UAW-GM Cohort Study

With additional model terms; exposure lagged 21 years

November 13, 2019

Introduction

In previous survival analyses, hazard ratios associated with exposure to the three metalworking fluid types were estimated simultaneously in the same Cox proportional hazards model. There was a concern that those estimates may have been biased or misleading, as those models assumed independent covariate (statistical) effects e.g. that the effect of exposure to straight metalworking fluids was constant across levels of exposure to other metalworking fluid types. One way we attempted to address this concern was to fit independent models for each exposure-outcome pair of interest with one additional term to capture changes in the log-hazard associated with the combination of reference-level exposure to one metalworking fluid type and greater than reference-level exposure to some other metalworking fluid type. The reference-level exposure to straight and synthetic metalworking fluids is 0 mg/m^3·years. That for exposure to soluble metalworking fluids is 0.055 mg/m^3·years or less (the upper limit is analogous to 10 years of exposure at the ambient level of 5.5 μg/m^3).

Model

Let $\boldsymbol{W}(t)$ represent the vector of potential confounders at time t. Let X_{St}, $X_{\text{So}}(t)$, and $X_{\text{Sy}}(t)$ represent cumulative exposure to straight, soluble, and synthetic metalworking fluids, respectively at time t. If we were interested in straight metalworking fluids, then the log hazard for the outcome could be modeled:

$$
\begin{aligned}
\log\left[h\left(t \mid \boldsymbol{W}(t) = \boldsymbol{w}(t), \boldsymbol{X}(t) = \boldsymbol{x}(t), \hat{\boldsymbol{\beta}}\right)\right] = \; & \log\left[h_0(t)\right] \\
& + \hat{\beta}_1 \mathbb{1}\left[x_{\text{St}}(t) \in (0, \text{St}_{\text{low}}]\right] \\
& + \hat{\beta}_2 \mathbb{1}\left[x_{\text{St}}(t) \in (\text{St}_{\text{low}}, \text{St}_{\text{mid}}]\right] \\
& + \hat{\beta}_3 \mathbb{1}\left[x_{\text{St}}(t) \in (\text{St}_{\text{mid}}, \text{St}_{\text{high}}]\right] \\
& + \hat{\beta}_4 \mathbb{1}\left[x_{\text{So}}(t) \in (0.055, \text{So}_{\text{low}}]\right] \\
& + \hat{\beta}_5 \mathbb{1}\left[x_{\text{So}}(t) \in (\text{So}_{\text{low}}, \text{So}_{\text{mid}}]\right] \\
& + \hat{\beta}_6 \mathbb{1}\left[x_{\text{So}}(t) \in (\text{So}_{\text{mid}}, \text{So}_{\text{high}}]\right] \\
& + \hat{\beta}_7 \mathbb{1}\left[x_{\text{Sy}}(t) \in (0, \text{Sy}_{\text{low}}]\right] \\
& + \hat{\beta}_8 \mathbb{1}\left[x_{\text{Sy}}(t) \in (\text{Sy}_{\text{low}}, \text{Sy}_{\text{mid}}]\right] \\
& + \hat{\beta}_9 \mathbb{1}\left[x_{\text{Sy}}(t) \in (\text{Sy}_{\text{mid}}, \text{Sy}_{\text{high}}]\right] \\
& + \hat{\beta}_{10} \mathbb{1}\left[x_{\text{St}}(t) = 0\right] \mathbb{1}\left[x_{\text{So}}(t) > 0.055\right] \mathbb{1}\left[x_{\text{Sy}}(t) > 0\right] \\
& + \hat{\beta}_{11} w_1(t) + \hat{\beta}_{12} w_2(t) + \hat{\beta}_{13} w_3(t) + \cdots
\end{aligned}
$$

where St_{low}, So_{low}, and Sy_{low} represent the upper boundaries of low exposure to the three types of metalworking fluids among cases at time of death, respectively; St_{mid}, So_{mid}, and Sy_{mid} represent the upper boundaries of moderate exposure among cases at time of death; and St_{high}, So_{high}, and Sy_{high} represent maximum exposure among cases at time of death. If we were interested in exposure to soluble metalworking fluids, we would replace the 10$^{\text{th}}$ covariate with $\mathbb{1}\left[x_{\text{So}}(t) \leq 0.055\right] \mathbb{1}\left[x_{\text{St}}(t) + x_{\text{Sy}}(t) > 0\right]$. For synthetic, we would replace with $\mathbb{1}\left[x_{\text{Sy}}(t) = 0\right] \mathbb{1}\left[x_{\text{St}}(t) > 0\right] \mathbb{1}\left[x_{\text{So}}(t) > 0.055\right]$. Note that if all three terms were included simultaneously, we would have a rank-deficient model matrix.

Results

Table 1: Cox model estimates of the hazard ratio for selected cancer outcomes associated with exposure to **straight** metalworking fluids, controlling for other fluid types, calendar year, calendar year of hire, age, race, sex, and plant.

		Number of cases	HR	p	95% CI	
Laryngeal cancer (73 cases)						
0	mg/m^3·years	40				
> 0 to 0.5	mg/m^3·years	17	1.06	0.89	(0.50, 2.25)	
> 0.5	mg/m^3·years	16	0.74	0.40	(0.36, 1.51)	
Trend				0.13		
Lung cancer (1894 cases)						
0	mg/m^3·years	967				
> 0 to 0.3	mg/m^3·years	309	1.08	0.38	(0.92, 1.26)	
> 0.3 to 1.6	mg/m^3·years	309	0.96	0.64	(0.82, 1.13)	
> 1.6	mg/m^3·years	309	0.91	0.20	(0.78, 1.05)	
Trend				0.26		
Esophageal cancer (176 cases)						
0	mg/m^3·years	83				
> 0 to 0.4	mg/m^3·years	31	1.18	0.54	(0.70, 1.97)	
> 0.4 to 2.1	mg/m^3·years	32	1.20	0.48	(0.72, 1.99)	
> 2.1	mg/m^3·years	30	1.17	0.53	(0.72, 1.89)	
Trend				0.64		
Stomach cancer (194 cases)						
0	mg/m^3·years	104				
> 0 to 0.3	mg/m^3·years	30	1.25	0.40	(0.75, 2.08)	
> 0.3 to 2.9	mg/m^3·years	30	0.87	0.59	(0.52, 1.45)	
> 2.9	mg/m^3·years	30	1.89	0.01	(1.17, 3.04)	*
Trend				0.06		.
Colon cancer (407 cases)						
0	mg/m^3·years	211				
> 0 to 0.5	mg/m^3·years	66	0.89	0.49	(0.63, 1.24)	
> 0.5 to 2.1	mg/m^3·years	65	0.92	0.64	(0.65, 1.30)	
> 2.1	mg/m^3·years	65	0.92	0.60	(0.67, 1.26)	
Trend				0.66		
Rectal cancer (83 cases)						
0	mg/m^3·years	44				
> 0 to 1	mg/m^3·years	20	0.87	0.72	(0.42, 1.80)	
> 1	mg/m^3·years	19	0.98	0.96	(0.50, 1.93)	
Trend				0.90		
Bladder cancer (138 cases)						
0	mg/m^3·years	73				
> 0 to 0.3	mg/m^3·years	20	1.11	0.74	(0.61, 2.00)	
> 0.3 to 1.8	mg/m^3·years	22	0.83	0.52	(0.46, 1.47)	
> 1.8	mg/m^3·years	23	0.82	0.45	(0.48, 1.39)	
Trend				0.37		
Liver cancer (123 cases)						
0	mg/m^3·years	55				
> 0 to 0.5	mg/m^3·years	22	0.98	0.96	(0.53, 1.83)	

Table 1: Cox model estimates of the hazard ratio for selected cancer outcomes associated with exposure to **straight** metalworking fluids, controlling for other fluid types, calendar year, calendar year of hire, age, race, sex, and plant.

		Number of cases	HR	p	95% CI	
> 0.5 to 1.6	mg/m^3·years	23	1.78	0.05	(0.99, 3.20)	·
> 1.6	mg/m^3·years	23	1.19	0.54	(0.68, 2.07)	
Trend				0.98		
Pancreatic cancer (315 cases)						
0	mg/m^3·years	154				
> 0 to 0.3	mg/m^3·years	54	1.16	0.44	(0.79, 1.72)	
> 0.3 to 1.1	mg/m^3·years	53	1.08	0.72	(0.72, 1.60)	
> 1.1	mg/m^3·years	54	0.80	0.23	(0.56, 1.15)	
Trend				0.16		
Skin cancer (69 cases)						
0	mg/m^3·years	32				
> 0 to 0.9	mg/m^3·years	18	1.23	0.59	(0.59, 2.58)	
> 0.9	mg/m^3·years	19	1.37	0.38	(0.68, 2.77)	
Trend				0.40		
Prostate cancer (418 cases)						
0	mg/m^3·years	192				
> 0 to 0.5	mg/m^3·years	76	1.20	0.26	(0.87, 1.66)	
> 0.5 to 2	mg/m^3·years	75	1.15	0.40	(0.83, 1.61)	
> 2	mg/m^3·years	75	1.07	0.66	(0.79, 1.45)	
Trend				0.96		
Brain and nervous system cancers (128 cases)						
0	mg/m^3·years	74				
> 0 to 1	mg/m^3·years	27	0.60	0.10	(0.33, 1.10)	·
> 1	mg/m^3·years	27	0.72	0.25	(0.42, 1.26)	
Trend				0.73		
Leukemia (200 cases)						
0	mg/m^3·years	100				
> 0 to 0.3	mg/m^3·years	34	1.06	0.82	(0.64, 1.75)	
> 0.3 to 2.3	mg/m^3·years	33	0.74	0.25	(0.45, 1.23)	
> 2.3	mg/m^3·years	33	0.92	0.72	(0.57, 1.47)	
Trend				0.84		
Breast cancer (76 cases)						
0	mg/m^3·years	43				
> 0 to 0.7	mg/m^3·years	16	1.26	0.57	(0.57, 2.77)	
> 0.7	mg/m^3·years	17	2.03	0.06	(0.96, 4.31)	·
Trend				0.16		

Table 2: Cox model estimates of the hazard ratio for selected cancer outcomes associated with exposure to **soluble** metalworking fluids, controlling for other fluid types, calendar year, calendar year of hire, age, race, sex, and plant.

	Number of cases	HR	p	95% CI
Laryngeal cancer (73 cases)				

Table 2: Cox model estimates of the hazard ratio for selected cancer outcomes associated with exposure to **soluble** metalworking fluids, controlling for other fluid types, calendar year, calendar year of hire, age, race, sex, and plant.

		Number of cases	HR	p	95% CI	
0 to 0.055	mg/m^3·years	18				
> 0.1 to 7.3	mg/m^3·years	28	0.86	0.67	(0.42, 1.75)	
> 7.3	mg/m^3·years	27	0.95	0.90	(0.45, 2.03)	
Trend				0.90		
Lung cancer (1894 cases)						
0 to 0.055	mg/m^3·years	437				
> 0.1 to 3.3	mg/m^3·years	486	0.97	0.65	(0.83, 1.12)	
> 3.3 to 11.2	mg/m^3·years	485	0.89	0.14	(0.76, 1.04)	
> 11.2	mg/m^3·years	486	1.00	0.96	(0.85, 1.17)	
Trend				0.60		
Esophageal cancer (176 cases)						
0 to 0.055	mg/m^3·years	34				
> 0.1 to 3.3	mg/m^3·years	46	1.03	0.91	(0.62, 1.70)	
> 3.3 to 10.8	mg/m^3·years	47	1.01	0.97	(0.60, 1.70)	
> 10.8	mg/m^3·years	49	1.15	0.61	(0.66, 2.00)	
Trend				0.01		*
Stomach cancer (194 cases)						
0 to 0.055	mg/m^3·years	59				
> 0.1 to 4.2	mg/m^3·years	45	0.65	0.07	(0.41, 1.04)	·
> 4.2 to 9.7	mg/m^3·years	45	1.02	0.94	(0.63, 1.64)	
> 9.7	mg/m^3·years	45	0.62	0.06	(0.37, 1.03)	·
Trend				0.37		
Colon cancer (407 cases)						
0 to 0.055	mg/m^3·years	80				
> 0.1 to 3.5	mg/m^3·years	109	1.20	0.28	(0.86, 1.65)	
> 3.5 to 12	mg/m^3·years	109	1.01	0.94	(0.72, 1.42)	
> 12	mg/m^3·years	109	0.99	0.96	(0.69, 1.41)	
Trend				0.59		
Rectal cancer (83 cases)						
0 to 0.055	mg/m^3·years	20				
> 0.1 to 4.6	mg/m^3·years	19	0.83	0.61	(0.40, 1.72)	
> 4.6 to 8.6	mg/m^3·years	23	2.11	0.04	(1.02, 4.37)	*
> 8.6	mg/m^3·years	21	0.83	0.64	(0.38, 1.80)	
Trend				0.61		
Bladder cancer (138 cases)						
0 to 0.055	mg/m^3·years	26				
> 0.1 to 3.7	mg/m^3·years	37	1.08	0.79	(0.62, 1.89)	
> 3.7 to 11.1	mg/m^3·years	36	1.16	0.61	(0.66, 2.04)	
> 11.1	mg/m^3·years	39	1.11	0.72	(0.62, 1.99)	
Trend				0.71		
Liver cancer (123 cases)						
0 to 0.055	mg/m^3·years	22				
> 0.1 to 2.3	mg/m^3·years	34	1.27	0.44	(0.70, 2.30)	
> 2.3 to 9.2	mg/m^3·years	32	0.74	0.34	(0.40, 1.37)	
> 9.2	mg/m^3·years	35	0.91	0.78	(0.49, 1.71)	

Table 2: Cox model estimates of the hazard ratio for selected cancer outcomes associated with exposure to **soluble** metalworking fluids, controlling for other fluid types, calendar year, calendar year of hire, age, race, sex, and plant.

		Number of cases	HR	p	95% CI	
Trend				0.78		
Pancreatic cancer (315 cases)						
0 to 0.055	mg/m^3·years	70				
> 0.1 to 3.4	mg/m^3·years	82	0.78	0.19	(0.54, 1.13)	
> 3.4 to 9.3	mg/m^3·years	81	0.89	0.56	(0.61, 1.31)	
> 9.3	mg/m^3·years	82	0.78	0.22	(0.53, 1.16)	
Trend				0.46		
Skin cancer (69 cases)						
0 to 0.055	mg/m^3·years	15				
> 0.1 to 4.7	mg/m^3·years	26	1.66	0.21	(0.76, 3.66)	
> 4.7	mg/m^3·years	28	1.61	0.27	(0.69, 3.76)	
Trend				0.70		
Prostate cancer (418 cases)						
0 to 0.055	mg/m^3·years	68				
> 0.1 to 5.1	mg/m^3·years	117	0.77	0.12	(0.55, 1.07)	
> 5.1 to 15.6	mg/m^3·years	116	0.79	0.19	(0.56, 1.12)	
> 15.6	mg/m^3·years	117	0.82	0.27	(0.58, 1.16)	
Trend				0.81		
Brain and nervous system cancers (128 cases)						
0 to 0.055	mg/m^3·years	32				
> 0.1 to 2.7	mg/m^3·years	32	1.50	0.16	(0.85, 2.63)	
> 2.7 to 9.2	mg/m^3·years	32	1.46	0.21	(0.81, 2.65)	
> 9.2	mg/m^3·years	32	1.52	0.20	(0.80, 2.88)	
Trend				0.58		
Leukemia (200 cases)						
0 to 0.055	mg/m^3·years	48				
> 0.1 to 3.3	mg/m^3·years	51	1.00	0.99	(0.63, 1.60)	
> 3.3 to 9.7	mg/m^3·years	50	1.05	0.83	(0.65, 1.71)	
> 9.7	mg/m^3·years	51	0.85	0.53	(0.51, 1.42)	
Trend				0.05		*
Breast cancer (76 cases)						
0 to 0.055	mg/m^3·years	36				
> 0.1 to 2.9	mg/m^3·years	22	0.56	0.10	(0.29, 1.11)	·
> 2.9	mg/m^3·years	18	0.52	0.11	(0.24, 1.16)	
Trend				0.61		

Table 3: Cox model estimates of the hazard ratio for selected cancer outcomes associated with exposure to **synthetic** metalworking fluids, controlling for other fluid types, calendar year, calendar year of hire, age, race, sex, and plant.

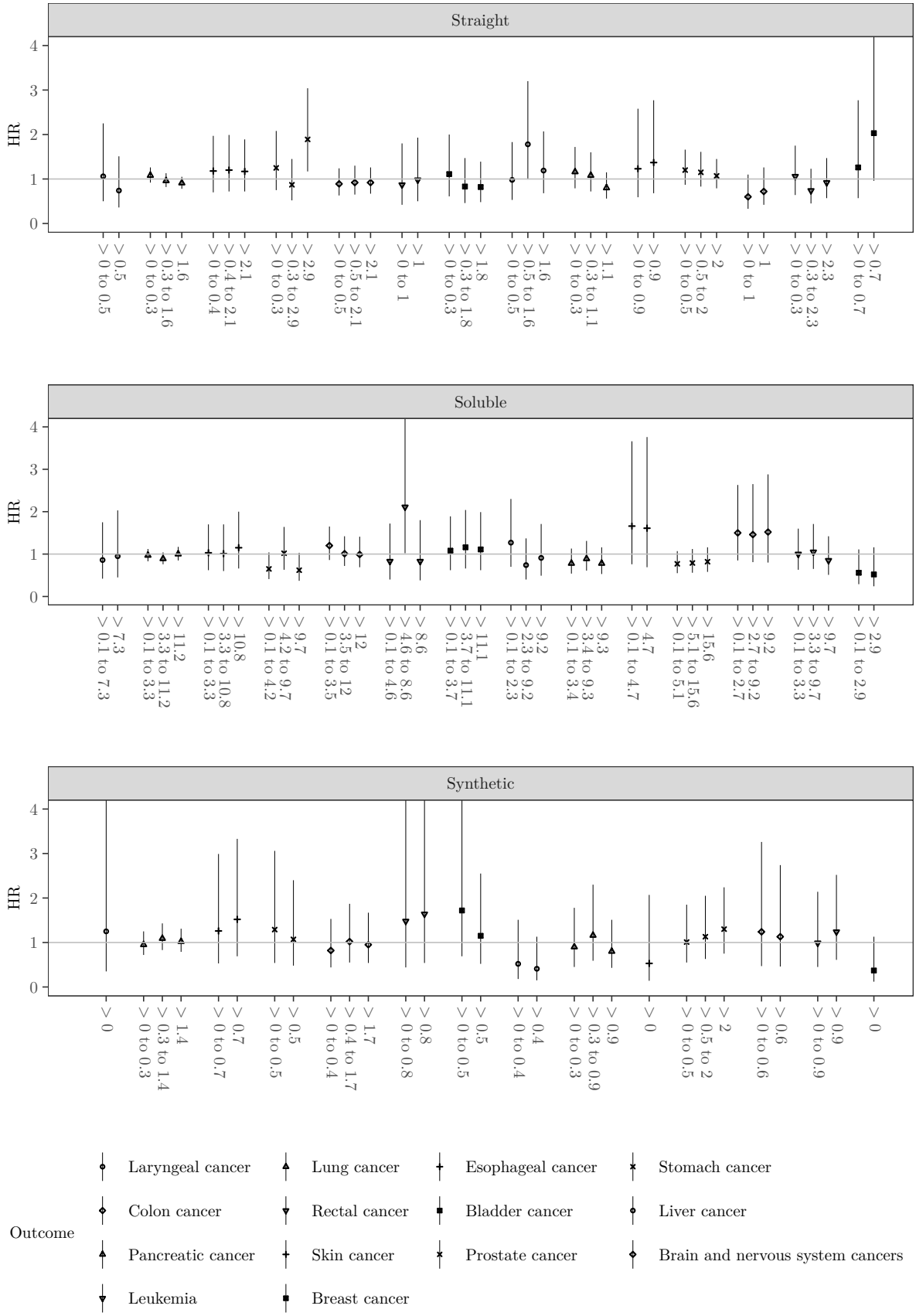
		Number of cases	HR	p	95% CI
Laryngeal cancer (73 cases)					
0	mg/m^3·years	54			

Table 3: Cox model estimates of the hazard ratio for selected cancer outcomes associated with exposure to **synthetic** metalworking fluids, controlling for other fluid types, calendar year, calendar year of hire, age, race, sex, and plant.

		Number of cases	HR	p	95% CI
> 0	mg/m^3·years	19	1.25	0.73	(0.35, 4.39)
Lung cancer (1894 cases)					
0	mg/m^3·years	1377			
> 0 to 0.3	mg/m^3·years	173	0.95	0.71	(0.72, 1.25)
> 0.3 to 1.4	mg/m^3·years	172	1.09	0.53	(0.83, 1.43)
> 1.4	mg/m^3·years	172	1.02	0.88	(0.79, 1.31)
Trend				0.95	
Esophageal cancer (176 cases)					
0	mg/m^3·years	126			
> 0 to 0.7	mg/m^3·years	25	1.26	0.60	(0.53, 2.99)
> 0.7	mg/m^3·years	25	1.52	0.30	(0.69, 3.33)
Trend				0.33	
Stomach cancer (194 cases)					
0	mg/m^3·years	150			
> 0 to 0.5	mg/m^3·years	22	1.29	0.56	(0.54, 3.06)
> 0.5	mg/m^3·years	22	1.07	0.87	(0.48, 2.40)
Trend				0.81	
Colon cancer (407 cases)					
0	mg/m^3·years	310			
> 0 to 0.4	mg/m^3·years	33	0.82	0.54	(0.44, 1.53)
> 0.4 to 1.7	mg/m^3·years	32	1.02	0.96	(0.55, 1.87)
> 1.7	mg/m^3·years	32	0.95	0.86	(0.54, 1.67)
Trend				0.99	
Rectal cancer (83 cases)					
0	mg/m^3·years	59			
> 0 to 0.8	mg/m^3·years	12	1.48	0.52	(0.44, 4.97)
> 0.8	mg/m^3·years	12	1.64	0.38	(0.54, 4.98)
Trend				0.51	
Bladder cancer (138 cases)					
0	mg/m^3·years	104			
> 0 to 0.5	mg/m^3·years	17	1.72	0.24	(0.69, 4.28)
> 0.5	mg/m^3·years	17	1.15	0.73	(0.52, 2.55)
Trend				0.80	
Liver cancer (123 cases)					
0	mg/m^3·years	89			
> 0 to 0.4	mg/m^3·years	17	0.52	0.23	(0.18, 1.51)
> 0.4	mg/m^3·years	17	0.41	0.08	(0.15, 1.13)
Trend				0.55	
Pancreatic cancer (315 cases)					
0	mg/m^3·years	227			
> 0 to 0.3	mg/m^3·years	30	0.90	0.76	(0.45, 1.78)
> 0.3 to 0.9	mg/m^3·years	29	1.16	0.66	(0.59, 2.30)
> 0.9	mg/m^3·years	29	0.80	0.50	(0.43, 1.51)
Trend				0.29	
Skin cancer (69 cases)					

Table 3: Cox model estimates of the hazard ratio for selected cancer outcomes associated with exposure to **synthetic** metalworking fluids, controlling for other fluid types, calendar year, calendar year of hire, age, race, sex, and plant.

		Number of cases	HR	p	95% CI	
0	mg/m^3·years	52				
> 0	mg/m^3·years	17	0.53	0.36	(0.14, 2.07)	
Prostate cancer (418 cases)						
0	mg/m^3·years	301				
> 0 to 0.5	mg/m^3·years	39	1.01	0.99	(0.55, 1.85)	
> 0.5 to 2	mg/m^3·years	39	1.13	0.68	(0.63, 2.05)	
> 2	mg/m^3·years	39	1.30	0.35	(0.75, 2.24)	
Trend				0.10		·
Brain and nervous system cancers (128 cases)						
0	mg/m^3·years	94				
> 0 to 0.6	mg/m^3·years	17	1.24	0.67	(0.47, 3.26)	
> 0.6	mg/m^3·years	17	1.13	0.79	(0.46, 2.74)	
Trend				0.97		
Leukemia (200 cases)						
0	mg/m^3·years	142				
> 0 to 0.9	mg/m^3·years	29	0.99	0.97	(0.45, 2.14)	
> 0.9	mg/m^3·years	29	1.24	0.55	(0.61, 2.52)	
Trend				0.03		*
Breast cancer (76 cases)						
0	mg/m^3·years	60				
> 0	mg/m^3·years	16	0.37	0.08	(0.12, 1.13)	·


Straight
Soluble
Synthetic
HR
0
1
2
3
4
> 0 to 0.5
> 0.5
> 0 to 0.3
> 0.3 to 1.6
> 1.6
> 0 to 0.4
> 0.4 to 2.1
> 2.1
> 0 to 0.3
> 0.3 to 2.9
> 2.9
> 0 to 0.5
> 0.5 to 2.1
> 2.1
> 0 to 1
> 1
> 0 to 0.3
> 0.3 to 1.8
> 1.8
> 0 to 0.5
> 0.5 to 1.6
> 1.6
> 0 to 0.3
> 0.3 to 1.1
> 1.1
> 0 to 0.9
> 0.9
> 0 to 0.5
> 0.5 to 2
> 2
> 0 to 1
> 1
> 0 to 0.3
> 0.3 to 2.3
> 2.3
> 0 to 0.7
> 0.7
> 0.1 to 7.3
> 7.3
> 0.1 to 3.3
> 3.3 to 11.2
> 11.2
> 0.1 to 3.3
> 3.3 to 10.8
> 10.8
> 0.1 to 4.2
> 4.2 to 9.7
> 9.7
> 0.1 to 3.5
> 3.5 to 12
> 12
> 0.1 to 4.6
> 4.6 to 8.6
> 8.6
> 0.1 to 3.7
> 3.7 to 11.1
> 11.1
> 0.1 to 2.3
> 2.3 to 9.2
> 9.2
> 0.1 to 3.4
> 3.4 to 9.3
> 9.3
> 0.1 to 4.7
> 4.7
> 0.1 to 5.1
> 5.1 to 15.6
> 15.6
> 0.1 to 2.7
> 2.7 to 9.2
> 9.2
> 0.1 to 3.3
> 3.3 to 9.7
> 9.7
> 0.1 to 2.9
> 2.9
> 0
> 0 to 0.3
> 0.3 to 1.4
> 1.4
> 0 to 0.7
> 0.7
> 0 to 0.5
> 0.5
> 0 to 0.4
> 0.4 to 1.7
> 1.7
> 0 to 0.8
> 0.8
> 0 to 0.5
> 0.5
> 0 to 0.4
> 0.4
> 0 to 0.3
> 0.3 to 0.9
> 0.9
> 0
> 0 to 0.5
> 0.5 to 2
> 2
> 0 to 0.6
> 0.6
> 0 to 0.9
> 0.9
> 0
Outcome
Laryngeal cancer
Lung cancer
Esophageal cancer
Stomach cancer
Colon cancer
Rectal cancer
Bladder cancer
Liver cancer
Pancreatic cancer
Skin cancer
Prostate cancer
Brain and nervous system cancers
Leukemia
Breast cancer