

Longer follow-up of workers first exposed after 1970

Figure 4

Dr. LAWRENCE FINE, NIOSH: I would like to ask the earlier speakers to come forward if they would be willing to do that and then we will open it up for discussions, questions, comments. I would like people to go to the microphones which are in the major aisles and I'll just work my way across the room. And I would like you also to identify yourself; also, if you would, if you have a question for a specific speaker, please indicate that. Okay, starting over here.

Mr. Gordon Taylor: My name is Gordon Taylor, Health and Safety Representative, General Motors Transmission Plant for the CAW [Canadian Auto Workers Union] in Windsor, Ontario.

Now, my question is to the epidemiologists at the tables. When you're evaluating death certificates, you look at the cause of death. If a person who had let's say for example some form of cancer in their body, lung cancer, kidney cancer, whatever. If they died of what you suspected was

a heart attack, how would that be classified as cause of death? Would you classify it as a death by the particular cancer, or would you classify it as death by heart attack?

Dr. ELLEN EISEN: In the case control studies that I presented today, you are defined as a case if the cancer of interest appeared either as the primary cause of death, or as an other significant condition present at the time of death, so in the case control studies, if you had lung cancer, but died of a heart attack, then you would have been counted as a lung cancer case.

Dr. JANE TETA: For purposes of the cohort study, I would make an addition here. There are very clear rules that qualifying nosologists use when they look at a death certificate and there are four or five causes on there. There are rules they use to come up with the underlying cause of death and that would be the one that would be used in these cohort studies for the observed number.

Dr. Roger Jenkins: Good afternoon. My name is Roger Jenkins. I'm with the Oakridge National Laboratory in Tennessee. I had a question for the epidemiologists and specifically Dr. Calvert up there in his summary of many of the studies that had been done. But I think that this is an issue that sort of speaks through all of the epidemiologic presentations. My background is in analytical chemistry and so perhaps I tend to look at things more black and white than my friends on the toxicological or epidemiologic side of the house.

Many of these studies have shown supposedly an increase, a small increase in risk or a large increase in risk, and yet when you look at the statistical significance of those increases and risks, many of the studies appear not to show statistically significant increases in risk.

Dr. Calvert, in your presentation, you indicated that there was sort of a consistency in this increase in risk and yet less than half of the studies were really showing a statistically significant increase in risk. Now, again, to my simple minded analytical chemist approach to things, if it's not statistically significant, it didn't happen, or at least we can't say that it happened. Am I looking at it too black and white, or is there something else wrong with my interpretation?

Dr. GEOFFREY CALVERT: What you have to also consider is the power of the study or the number of participants in the study. So even if a risk is there, you need to have a certain number of participants in that study to be able to identify that risk and to measure it as being statistically significant. So the problem with many of those studies may have been that they were small in size and, therefore, did not have enough power to find a significant elevation. What you need to do is look at the confidence intervals around the risk estimates and if they're wide, that indicates that the study probably could have used more power.

Dr. Jenkins: Oh, I understand that. But my reading of it was that there was actually less than half of the studies and they showed a

statistically significant increase in risk and yet you were saying that there was a consistent increase in risk and to me if less than half of the studies are showing a statistically significant increase in risk, how does that come out as being a consistent increase in risk?

Dr. CALVERT: I always define consistency in terms of the point estimates.

Dr. FRANKLIN MIRER: Can I, being a chemist myself and not an epidemiologist, maybe I can make a better run at it. The risk rate is a function of the dose to which people are exposed, and will vary with the dose. Statistical significance is purely an artifact of the size of the sample. In other words, a given risk rate involving a group of ten people will not be statistically significant. It might be significant with a group of a thousand. It's purely an artifact of the size of the group. So statistical significance is important, I think, that some of the studies show statistical significance, but a series of studies done by different methods in different groups with similar exposures, different cohorts, the consistency between those studies in terms of the observed risk rate is more important than whether any particular one or most of them were statistically significant.

So as you said at the beginning, it is simple minded to reject all those studies that are not statistically significant when you're looking for consistency between a group of them.

Dr. LAWRENCE FINE: I'm sure we could discuss this particular question for quite a while. I think I would like to move on, given that there are a number of other people who are waiting.

Dr. Susan Woskie: My name is Susan Woskie. I'm a Research Industrial Hygienist at the University of Massachusetts in Lowell and I'd like to start with a plea to the metalworking fluid formulators and oil refiners that are here today. And that is that I have worked with Dr. Eisen on

the exposure assessment for the cancer studies that she described earlier and she's now in the process of updating that cohort to collect deaths and exposure information on the group from 1984 to 1994.

In the process of doing that, we're also trying to collect some more detailed information about how the formulations have changed over time, so I have requested a great deal of information from formulators and refiners and I have yet to receive any information back. So I am suggesting a plea to you that you help me in the attempt to collect this information on how base oils have changed over time.

This would give us an opportunity, as suggested earlier, to look at whether or not the risk really is associated with high exposures to high pH content oils back in time or not.

Now, I also have a question I wanted to relate to Dr. Skisak. Could you comment further on the timing of the changes in the base oil composition in the United States? I noticed on your second slide, you said that refining improvements post 1950 had eliminated the PAC risk. And I was wondering if you could describe in a little bit more detail how the timing and nature of this change had occurred.

For example, when it began, when we reached the midpoint in change so that half of the formulations didn't have, or did have severely refined oils and then when we reached a point where most all formulations contained highly refined oils, and then the last piece I would ask you to comment on is maybe describe a little bit about where you gathered this historical information from. Thank you.

Dr. CHRISTOPHER SKISAK: The refining techniques, in particular solvent refining and hydrotreatment have been around, I think, as John Howell indicated this morning, solvent refining from the thirties and forties and hydrotreatment more from the fifties and I think that a lot of that had more to do with performance as opposed to health initially because the data just wasn't available and it's a continual process so it's been going on. Some formulators were probably

adhering to these more stringent parameters because they had the technology in the fifties, certainly in the sixties, many by the seventies, but I think the OSHA Hazard Communication Standard in 1985 really put everyone over the threshold there and the data was there and there was the regulatory onus there that I would say the overwhelming majority of refiners today follow those practices.

And that data was derived primarily from several sources, the American Petroleum Institute for one. That was probably the prime source of collecting not just with the historical data that we have available. Some was derived from the World Health Organization and others from just peer reviewed public literature.

Dr. Woskie: I think it would be helpful in linking the toxicological studies that have been done with the Epi studies if we could figure out a way to collaborate on getting this information into the Epi studies.

Dr. SKISAK: I wrote that down. I think it's a good idea.

Dr. Woskie: Great. Thank you.

Dr. Kenneth Rosenman: Ken Rosenman, Michigan State University. This is a methodological question for Dr. Delzell. I guess I'm concerned about your matching on race. Based on past discriminatory hiring, blacks and whites were given different jobs in industry and that's been well documented in the epidemiologic literature that because of that, hiring practices, for instance in the steel industry or the chromate production industry or even in the foundry industry, that blacks are at higher risk and had different jobs than whites. And so by matching, it seems to me, you reduce the likelihood that your cases and controls had different jobs and you're less likely to find a difference between your job histories of your cases and controls, and I was wondering if you had any data to negate what I just

said.

Dr. ELIZABETH DELZELL: No, I don't. In fact, the idea that blacks and whites might have had different job histories in the industry was the idea that led us to choose to match on race, in that we felt that race might be a confounder, that is, something that is associated both with exposure and with the cancer that we were interested in studying.

Dr. William Lucke: Bill Lucke with Cincinnati Milacron. I have a comment and a question. The comment was one I made a year ago. Twenty years ago they were finding parts per hundred levels of nitrosamines in the metalworking fluids. Now we're getting parts per billion levels. Twenty years ago, the detection limit was one part per million roughly and now we're down into the parts per trillion in range, so we're climbing out of a hole that keeps getting deeper.

At the part per million level, there were some studies 20 years ago that had to be retracted because of analytical artifacts and I would suggest that we have some of the same problems going on right now. The parts per billion levels that are being reported, I'm not aware are being confirmed by one means or another and when you're finding nitrosamines present for amine that aren't present in the fluids, I think that's a very urgent question. It's possible to confirm these things by either finding dimethylamine or diethylamine in the bulk fluid to start with, or by splitting your sample, irradiating half of it with UV light and then analyzing both portions for nitrosamines. The UV will destroy a nitrosamine if it's there. If you get a peak in the irradiated portion, you shouldn't consider either one significant.

The question I have is for Dr. Eisen, and Dr. Teta may have answered part of that. In proposing that the PAHs are a possible cause of rectal cancer, how do you account for the deficit in

skin cancers, when that's the primary site that you see from that exposure?

Dr. ELLEN EISEN: I don't remember talking about any deficit in skin cancer.

Dr. Lucke: Well, Dr. Teta mentioned there was a deficit in skin cancer for Plant 1.

Dr. JANE TETA: Yes, that was just Plant 1. In the published overall cohort analysis, Plant 1 had deficit of skin cancer.

Dr. Lucke: Let me rephrase the question. Was there an excess of skin cancers that you would predict on the basis of PAHs causing rectal cancer?

Dr. EISEN: I really don't remember the data on skin cancer. Our study was focusing on airborne exposures, on inhalation exposures. We didn't measure dermal exposure and I really don't recall.

Dr. GEOFFREY CALVERT: I think another point there is that mortality studies are only good for things that you die of and generally people don't die of skin cancer, so a mortality study probably is not the approach to take when studying skin cancer and that may be why you did not see skin cancer elevated in the Eisen/Tolbert studies.

Dr. Michael Silverstein: My name is Michael Silverstein. I'm with the Washington State Department of Labor and Industries. I have got one quick comment and then a question for the panel. The comment is relative to the discussion that took place just a couple of minutes ago. To say that a finding is not statistically significant, does not mean that something did not happen. If a finding is not statistically significant by usual academic criteria, it does mean that there's less than 90 or 95 percent certainty that that finding was not falsely positive. But there may very well be 85 or 80 percent certainty that the finding is real. So something can be not statistically

significant, but nevertheless, very compelling and very important. Okay, that's the comment.

The question is this: I think a lot of us, as Frank Mirer suggested earlier, would like to take comfort from the fact that certain indisputably toxic ingredients to some of these formulations have decreased or been eliminated over the years, the chlorinated paraffins, the nitrites, some of the PAHs. But none of the studies that I'm aware of that have been published or presented here, and I may very well have missed something, but none of the ones that I'm aware of, have revealed that those ingredients that have been decreasing over the years, are in fact, those that are associated with and likely to be responsible for the digestive cancers that people have been talking about, and given that pattern of findings or that set of facts, I'm puzzled as to how someone could conclude that the historic findings are irrelevant for purposes of modern regulatory decision making and I'm interested if some of the panelists would comment on that.

Dr. CHRISTOPHER SKISAK: Sure, I'll take a quick crack from the tox end. If you know you had oils produced with a higher PAC content in the fifties and sixties and you saw those as being carcinogenic, and you eliminate those PACs and you no longer produce a carcinogenic oil, certainly you have to conclude that the PACs had something to do with it and that if you have absolutely no response, then you have to think that you're making some strides in the right direction. That's just from the base oil end. From the other end, from the other ingredients, I can't comment on that.

Dr. JANE TETA: I guess I'm a little puzzled by the question. Would you repeat the point again about the ingredients not, the oil.

Dr. Silverstein: There's been a decrease, presumably, in the levels of chlorinated paraffins in the formulations that are in use today compared to those that were in use 20, 30, 40 years ago.

Dr. TETA: And they, too, may have been eliminated by now. Many of those are also subject

to -- go ahead

Dr. Silverstein: Now, if somebody had presented findings that showed that stomach cancer excesses were the result of chlorinated paraffin exposures or nitrosamine exposures and those chemicals had now been eliminated, then I'd feel pretty comfortable. But the studies have not revealed those particular associations. An analogy would be this: There are 400 known toxic ingredients in tobacco smoke. Now just the fact that over the years nicotine levels have declined, doesn't necessarily give me comfort that it is now safe to smoke cigarettes.

Dr. TETA: Okay. I'm sorry. I get your point now. I guess how I'd respond to that is epidemiology is not going to give you that answer. I don't believe, as much credit as I give to Dr. Eisen and her colleagues trying to break out those components, I don't believe they'll be able to do it effectively going back in time. So I don't think you'll have that kind of comfort level, if that's what you are looking for.

However, where I would take comfort is the fact that the general levels of exposure in general have dropped precipitously over time. That in addition to the concerns that are mostly toxicologically driven combined, should give some comfort.

Dr. Silverstein: That's a different issue.

Dr. LAWRENCE FINE: Anyone else?

Dr. FRANKLIN MIRER: Just one comment on PAH levels and refining. I think we made a step forward today with the notion that you define the safety or hazard of a material by the PAC content, rather than by its exposure history it's processing history. I think if we're going to examine the effect of dropping PAC content, you have to do it quantitatively and understand that the criteria for safe, that the best I can tell, the criteria for safe now is something that falls below the limit of detection in the skin painting bioassay and that presumably, there are effects below the limit of

detection in the skin painting bioassay and that we need to have a more quantitative extrapolation of risk, rather than the simple yes/no that we have now, but we have moved forward. But in terms of processing history, if they had 15 milligrams and it was two percent PAH back then, we can now calculate current, rather than say forget it, it's different. I mean, we have a quantitative, we have identified the hazard through the past exposures, that's the hazard identification step. Now we ought to think quantitatively about what the current risks might be.

Dr. CHRISTOPHER SKISAK: Perhaps even mechanistically, if not quantitatively, the PAH levels, these skin painting tests are done in mice which are a very conservative model. These are tumor susceptible models which even by the notion that they have a high background rate of tumors is not so surprising. The American Petroleum Institute is also in the process of doing consortium work in which we're looking at the effects of different petroleum products on rodent skin versus human skin transplanted onto a thymic nude mice and at least the preliminary work indicates, not surprisingly, that the tumor susceptible mouse skin is nothing like human skin and there's some mechanistic data that hopefully will shed some light as well as quantitative in the future.

Mr. Richard Eberhard: There seems to be in the studies that have been done, either a desire or a look to see if there's an association of cancers with classifications. There's the straight oils, the soluble oils and the synthetic coolants. The thing that bothers me and John Howell had gone through a basic definition of these products, but of the three classes, the messiest one by far is synthetics, where you can go from a true solution synthetic all the way up to synthetics that are made from polyisobutenes or poly-ethyl olefins that look and behave very much like a soluble oil. And they run the whole gamut in between there, and we like to associate these problems or cancers with certain

classes.

I guess is there any concern, has anybody really taken a close look at the definition or what synthetic coolant is being used because that's the class I think is most messiest that represents such a broad range of chemicals and in further to that, I wonder, it seems to be the worst process is your grinding. Is the problem synthetics, synthetics in grinding, or a combination, or is it because synthetics are the overwhelming fluid used with your grinding operations?

Dr. LAWRENCE FINE: Thank you, sir. Ellen, you might want to respond to that grinding part.

Dr. ELLEN EISEN: I can respond to part of it, anyway. With respect to your very last question about how much of grinding is done with synthetics, at least in our study, it wasn't the majority. The majority of grinding was done with solubles. And it was a fair bit done with synthetics, but it certainly was well under half, probably under a quarter of the grinding was done with synthetics.

Mr. Eberhard: Do you know what type of synthetic that was? Was it a true solution or in any of these studies, does anybody know what type of synthetic was used? Was it a true solution synthetic, or a synthetic made with oil because the definition for a synthetic fluid seemed to be one which does not contain petroleum oil, but you can blend a product with man-made oil and fit that definition very nicely, and my experience is limited just to my plant and to our plants and things that I've seen, but what I have seen in my very limited experience and exposure is the synthetics that seem to be working the best in our plants are not those that are true solution synthetics, not a chemical synthetic, but rather they are the ones blended with the cf polyisobutane or polyethylolefin, which behave like a soluble oil.

Dr. LAWRENCE FINE: Excuse me, sir. Could you identify yourself. We'd appreciate it.

Mr. Eberhard: Richard Eberhard from Chrysler Corporation.

Dr. EISEN: I would just ask whether Susan Woskie or Tom Smith have anything to say about the synthetics in the study. I don't know. And they don't seem to be rushing up.

Dr. FRANKLIN MIRER: UAW petitioned the EPA for a test rule under the Toxic Substance Control Act to test particular ingredients of materials because we thought that we had reached the limit of epidemiology in resolving power, and that test rule was initially denied. It would potentially answer some of your questions. That was originally denied on the basis that machining fluids were too complicated to test and we have some hopes of getting together and cooperatively putting something on the line for testing and you have raised a class of fluids that I have no notion existed actually to this point, so that goes on our list.

Dr. Thomas Smith: Tom Smith, Harvard. Just a quick comment. We used a very broad definition of synthetic fluids, but it did not include those that had oil components in them. However, as you heard this morning, there was a wide variety of things that were called synthetics. I'm also very uncomfortable with these broad classifications because they are extremely broad and included many, many different things, all under the category of soluble or synthetic or straight oils.

Dr. LAWRENCE FINE: Now we will take our last two questions.

Dr. Bengt Jarvholm: My name is Bengt Jarvholm from Sweden. I have a comment on a question to the reviewers. You are handling these findings as if you would expect some consistent result in the literature. Concerning the great

variety of components within the cutting fluids, would you really have expected to find a consistency? I had the pleasure to review the toxicology of components in cutting fluids in the mid-eighties and the suppliers sent me a list of what they used and I got a list of about 200 substances and of these 200, they could identify about 150 and about this 150, there was some toxicological data about half of them. So why should there be a consistency in the literature? Isn't it too much [to expect] consistency considering the great variety of substances that we use in these components?

Dr. JANE TETA: I might say that if your problem is something that occurs and is not a high prevalent additive, then it wouldn't make sense to do what we're doing, but if you're interested, for example, in whether the mineral oil is a problem and you know that's in straight oils and it's in solubles, or if you're worried about a very prevalent additive like ethanolamines and you know that's in almost every synthetic, then it makes sense to do this, but if the carcinogen, assuming it's only one, is not very prevalent in the oils, the fluids, then this would not be a very useful approach to take.

Dr. LAWRENCE FINE: One last question.

Dr. Suran Peiris: I'm Suran Peiris from the Chemical Technology Department of Detroit Diesel Corporation. My question is again about synthetics. We had some data given to us about the effects of synthetics and oils. But is there any comparative studies done between these two - which is more toxic is my question. To put it more simply, if we have a plant working in synthetics today and we convert to mineral oil based coolants tomorrow, will the health risk be higher after the conversion or before the conversion? That's a simple way of putting it.

Dr. LAWRENCE FINE: Which brave

soul wants to tackle that question? Frank is always brave.

Dr. FRANKLIN MIRER: My motto is 'often in error, but never in doubt.' There will be some data presented tomorrow on irritancy and we have the impression generally that there's greater irritancy in respiratory complaints in the presence of synthetics than soluble oils, but that may not be borne out by the data.

With regard to the occupational cancer risk, our view within the UAW Health and Safety Department is that the level of particulate material in the air is the best index of what we should be controlling and we proposed the provisional limit of half a milligram and so our sense is that reducing the airborne particulate is a better strategy than trying to shift from component to component.

I would add by analogy, and I don't know if it helps a lot or hurts. The current thinking about diesel particulate is that the carcinogenic element in diesel particulate is simply the particulate itself and not any of the particular chemical components. It's just a working idea. It's the total quantity of stuff people are breathing in is the issue, not the specific components, from our point of view.

Dr. LAWRENCE FINE: Anyone else on the panel?

Dr. CHRISTOPHER SKISAK: Just a brief comment on the diesel. It is the components, but there is also a lot which suggests that overloading of the lung in these studies has a lot to do with it as well, so let's not ignore that either.

Dr. LAWRENCE FINE: Okay. I think on that note I'd like to thank all of the Discussants and all the presenters and the audience for staying with us for a long afternoon.

Thank you all very much.

Mr. DAVID FELINSKI: Thank you, everyone. Continental breakfast begins at 7:00 a.m. tomorrow out in the Hubbard Foyer, and the first presentation of the Toxicology Plenary tomorrow begins at 7:30. Have a good evening.