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Environmental Exposures and Risk of Digestive Cancers

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16. Abstract (Limit: 200 words) The elevated risks for cancer of the esophagus, stomach, pancreas, colon, and rectum previously identified in a cohort mortality study of auto workers with exposure to machining fluids (MF) were examined to identify the specific type of fluids or agents in the fluids associated with these cancers. An existing historical database was expanded to include cumulative exposure based on quantitative estimates of sulfur compounds. Conditional logistic regression models were fit to the case control data for each outcome of interest to examine exposure response associations and provide estimates of the magnitude of risk. Strong evidence was found supporting the duration of exposure to metalworking fluids in grinding operations using either soluble or synthetic fluid, as associated with an elevated risk of esophageal cancer. Exposure to synthetic metalworking fluid was associated with increased risk of pancreatic cancer and straight fluids were associated with rectal cancer. The magnitude of the risks ranged from less than two fold for stomach cancer and solubles up to 5.3 fold for esophageal cancer and grinding with soluble metalworking fluids.			
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Significant Findings

The findings reported here provide strong evidence that

1. Duration of exposure to MWF in grinding operations - using either soluble or synthetic fluid- is associated with elevated risk of esophageal cancer,
2. Exposure to synthetic MWF is associated with increased risk of pancreatic cancer, and
3. Straight fluids are associated with rectal cancer,
4. There is a modest association between stomach cancer and soluble fluids, primarily in grinding operations.
5. In summary, digestive cancer risk was found to be elevated among workers exposed to all three types of metalworking fluids. The magnitude of the risks range from less than 2-fold for stomach cancer and solubles up to 5.3 for esophageal cancer and grinding with soluble MWF.

Usefulness of Findings

NIOSH is currently preparing a Criteria Document on Metalworking fluids (MWF). OSHA has included MWF high on its priority list for regulatory action. Our cancer mortality studies contribute substantially towards the state of our knowledge about the carcinogenic effects of these materials.

Abstract

The primary focus of this research was to further examine the elevated risks for cancer of the esophagus, stomach, pancreas, colon and rectum previously identified in a cohort mortality study of autoworkers with exposure to machining fluids (MF). The objective of these analyses was to identify the specific types of fluids or agents(s) in the fluids that are associated with these cancers. Conditional logistic regression models were fit to the case-control data for each outcome of interest (cancer of the esophagus, stomach, pancreas, colon and rectum) to examine exposure-response

associations and provide estimates of the magnitude of risk.

Body of the Report

Excesses of several digestive cancers of *a priori* interest had been identified in a large cohort of automobile workers with exposure to metal working fluids. Based on NIOSH estimates, 1.2 million workers in the U.S. engaged in metal grinding or machining operations are exposed to these fluids, while over 6 million workers are more generally exposed to the various components of the fluids.

Based on results of Poisson regression models, statistically significant relative risks of up to three fold had been found between esophagus cancer and increasing levels of exposure of machining fluids used in the course of grinding operations. Evidence of weaker associations, between 1.5 and 2.0, were observed between grinding and stomach and pancreatic cancer. Strong evidence was also observed for associations between straight machining fluids and rectal and larynx cancer.

The objective of this grant proposal was to further examine the elevated risks for cancer of the esophagus, stomach, pancreas, colon and rectum in this cohort of autoworkers to identify the specific agents(s) in the machining fluids which are causing the elevated cancers. Better specification of the causal agents is necessary for an assessment of risk associated with metal working fluids in use today.

Specific Aims:

As stated in the proposal, the specific aims are to:

I. Expand existing historical database to include cumulative particulate exposure based on quantitative estimates of sulfur and sulfur compounds;

In Hallock et al, 1994 the process for collecting historical chemical use information for the original mortality study was described. For each group of job titles in a department having homogeneous exposures, a Machining Fluid History Code (Hiscode) Sheet was filled out. The information for this code sheet came from interview summary sheets where it was also indicated what metalworking fluid was used etc.

We acquired copies of the original interview files and Hiscode sheets from Marilyn Hallock. Then we went back and expanded each Hiscode sheet to include the type of metalworking fluid used (brand) and added new dichotomous variables for sulfur and chlorine. This new variable for sulfur included any compound listed on the MSDS's that had sulfur, so for example petroleum sulfonates, not just the elemental sulfur used in the original sulfur coding. The new chlorine variable included

any chlorinated compound, not just the chlorinated paraffins.

Next, we used the 87 stacked filter samples taken for elemental analysis to estimate the percentage of the personal inhalable mass concentration that was sulfur or chlorine, based on whether the operation was machining or grinding, or whether the metalworking fluid contained sulfur or chlorine (see Appendix A). Although the difference between the percentage of sulfur or chlorine in machining and grinding operations is not significantly different, the difference between the % of the air concentration that is sulfur or chlorine is significantly different for MWF's that have these compounds in their compositions, compared to those that do not. For MWF's that contain sulfur or chlorine in their compositions, this percentage reflects the average percent of the airborne mass concentration that is sulfur or chlorine due to the fluid composition. For MWF's without sulfur or chlorine, the existence of these elements in the air samples suggests that exposures come in part from a plant-wide MWF cloud. We do not have reason to believe that the range of percent sulfur or chlorine found in MWF's that contained these elements varies across time in any systematic way. Although it seemed plausible that the percent sulfur or chlorine in an air sample would be reflective of the percentage in the bulk MWF, our analysis of the stacked filter samples found no significant brand effect on the percentage of these elements in the air samples. In light of the absence of trends over time, in the historical reconstruction we used the same average percentage sulfur or chlorine across time for those MWF's that contain these elements (See table below).

Percentage of Inhalable Mass Concentration Attributable to Sulfur or Chlorine

	Machining Operations	Grinding Operations
% Sulfur if MWF has sulfur compounds	1.3%	1.8%
% Sulfur if MWF has no sulfur compounds	0.8%	1.1%
% Chlorine if MWF has chlorine compounds	1.6%	1.5%
% Chlorine if MWF has no chlorine compounds	0.7%	0.7%

These fixed percentages were applied to job specific gravimetric measures. The result were estimated sulfur and chlorine concentrations that changed over time due to the variability in gravimetric air concentration across different operations, fluid types and time periods.

II. Expand the existing historical exposure database to include semiquantitative estimates of the carcinogenic potential of the oil components of MF, a surrogate for PAH content; and

A detailed literature search was done on the history and technology of oil refining and on the toxicological data available on MWF's and the oil components of MWF's. The reports show that as early as the late 1960's and early 1970's a body of evidence of the carcinogenicity of petroleum oils was developing. Even then, the belief was that polynuclear aromatic hydrocarbons were the causative agents and that both carcinogenicity and PAH content could be reduced by solvent extraction. There was also some evidence of enhanced potency with the presence of sulfur.

Anecdotal information about the history of petroleum refining and MWF formulation was gathered through numerous phone conversations with tribologists involved in metal working formulation and those from the petroleum industry involved in petroleum refining. Letters requesting information on the history of specific MWF's were sent to the formulators of MWF's used in the plants under study (see Appendix B). However, no information was returned. At a meeting with the Independent Lubricant Manufacturers Association at a Symposium on the representatives expressed grave concern about releasing information with any company identifiers. It was explained that it was essential that a means be provided to link the formulation/refining information with a specific product which in turn would be linked with the individual work histories of the mortality cohort. No information was provided.

The following is a summary of the anecdotal information I was able to collect:

It is my impression that major changes in the refining of the base stocks of petroleum oils used in MWFs did not occur on a large scale in the U. S. until the 1980's, and on a smaller scale prior to that. In 1982 (Monograph 33) IARC concluded that there was sufficient evidence of the carcinogenicity of metal machining. Then in 1987 (Suppl 7) IARC determined that untreated and mildly treated mineral oils were carcinogenic, while there was inadequate evidence to determine the carcinogenic potential of severely hydrotreated oils and of severely solvent treated oils, there was no evidence of carcinogenicity. In 1983 the OSHA Hazard Communication Standard was promulgated, requiring that if IARC carcinogens were present in a product at > 0.1% they must be listed on the MSDS. In 1985, OSHA published an interpretation of the Hazard Communication Standard regarding lubricating oils. This interpretation stated that if the material used a refinery stream the was mildly hydrotreated or mildly solvent refined then the MSDS must reflect that they are carcinogens. If the material used a severely hydrotreated oil, then if and when any data was produced showing it was carcinogenic it would have to be treated as such. For severely solvent refined oils, no labeling was necessary. As a result of these developments, there was a push by the formulators to use severely hydrotreated or solvent refined oils in their products.

In my discussions with refiners and formulators, it seems clear that until recently MWFs have primarily been formulated using naphthenic base stocks with little(only hydrofinishing) or no treatment to reduce the polyaromatic content of the oil base stock. In automotive lubricating oils, the move toward solvent refining and severe hydrotreating did occur earlier, but it was driven by the development of engines with higher compression ratios, and the resulting need for lubricating oils

with high viscosity indexes and good oxidation stability. In MWFs these are not crucial characteristics, so that the move to solvent refining and severe hydrotreating, which are costly, was driven by health issues which came to a head in the 1985, not by process needs.

It is my impression that the majority of the current base stocks still in use in the U.S. are naphthenic, while those from Europe are paraffinic. This came about largely because naphthenics were available in U.S. oil fields, could be used in MWFs without lots of refining steps like dewaxing or other cleanup, so they were cheap and also had useful properties, like greater polarity than paraffinics, for dissolving additives. Now U.S. fields with naphthenic stock are being depleted and the naphthenics need more refining to meet health concerns so this may change. From the standpoint of the metal working process, I don't believe the degree of refining has a lot of impact, so that MWF mixtures of different degrees of refining used to exist so that the cheapest base oil with the desired characteristics could be produced. Now mixtures are used so that the cheapest base oil with the desired metal working characteristics and lowest PAH content can be produced.

Since the refiners and formulators involved in the MWF products used at the plants in the mortality study were unwilling to provide historical information on their products, the only information we have is the anecdotal data and the information developed by Dr. S.K. Hammond using normal phase high pressure liquid chromatography to fractionate the samples into aliphatic compounds, polar compounds and PACS. The PAH fraction was measured with a fluorescence detector. The output of the fluorescence detector should be seen as an overall indicator of relative PAH content for two reasons: 1) different PACS have different intensities of fluorescence under any set of conditions and, 2) the fluorescence detector is highly sensitive to quenching from the oxygen in the mobile phase solvents, as well as from other sources. For these reasons it has been estimated that the overall fluorescence measure is correct within 50%, that is if two values are within a factor of two of each other they should not be viewed as different. One part of the work reported by Dr. Hammond to the UAW/GM National Joint Committee on Health and Safety in 1993 was the fluorescence level of the bulk used and unused MWF fluids. The result was that high PAH levels were found in the major soluble fluid used during the period of 1981-1990, whereas another soluble fluid was quite low. The straight oil levels of PAH at that time were in a medium category. Dr Hammond also reported that fluorescent materials primarily enter with the bulk fluids and are not extensively formed by the metal working operations. A paper by R.H. McKee et al, Journal of Applied Toxicology 10(4):251-256, 1990 also found no greater dermal carcinogenic response in mice treated with used versus fresh cutting fluids.

We used the information on the bulk PAH level along with information on the changes in major refiners to develop a qualitative rating of Low, Medium and High PAH level for Plant 1, where the majority of the digestive cancers were present (Appendix C)

Summary of PAH Categories for Plant 1 MWF's

MWF type	MWF brand	Dates	Epi PAH Category
Sol	C-60	1934-70	High
Sol	C-60	1970-81	Med
Sol	C-60	1981-90	High
Sol	VS710	1934-86	High
Sol	VS710	1986-90	Low
Min	Clav68	1934-74	Hi
Min	Clav68	1974-90(?)	Med
Min	Lap	1934-60(?)could be later	Hi
Min	Lap	1960-90(?)	Low
Min	Cutting Oil	1934-1970	High
Min	Kompkut Cutting Oil	1970-86	Med
Min	Kompkut Cutting Oil	1986-90	Low
Quench Oil	Quench Oil Fenso or Fenson 71	1934-90	High
Min	White & Bagley 1572 Grinding oil	1934-86	High
Min	White & Bagley 1572 Grinding oil	1986-90(?)	Low

III. Fit conditional logistic regression models to the data for each outcome of interest

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 [1-7]. 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 was initiated to further examine the risks for selected causes of death. These studies were designed to examine confounding by other concomitant 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.

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 predominately white male, it also includes 7,750 blacks and 4,680 females.

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 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 yrs), 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.

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.

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.

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 was 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 nonexponential 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 covariates 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.

Esophagus Cancer: The esophageal cancer case control study was based on 60 deceased cases and 1008 matched controls. Results suggest that grinding with either synthetic or soluble fluid is significantly associated with esophageal cancer. The odds ratio (OR) increased as years of grinding exposure increased, up to a risk of 5.5 for those with more than 12 years of exposure to solubles and up to 3.8 for exposure to synthetics. Two components, nitrosamine and biocides, appeared to account for some of the risk. However, because these components are commonly found in water based fluids, particularly those used in grinding operations, allocation between various exposure agents could not be definitely sorted out. (See appended paper)

Stomach Cancer: There were 125 cases of stomach cancer and 2212 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 1880 controls were selected. Synthetic years appeared to be the strongest predictor of risk, ie., the odds ratio as highest and the fit of the model was better than that of any other model with a single exposure variable [7]. 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. (See appended manuscript)

Colon Cancer: The 162 cases of colon cancer were matched to 2917 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 ($p=.02$). 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 unlagged variables.

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.

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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	1.7 - 17.4
	Grinding with Synthetics (lag 20)	8	3.4	1.0 - 11.7
Stomach	Soluble (lag 0)	29	1.9	0.6 - 5.6
Pancreas	Grinding with Synthetics (lag 0)	9	3.0	1.2 - 7.5
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

Publications

(Abstracts)

Sullivan PA, Eisen EA, Woskie SR, Kriebel D, Wegman DH. Metalworking fluid exposure in the automobile industry: A case-control study of esophageal cancer mortality. American College of Epidemiology Annual Scientific Sessions. Baltimore MD, 1996

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(Peer-Review)

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Sullivan PA, Eisen EA, Woskie SR, Kriebel D, Wegman DH, Monson RR, Smith TJ. Mortality studies of machining fluid exposure in the automobile industry VI: A case-control study of esophageal cancer. Am J Ind Med (Submitted)

(Planned Publications):

Sullivan PA, Eisen EA, Woskie SR, Kriebel D, Wegman DH, Monson RR, Smith TJ. Mortality studies of machining fluid exposure in the automobile industry VII: A case-control study of stomach cancer (Draft)

Tolbert PE, Eisen EA, Hallock MF, Tolbert PE, Hammond SK, Monson RR, Smith TJ. Mortality studies of machining fluid exposure in the automobile industry VIII: Case-control studies of colon and rectal cancer

Appendix A

Elemental Analysis

The aim of the study was to obtain quantitative measures of exposure to machining fluid elements (S, Cl, P, Ca), metals (Fe, Mn, Si, Cr, W, Mo, V, Ti, Zn, Ni, Co, Cu, Pb, Mg) and specific elements and metals present in the machining fluids such as sulfur, chlorine, aluminum and iron. These measures would be in the units of percent total-dust, and would be applied to gravimetric exposure to obtain elemental exposure concentration. The intention was to apply a mean elemental percent to each of the operation/machining fluid type combination groups. To complete this task, statistical models of the determinants of elemental exposure were developed.

For this study, filters previously analyzed for elements by x-ray fluorescence (xrf) technique were augmented with a set of filters currently analyzed by proton induced x-ray emission (pixe) technique. All air samples were collected using a two stage size selective stacked filter unit. The first filter was a nucleopore filter collecting larger particles and the second filter was a zeflour filter collecting the remaining smaller particles. Forty six (46) stacked filter units previously analyzed for elements by the xrf method were available for statistical analysis. In addition, 47 stacked filter units were analyzed for elements via the pixe method, 6 of which had previously been analyzed by the xrf method. The analysis of the 6 stacked filter units by the two methods was necessary in order to allow for a comparison of the two methods. The pixe method of analysis was used with the second set of filters because the company that had done the previous analysis was no longer in business. Both pixe and xrf utilize similar analytical techniques except pixe is more sensitive than xrf for certain elements.

Prior to combining filters from the two methods of analysis, the 6 common stacked filter units were analyzed in several ways to compare the two methods. All the results indicated that xrf and pixe were inconsistent and dissimilar. Since the ultimate aim of the study was to obtain mean exposure of a group to elements and not individual worker estimates, and since the sample size of the common filters (6 stacked filter units) was small, it was decided to examine the group means by methods of analysis (pixe and xrf). The main obstacle to performing this task was that the filters used to calculate means of the groups by pixe and xrf were not paired samples. This was partially overcome by normalizing the data by dividing the elemental mass by the total dust mass. The resulting elemental fraction of the total dust was used in multivariate anova models to estimate the means of the groups and to determine the effect of method of analysis. Since logging the data resulted in greatly improved model R^2 , the logged elemental fraction of the total dust was modeled.

This report is confined to results from the analysis of Sulfur and Chlorine models. Two of the dichotomous explanatory variables Sulfur Yes/No and Chlorine Yes/No were re-coded. Initially, these variables represented the presence of elemental sulfur or chlorinated parafins in the fluids. The newly created variables represented the presence of any sulfur containing material (ie. Petroleum sulfonates, elemental sulfur) and any chlorinated compound. This was done because the analytical methods do not distinguish between the different forms of an element (ie. elemental vs. compound). Statistical models were also improved by using the newly create variables.

For sulfur models, xrf and pixe data were modeled separately and as combined with method of analysis term in the combined model. The final model had the following terms: operation, new sulfur yes/no, and analysis method. Only the terms for sulfur yes/no and method of analysis were significant. The term for operation was not significant, but was kept in the model. Using the full data set in the anova models resulted in a tighter 95% CI around the predicted group mean. The xrf method group means were used to assign sulfur levels to the cohort.

For chlorine models, xrf and pixe data were modeled separately and as combined with method of analysis term in the combined model. The final model had the following terms: operation, new chlorine yes/no, and analysis method. Only the terms for chlorine yes/no and method of analysis were significant. The term for operation was not significant, but was kept in the model. Using the full data set in the anova models resulted in a tighter 95% CI around the predicted group mean. The xrf method group means were used to assign chlorine levels to the cohort.

Tasks Remaining:

1. Apply percent elemental exposure to gravimetric concentration for inhalable fraction by operation type and new sulfur category or new chlorine category.
2. Cumulate elemental exposure.

Final Sulfur Model :

$$\text{LnfracS} = B_0 + B_1 (\text{Operation}) + B_2 (\text{Sulfur}) + B_3 (\text{Method})$$

p=0.10 P<0.01 p=0.02

Model F= 6.79 df=3 p=0.0004 R²=0.19

	Grinding	Machining
Sulfur Yes	X _L = -4.02 S _L = 0.22 X _g = 0.018 = 1.8% MLE = 1.8%	X _L = -4.33 S _L = 0.16 X _g = 0.013 = 1.3% MLE = 1.3%
Sulfur No	X _L = -4.49 S _L = 0.20 X _g = 0.011 = 1.1% MLE = 1.1%	X _L = -4.80 S _L = 0.18 X _g = 0.008 = 0.8% MLE = 0.8%

X_L = estimated mean of log elemental fraction

$$S_L = \frac{95\%UCL_L - X_L}{1.96}$$

$$MLE = \exp(X_L + S_L^2/2)$$

Final Chlorine Model:

$$\text{LnfracCl} = B_0 + B_1 (\text{Operation}) + B_2 (\text{Chlorine}) + B_3 (\text{Analysis})$$

P=0.84 p<0.01 p<0.01

Model F=16.46 df=3 p=<0.01 R²=0.36

	Grinding	Machining
Chlorine Yes	X _L = -4.19 S _L = 0.16 X _g = 0.015 = 1.5% MLE = 1.5%	X _L = -4.16 S _L = 0.15 X _g = 0.0156 = 1.6% MLE = 1.6%
Chlorine No	X _L = -5.01 S _L = 0.13 X _g = 0.0067 = 0.67% MLE = 0.67%	X _L = -4.99 S _L = 0.10 X _g = 0.0068 = 0.68% MLE = 0.69%

$$S_L = \frac{95\%UCL_L - X_L}{1.96}$$

$$MLE = \exp(X_L + S_L^2/2)$$

Appendix C
PAH Estimates for Plant 1 (Gear and Axle)

Mftype	Mfbrand	Dates	Epi PAH Category	Manf Brand	Bulk Sample Fluorescence (samples 85-87) *	Historical Info
Sol	C-60	1934-50	High	Unknown		no one was treating at this point, naphthenics widely used
Sol	C-60	1950-70	High	Sunseco Sun Oil Co.		Mildly treated(hydrofinished) naphthenics used
Sol	C-60	70-81	Med	Sunseco Sun Oil Co.	?120? (See Kompkut)	Blended 25%hydrotreated +75% mildly hydrofinish naphthenic (From 1970-1986...Circosol oils).
Sol	C-60	not used	Low	Sunseco Sun Oil Co.		All severely hydrotreated naphthenics (1986+ sunthene oils)
Sol	C-60	81-90	High	Metkool 711 Metalworking Lubricants	880	No information from manufacturer
Sol	VS710	1934-70	High	Unknown		no one was treating at this point, naphthenics widely used
Sol	VS710 Vantrol	1970-86	High	VanStratten bought in 1980 by Castrol		No information...no one did any treatment or blending until the mid to late 60's (Mobil, Sun, Exxon), more likely it was early 70's
Sol	VS710	1986-90	Low	Van Stratten /Castrol	5	No information
Min	Clavus68	1934-50	Hi	Unknown		no one was treating at this point, naphthenics widely used
Min	Clavus68	1950(?) -74 could be later	Hi	Clavus68 Shell Oil		untreated naphthenic

Min	Clavus68	1974-90(?)	Med	Clavus68 Shell Oil	150	Added hydrotreater to refinery in 1974. This naphthenic oil is not a regular MWF, rather it is a compressor and general lubrication oil
Min	Lap	1934-60	Hi	NY & NJ Oil Co. Lapping Compound		No info but spec sheet in 1960
Min	Lap	1960-90(?) Could be later	Low	HA Montgomery now owned by Metal Lubricants (Fuchs)	40	Only 1984 info using HA Montgomery product
Min	Cutting Oil	1934-1970	High	Most likely source was Sun		no one was treating at this point, naphthenics widely used
Min	Kompkut Cutting Oil	70-86	Med	Pillsbury purchased by Novamax in 1990	120	See record of use in 1982... Was told their oil source was Sun: Blended 25%hydrotreated +75% mildly hydrofinish naphthenic (.Circosol oils).
Min	Kompkut Cutting Oil	86-90	Low	Pillsbury purchased by Novamax in 1990		Was told their oil source was Sun: All severely hydrotreated naphthenics (1986+ sunthene oils)
Quench Oil	Quench Oil Fenso or Fenson 71	1934-90	High	Fenso or Exxon		Not sure of source before 1982 but very high PAH.... Look for HT, heat treat or MHT, heat treat job in a mixed fluid exposure dept under "ofhr or look for job = HT in other departments"
Min	White & Bagley 1572 Grinding oil	1934-86	High	White & Bagley sold to Enterprise Oil in 1988-89		Very minor use... record of use in 1960 and 1984 Don't know who refinery supplier was

Min	White & Bagley 1572 Grinding oil	1986-90(?)	Low	White & Bagley sold to Enterprise Oil in 1988-89	Very minor use record of use in 1960 and 1984
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* See body for explanation of how bulk sample PAH fluorescence from samples taken during sampling campaigns of 1985-87 to 1987 were analyzed.

Tasks Remaining:

1. Apply category of PAH exposure to Miftype and gravimetric concentration
2. Cumulate years of High Min; Med Min and Low Min exposure. Likewise for Sol and Quench Oil
Cumulate mg/m3 of High Min; Med Min and Low Min exposure. Likewise for Sol and Quench Oil
3. Re-examine cancers associated with soluble or straight MWF. Develop index of cumulative exposure to PAH and examine exposure-response for esophagus, rectal and stomach cancer in Plant I and fit logitistic models to the case-control data.

Appendix D

Bardin J, Eisen EA, Hallock MF, Tolbert PE, Hammond SK, Monson RR, Smith TJ. Mortality studies of machining fluid exposure in the automobile industry V: A case-control study of pancreatic cancer Am J Ind Med 1997 (In Press)

Appendix E

Sullivan PA, Eisen EA, Woskie SR, Kriebel D, Wegman DH, Monson RR, Smith TJ. Mortality studies of machining fluid exposure in the automobile industry VII: A case-control study of stomach cancer. Am J Ind Med (Submitted).

