# UAW-GM Cohort Study

Clean referent group, messy exposure groups; exposure lagged 30 years

*November 12, 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 where person-time included in the analytic dataset would be restricted to those where either (1) cumulative exposure was zero or (2) cumulative exposure to the exposure of interest was nonzero. In other words, we excluded person-time satisfying both (1) zero exposure to the metalworking fluid type of interest *and* (2) nonzero exposure to some metalworking fluid other than the type in which we were interested. Coding of exposure and potential confounders was equivalent as that in the original analyses. As in the previous analyses, the category cut-points for the continuous covariates were determined in a data-adaptive way, so covariate definitions may vary from model to model. The results from the $13 \times 3 = 39$ models are presented below.

## 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 (55 cases) | | | | | | |
| 0 | mg/m$^3$·years | 27 | | | | |
| > 0 to 0.3 | mg/m$^3$·years | 14 | 0.98 | 0.99 | (0.12, 8.25) | |
| > 0.3 | mg/m$^3$·years | 14 | 0.75 | 0.78 | (0.09, 6.01) | |
| Trend | | | | 0.04 | | * |
| Lung cancer (1400 cases) | | | | | | |
| 0 | mg/m$^3$·years | 682 | | | | |
| > 0 to 0.3 | mg/m$^3$·years | 240 | 1.22 | 0.25 | (0.87, 1.71) | |
| > 0.3 to 1.4 | mg/m$^3$·years | 239 | 1.07 | 0.70 | (0.76, 1.51) | |
| > 1.4 | mg/m$^3$·years | 239 | 0.99 | 0.97 | (0.72, 1.38) | |
| Trend | | | | 0.70 | | |
| Esophageal cancer (127 cases) | | | | | | |
| 0 | mg/m$^3$·years | 57 | | | | |
| > 0 to 0.5 | mg/m$^3$·years | 24 | 1.85 | 0.20 | (0.72, 4.76) | |
| > 0.5 to 2.2 | mg/m$^3$·years | 23 | 2.56 | 0.05 | (1.00, 6.56) | * |
| > 2.2 | mg/m$^3$·years | 23 | 2.32 | 0.07 | (0.94, 5.70) | · |
| Trend | | | | 0.54 | | |
| Stomach cancer (160 cases) | | | | | | |
| 0 | mg/m$^3$·years | 91 | | | | |
| > 0 to 0.3 | mg/m$^3$·years | 23 | 0.79 | 0.68 | (0.25, 2.45) | |
| > 0.3 to 2.6 | mg/m$^3$·years | 23 | 0.60 | 0.38 | (0.19, 1.89) | |
| > 2.6 | mg/m$^3$·years | 23 | 1.20 | 0.74 | (0.41, 3.53) | |

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 | |
|---|---|---|---|---|---|---|
| Trend | | | | 0.41 | | |
| Colon cancer (291 cases) | | | | | | |
| 0 | mg/m$^3$·years | 140 | | | | |
| > 0 to 0.3 | mg/m$^3$·years | 51 | 0.53 | 0.16 | (0.22, 1.29) | |
| > 0.3 to 2.4 | mg/m$^3$·years | 50 | 0.41 | 0.05 | (0.17, 0.99) | * |
| > 2.4 | mg/m$^3$·years | 50 | 0.56 | 0.18 | (0.24, 1.32) | |
| Trend | | | | 0.67 | | |
| Rectal cancer (62 cases) | | | | | | |
| 0 | mg/m$^3$·years | 33 | | | | |
| > 0 to 0.6 | mg/m$^3$·years | 15 | 2.34 | 0.22 | (0.61, 9.04) | |
| > 0.6 | mg/m$^3$·years | 14 | 1.82 | 0.37 | (0.49, 6.80) | |
| Trend | | | | 0.81 | | |
| Bladder cancer (96 cases) | | | | | | |
| 0 | mg/m$^3$·years | 41 | | | | |
| > 0 to 0.5 | mg/m$^3$·years | 27 | 2.12 | 0.15 | (0.76, 5.93) | |
| > 0.5 | mg/m$^3$·years | 28 | 1.12 | 0.83 | (0.41, 3.01) | |
| Trend | | | | 0.80 | | |
| Liver cancer (87 cases) | | | | | | |
| 0 | mg/m$^3$·years | 34 | | | | |
| > 0 to 0.9 | mg/m$^3$·years | 26 | 0.81 | 0.79 | (0.18, 3.70) | |
| > 0.9 | mg/m$^3$·years | 27 | 1.22 | 0.79 | (0.28, 5.37) | |
| Trend | | | | 0.32 | | |
| Pancreatic cancer (246 cases) | | | | | | |
| 0 | mg/m$^3$·years | 119 | | | | |
| > 0 to 0.2 | mg/m$^3$·years | 43 | 0.77 | 0.59 | (0.30, 1.99) | |
| > 0.2 to 0.8 | mg/m$^3$·years | 42 | 0.73 | 0.52 | (0.27, 1.93) | |
| > 0.8 | mg/m$^3$·years | 42 | 0.40 | 0.06 | (0.15, 1.03) | · |
| Trend | | | | 0.15 | | |
| Skin cancer (54 cases) | | | | | | |
| 0 | mg/m$^3$·years | 26 | | | | |
| > 0 to 0.9 | mg/m$^3$·years | 14 | 1.60 | 0.56 | (0.32, 7.94) | |
| > 0.9 | mg/m$^3$·years | 14 | 1.71 | 0.50 | (0.36, 8.19) | |
| Trend | | | | 0.54 | | |
| Prostate cancer (289 cases) | | | | | | |
| 0 | mg/m$^3$·years | 96 | | | | |
| > 0 to 0.3 | mg/m$^3$·years | 65 | 1.76 | 0.09 | (0.91, 3.40) | · |
| > 0.3 to 1.5 | mg/m$^3$·years | 64 | 1.49 | 0.24 | (0.76, 2.92) | |
| > 1.5 | mg/m$^3$·years | 64 | 1.28 | 0.45 | (0.68, 2.39) | |
| Trend | | | | 0.88 | | |
| Brain and nervous system cancers (94 cases) | | | | | | |
| 0 | mg/m$^3$·years | 52 | | | | |
| > 0 to 0.9 | mg/m$^3$·years | 21 | 0.59 | 0.50 | (0.13, 2.72) | |
| > 0.9 | mg/m$^3$·years | 21 | 0.84 | 0.82 | (0.19, 3.72) | |
| Trend | | | | 0.93 | | |
| Leukemia (151 cases) | | | | | | |

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 | mg/m$^3$·years | 70 | | | | |
| > 0 to 0.3 | mg/m$^3$·years | 27 | 1.52 | 0.40 | (0.58, 3.97) | |
| > 0.3 to 1.7 | mg/m$^3$·years | 27 | 1.24 | 0.67 | (0.46, 3.29) | |
| > 1.7 | mg/m$^3$·years | 27 | 1.16 | 0.76 | (0.46, 2.92) | |
| Trend | | | | 0.99 | | |
| Breast cancer (71 cases) | | | | | | |
| 0 | mg/m$^3$·years | 48 | | | | |
| > 0 to 0.7 | mg/m$^3$·years | 11 | 1.17 | 0.80 | (0.36, 3.79) | |
| > 0.7 | mg/m$^3$·years | 12 | 2.30 | 0.17 | (0.70, 7.60) | |
| Trend | | | | 0.08 | | · |

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 (72 cases) | | | | | | |
| 0 to 0.1 | mg/m$^3$·years | 27 | | | | |
| > 0.1 to 7.2 | mg/m$^3$·years | 23 | 0.92 | 0.83 | (0.44, 1.95) | |
| > 7.2 | mg/m$^3$·years | 22 | 1.35 | 0.48 | (0.59, 3.08) | |
| Trend | | | | 0.13 | | |
| Lung cancer (1861 cases) | | | | | | |
| 0 to 0.1 | mg/m$^3$·years | 702 | | | | |
| > 0.1 to 3 | mg/m$^3$·years | 387 | 1.00 | 0.99 | (0.86, 1.17) | |
| > 3 to 9.3 | mg/m$^3$·years | 386 | 1.03 | 0.69 | (0.88, 1.22) | |
| > 9.3 | mg/m$^3$·years | 386 | 1.08 | 0.40 | (0.90, 1.29) | |
| Trend | | | | 0.09 | | · |
| Esophageal cancer (168 cases) | | | | | | |
| 0 to 0.1 | mg/m$^3$·years | 57 | | | | |
| > 0.1 to 3 | mg/m$^3$·years | 35 | 1.27 | 0.38 | (0.75, 2.16) | |
| > 3 to 10.2 | mg/m$^3$·years | 38 | 1.46 | 0.18 | (0.83, 2.57) | |
| > 10.2 | mg/m$^3$·years | 38 | 1.90 | 0.04 | (1.03, 3.51) | * |
| Trend | | | | 0.12 | | |
| Stomach cancer (189 cases) | | | | | | |
| 0 to 0.1 | mg/m$^3$·years | 91 | | | | |
| > 0.1 to 4.3 | mg/m$^3$·years | 33 | 0.57 | 0.04 | (0.34, 0.97) | * |
| > 4.3 to 11.3 | mg/m$^3$·years | 32 | 0.90 | 0.70 | (0.51, 1.57) | |
| > 11.3 | mg/m$^3$·years | 33 | 0.89 | 0.71 | (0.49, 1.62) | |
| Trend | | | | 0.82 | | |
| Colon cancer (403 cases) | | | | | | |
| 0 to 0.1 | mg/m$^3$·years | 143 | | | | |
| > 0.1 to 3 | mg/m$^3$·years | 87 | 0.97 | 0.87 | (0.71, 1.34) | |
| > 3 to 11.6 | mg/m$^3$·years | 86 | 0.74 | 0.08 | (0.52, 1.04) | · |

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 | |
|---|---|---|---|---|---|---|
| > 11.6 | mg/m$^3$·years | 87 | 0.89 | 0.53 | (0.62, 1.28) | |
| Trend | | | | 0.91 | | |
| Rectal cancer (82 cases) | | | | | | |
| 0 to 0.1 | mg/m$^3$·years | 35 | | | | |
| > 0.1 to 6.5 | mg/m$^3$·years | 21 | 0.73 | 0.39 | (0.36, 1.48) | |
| > 6.5 | mg/m$^3$·years | 26 | 1.20 | 0.64 | (0.57, 2.54) | |
| Trend | | | | 0.40 | | |
| Bladder cancer (134 cases) | | | | | | |
| 0 to 0.1 | mg/m$^3$·years | 42 | | | | |
| > 0.1 to 3.2 | mg/m$^3$·years | 30 | 1.00 | 0.99 | (0.58, 1.74) | |
| > 3.2 to 8.7 | mg/m$^3$·years | 30 | 1.19 | 0.55 | (0.68, 2.08) | |
| > 8.7 | mg/m$^3$·years | 32 | 0.99 | 0.99 | (0.55, 1.79) | |
| Trend | | | | 0.65 | | |
| Liver cancer (122 cases) | | | | | | |
| 0 to 0.1 | mg/m$^3$·years | 36 | | | | |
| > 0.1 to 2 | mg/m$^3$·years | 29 | 1.51 | 0.17 | (0.84, 2.70) | |
| > 2 to 6.6 | mg/m$^3$·years | 28 | 1.28 | 0.43 | (0.70, 2.35) | |
| > 6.6 | mg/m$^3$·years | 29 | 0.93 | 0.82 | (0.48, 1.79) | |
| Trend | | | | 0.38 | | |
| Pancreatic cancer (309 cases) | | | | | | |
| 0 to 0.1 | mg/m$^3$·years | 119 | | | | |
| > 0.1 to 2.8 | mg/m$^3$·years | 64 | 0.71 | 0.07 | (0.49, 1.03) | · |
| > 2.8 to 8.3 | mg/m$^3$·years | 63 | 0.76 | 0.18 | (0.51, 1.14) | |
| > 8.3 | mg/m$^3$·years | 63 | 0.71 | 0.12 | (0.47, 1.09) | |
| Trend | | | | 0.59 | | |
| Skin cancer (68 cases) | | | | | | |
| 0 to 0.1 | mg/m$^3$·years | 27 | | | | |
| > 0.1 to 6.4 | mg/m$^3$·years | 21 | 1.15 | 0.73 | (0.52, 2.56) | |
| > 6.4 | mg/m$^3$·years | 20 | 1.67 | 0.27 | (0.67, 4.17) | |
| Trend | | | | 0.13 | | |
| Prostate cancer (411 cases) | | | | | | |
| 0 to 0.1 | mg/m$^3$·years | 102 | | | | |
| > 0.1 to 4 | mg/m$^3$·years | 103 | 0.92 | 0.63 | (0.67, 1.28) | |
| > 4 to 11.9 | mg/m$^3$·years | 103 | 0.95 | 0.76 | (0.68, 1.33) | |
| > 11.9 | mg/m$^3$·years | 103 | 0.88 | 0.49 | (0.62, 1.26) | |
| Trend | | | | 0.23 | | |
| Brain and nervous system cancers (127 cases) | | | | | | |
| 0 to 0.1 | mg/m$^3$·years | 53 | | | | |
| > 0.1 to 2.7 | mg/m$^3$·years | 25 | 1.46 | 0.22 | (0.80, 2.66) | |
| > 2.7 to 8 | mg/m$^3$·years | 24 | 1.77 | 0.08 | (0.93, 3.37) | · |
| > 8 | mg/m$^3$·years | 25 | 1.67 | 0.14 | (0.84, 3.32) | |
| Trend | | | | 0.60 | | |
| Leukemia (196 cases) | | | | | | |
| 0 to 0.1 | mg/m$^3$·years | 72 | | | | |
| > 0.1 to 2.5 | mg/m$^3$·years | 42 | 1.32 | 0.27 | (0.81, 2.15) | |

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 | |
|---|---|---|---|---|---|---|
| > 2.5 to 7.3 | mg/m$^3$·years | 41 | 1.18 | 0.53 | (0.70, 2.00) | |
| > 7.3 | mg/m$^3$·years | 41 | 0.82 | 0.49 | (0.47, 1.44) | |
| Trend | | | | 0.21 | | |
| Breast cancer (74 cases) | | | | | | |
| 0 to 0.1 | mg/m$^3$·years | 50 | | | | |
| > 0.1 to 2.2 | mg/m$^3$·years | 13 | 0.55 | 0.16 | (0.24, 1.27) | |
| > 2.2 | mg/m$^3$·years | 11 | 0.30 | 0.02 | (0.11, 0.82) | * |
| Trend | | | | 0.43 | | |

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 (42 cases) | | | | | |
| 0 | mg/m$^3$·years | 27 | | | |
| > 0 | mg/m$^3$·years | 15 | 0.00 | 0.99 | (0.00, Inf) |
| Lung cancer (1061 cases) | | | | | |
| 0 | mg/m$^3$·years | 682 | | | |
| > 0 to 0.2 | mg/m$^3$·years | 127 | 1.23 | 0.49 | (0.69, 2.19) |
| > 0.2 to 1.3 | mg/m$^3$·years | 126 | 1.17 | 0.59 | (0.66, 2.09) |
| > 1.3 | mg/m$^3$·years | 126 | 1.21 | 0.51 | (0.69, 2.11) |
| Trend | | | | 0.63 | |
| Esophageal cancer (92 cases) | | | | | |
| 0 | mg/m$^3$·years | 57 | | | |
| > 0 to 0.7 | mg/m$^3$·years | 18 | 2.52 | 0.28 | (0.47, 13.40) |
| > 0.7 | mg/m$^3$·years | 17 | 2.21 | 0.33 | (0.44, 11.04) |
| Trend | | | | 0.79 | |
| Stomach cancer (113 cases) | | | | | |
| 0 | mg/m$^3$·years | 85 | | | |
| > 0 to 0.4 | mg/m$^3$·years | 15 | 0.47 | 0.59 | (0.03, 7.02) |
| > 0.4 | mg/m$^3$·years | 13 | 0.35 | 0.44 | (0.02, 5.00) |
| Trend | | | | 0.55 | |
| Colon cancer (207 cases) | | | | | |
| 0 | mg/m$^3$·years | 140 | | | |
| > 0 to 0.2 | mg/m$^3$·years | 23 | 1.02 | 0.98 | (0.26, 4.04) |
| > 0.2 to 1.4 | mg/m$^3$·years | 22 | 0.75 | 0.68 | (0.19, 2.99) |
| > 1.4 | mg/m$^3$·years | 22 | 0.67 | 0.56 | (0.17, 2.55) |
| Trend | | | | 0.27 | |
| Rectal cancer (50 cases) | | | | | |
| 0 | mg/m$^3$·years | 33 | | | |
| > 0 to 0.5 | mg/m$^3$·years | 8 | 0.00 | 0.99 | (0.00, Inf) |
| > 0.5 | mg/m$^3$·years | 9 | 0.00 | 0.99 | (0.00, Inf) |

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 | |
|---|---|---|---|---|---|---|
| Trend | | | | 0.66 | | |
| Bladder cancer (68 cases) | | | | | | |
| 0 | mg/m$^3$·years | 41 | | | | |
| > 0 to 0.5 | mg/m$^3$·years | 14 | 0.00 | 0.99 | (0.00, Inf) | |
| > 0.5 | mg/m$^3$·years | 13 | 0.00 | 0.99 | (0.00, Inf) | |
| Trend | | | | 0.66 | | |
| Liver cancer (60 cases) | | | | | | |
| 0 | mg/m$^3$·years | 34 | | | | |
| > 0 to 0.4 | mg/m$^3$·years | 13 | 1.41 | 0.77 | (0.14, 14.19) | |
| > 0.4 | mg/m$^3$·years | 13 | 1.47 | 0.73 | (0.17, 12.97) | |
| Trend | | | | 0.60 | | |
| Pancreatic cancer (185 cases) | | | | | | |
| 0 | mg/m$^3$·years | 119 | | | | |
| > 0 to 0.2 | mg/m$^3$·years | 22 | 0.29 | 0.27 | (0.03, 2.59) | |
| > 0.2 to 0.7 | mg/m$^3$·years | 22 | 0.31 | 0.30 | (0.03, 2.80) | |
| > 0.7 | mg/m$^3$·years | 22 | 0.23 | 0.18 | (0.03, 2.01) | |
| Trend | | | | 0.58 | | |
| Skin cancer (39 cases) | | | | | | |
| 0 | mg/m$^3$·years | 26 | | | | |
| > 0 | mg/m$^3$·years | 13 | 0.00 | 0.99 | (0.00, Inf) | |
| Prostate cancer (198 cases) | | | | | | |
| 0 | mg/m$^3$·years | 96 | | | | |
| > 0 to 0.3 | mg/m$^3$·years | 34 | 2.20 | 0.16 | (0.73, 6.63) | |
| > 0.3 to 1.2 | mg/m$^3$·years | 34 | 2.72 | 0.07 | (0.91, 8.11) | · |
| > 1.2 | mg/m$^3$·years | 34 | 1.99 | 0.20 | (0.70, 5.69) | |
| Trend | | | | 0.98 | | |
| Brain and nervous system cancers (80 cases) | | | | | | |
| 0 | mg/m$^3$·years | 52 | | | | |
| > 0 to 0.2 | mg/m$^3$·years | 14 | 4.24 | 0.19 | (0.49, 36.43) | |
| > 0.2 | mg/m$^3$·years | 14 | 1.08 | 0.94 | (0.13, 9.23) | |
| Trend | | | | 0.68 | | |
| Leukemia (106 cases) | | | | | | |
| 0 | mg/m$^3$·years | 64 | | | | |
| > 0 to 0.6 | mg/m$^3$·years | 21 | 0.00 | 0.99 | (0.00, Inf) | |
| > 0.6 | mg/m$^3$·years | 21 | 0.00 | 0.99 | (0.00, Inf) | |
| Trend | | | | 0.66 | | |
| Breast cancer (58 cases) | | | | | | |
| 0 | mg/m$^3$·years | 48 | | | | |
| > 0 | mg/m$^3$·years | 10 | 0.00 | 0.99 | (0.00, Inf) | |

Clean referent group, messy exposure groups; exposure lagged 30 years; soluble referent at 0.1 mg/m$^3$·y