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Mortality Studies of Metalworking Fluid Exposure in the Automobile Industry: VI. A Case-Control Study of Esophageal Cancer

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Background *Results are reported from a nested case-control study of 60 esophageal cancer deaths among 46,384 automobile manufacturing workers potentially exposed to metalworking fluids (MWF) in machining and grinding operations.*
Methods *By using incidence-density sampling, controls were selected with a sampling ratio of 20:1 from among co-workers who remained at risk by the age of death of the case, matched on race, gender, plant, and year of birth. Conditional logistic regression was used to evaluate the risk associated with cumulative exposure (mg/m^3-years) to each of three types of metalworking fluid (straight, soluble, and synthetic MWF), as well as with years of exposure to selected components of MWF, including nitrosamines, sulfur, biocides, and several metals.*
Results *Esophageal cancer was found to be significantly associated with exposure to both soluble and synthetic MWF in grinding operations. The odds ratios (ORs) for grinding with soluble MWF were elevated at 2.5 or greater in all categories of cumulative exposure, although the exposure-response trend was statistically significant only when exposure was measured as duration. Those with 12 or more years exposure to soluble MWF in grinding operations experienced a 9.3-fold relative risk of esophageal cancer mortality (95% CI = 2.1–42.1). The OR for ever grinding with synthetic MWF was 4.1 (95% CI = 1.1–15.0). Elevated risk was also associated with two agents found in both synthetic and soluble fluids, nitrosamines, and biocides. For exposure to nitrosamines, the OR was 5.4 (95% CI = 1.5–19.9); for biocides the OR was 3.8 (95% CI = 0.8–18.9). However, because the same workers were exposed to grinding with synthetics, nitrosamines and biocides, it was not possible to separate the specific risks associated with these components.* Am. J. Ind. Med. 34:36–48, 1998. *© 1998 Wiley-Liss, Inc.*

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The case-control study described here was nested within a larger cohort mortality study of automobile manufacturing workers that was undertaken to evaluate health effects of metalworking fluids (MWF) [Eisen et al., 1992, 1994b; Tolbert et al., 1992]. Study subjects worked in grinding, machining, or assembly operations, with potential exposure to complex mixtures of straight, soluble, and synthetic MWF aerosols. The study cohort consisted of 46,384 United Autoworkers (UAW) General Motors (GM) workers from three Michigan auto plants who were followed for up to 45 yr. The cohort study evaluated over 10,000 deaths and had nearly 1 million person-years of follow-up. Previously reported results of Poisson regression analysis

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using the entire cohort demonstrated a statistically significant dose-response relationship between cumulative exposure to grinding particulate and esophageal cancer mortality. A relative risk of 3.7 was observed among those with 10 to 25 mg/m^3-years exposure, although there was some decrease in risk observed among those with more than 25 mg/m^3-years exposure [Eisen et al., 1994b]. Poisson regression analysis also detected a twofold elevated risk of esophageal cancer mortality among those who worked with synthetic MWF compared to those with no synthetic MWF exposure [Tolbert et al., 1992]. The case-control study described here was undertaken to further evaluate the risk of esophageal cancer among these workers while controlling for the potential confounding effects of components, contaminants, and additives of the metalworking fluid.

Metalworking fluids are used to lubricate or cool surfaces during metalworking operations involving grinding or machining of metal parts. MWF are complex mixtures, including numerous components, additives, and contaminants with the potential to act as cancer initiators or promoters. The constituents of MWF have recently been described [Burgess, 1995; NIOSH, 1996; Howell et al., 1996]. Metalworking fluids can be classified into three main types. (1) Straight fluids (cutting oils) are naphthenic or paraffinic mineral and fatty oils containing polycyclic aromatic hydrocarbons and extreme pressure additives that are chlorine, phosphorus or sulfur-based. (2) Soluble fluids (emulsified oils) are paraffinic or naphthenic mineral and fatty oils emulsified in water, and may contain alkanolamines to buffer pH; nitrites added to inhibit corrosion; and biocides, including triazine, oxazolidine and phenolic compounds, some of which may be formaldehyde releasing. (3) Synthetic fluids, contain no oil and consist of organic chemicals dissolved in water, ethanolamines as a corrosion inhibitor or pH buffer, and biocides. In the analysis reported here, semisynthetic fluids were classified as solubles.

Many suspected occupational risk factors for esophageal cancer are present in automobile manufacturing [Welter, 1978; Fadlallah et al., 1990; Tolbert et al., 1992; Kenyon et al., 1993; Hallock et al., 1994]. Based on existing literature, components, contaminants, and additives of MWF that may be risk factors for esophageal cancer include nitrosamine [Frank-Stromborg, 1989; Fraser et al., 1989], biocides [Mackerer, 1989; NIOSH, 1996], sulfur compounds [Frank-Stromborg, 1989; Fraser et al., 1989], polycyclic aromatic hydrocarbons [Gustavsson et al., 1988; Mackerer, 1989], and metal dusts [Neuget and Wylie, 1987; Magnani et al., 1987; Yu et al., 1988; Gustavsson et al., 1988; Frank-Stromborg, 1989].

NIOSH has estimated that 1.2 million U.S. workers are potentially exposed to MWF [NIOSH, 1977; NIOSH, 1996]. Previous studies of MWF environments have suggested elevated respiratory, digestive, and skin cancers in cohorts exposed to MWF [Vena et al., 1985; Jarvholm and Lavenius, 1987; Eisen et al., 1994a]. Although most previous studies have not had sufficient statistical power to evaluate esophageal cancer separately from other digestive cancers, several researchers have reported excess risk of esophageal cancer that was not statistically significant [Decouflé, 1978; Vena et al., 1985; Jarvholm and Lavenius, 1987; Park et al., 1988]. Silverstein et al. [1988] found significantly increased risk of esophageal cancer in bearing manufacturing workers exposed to MWF and abrasives for at least 5 yr (PMR 1.8; 95% CI = 1.1–3.1).

MATERIALS AND METHODS

Study Population

The UAW/GM mortality study subjects were hourly employees who worked at least 3 yr before 1985 in three Michigan automobile parts manufacturing facilities [Eisen et al., 1992; Tolbert et al., 1992]. Study subjects were hired between 1917 and 1981. Plant I began operation in 1917, plant II started up in 1939, and plant III in the 1920s. Plant I produced gears and axles for rear-wheel drive vehicles; plant II manufactured transmissions; plant III produced components for steering gears.

Demographic data (date of birth, race, gender, Social Security number) and work history (job, department, and work dates) were abstracted from company records. Details of data collection, cohort verification using Social Security 941 Quarterly Earnings reports, and vital status follow-up through the National Death Index and the Social Security Administration have been provided elsewhere [Eisen et al., 1992]. Overall, vital status was unknown for 6 percent of the study cohort. Cause of death was determined for 92% of the 10,159 (22%) workers known to have died during the period from 1941 through 1984. Underlying cause of death and ‘‘other significant conditions’’ were coded from death certificates using the 8th Revision of the International Classification of Diseases (ICD-8 codes).

Case-Control Selection

The relationship between MWF exposure and esophageal cancer mortality was evaluated using a nested case-control design. Cases were defined as deceased study subjects with esophageal cancer listed as either the underlying cause or other significant condition on the death certificate. Sixty cases were identified. Controls matched on race, gender, plant, and year of birth were selected from among co-workers who remained at risk by the age of death of the case. A 20:1 sampling ratio was used to minimize sampling variability, resulting in precision that approached a full cohort analysis. This analysis was based on the 53 cases with adequate work history data (no more than 25% of their work history missing).

Exposure Estimates

Details of the exposure assessment have been described elsewhere [Hallock et al., 1994; Woskie et al., 1994a,b]. Exposure to straight, soluble, or synthetic MWF was measured as mass concentration (mg/m^3) of total particulate. Direct MWF particulate exposure occurred during grinding or metal machining. Machining operations, which were collapsed into a single category in the retrospective exposure assessment, included bore/mill/turn, broaching, drill/tap/ream, gear cutting, lapping, screw machines, and transfer machines. Data were also collected on the presence or absence of exposure to MWF contaminants, including: metals (aluminum, steel, or iron), elemental sulfur as a MWF additive, biocides, ethanolamine, nitrite, and nitrosamine (defined as the copresence of ethanolamine and nitrite). For a limited number of jobs/departments in plants I and II, data were also collected on organic solvents and exposure to asbestos.

For each job/department/plant and calendar time period, an exposure matrix was created defined by operation and MWF type. Work histories were abstracted from company personnel records. Exposure estimates from the job exposure matrices were combined with work histories to calculate estimates of lifetime exposure for each study subject. Exposure estimates were developed both for cumulative lifetime exposure (mg/m^3-years) and duration of exposure (years) for each of the three primary fluid types, for grinding and machining operations, and for specific MWF type/operation combinations, such as grinding with synthetics or grinding with solubles. Similarly, duration of exposure to MWF components (aluminum, steel, cast iron, sulfur, biocides, ethanolamines, nitrites, nitrosamines) and other workplace exposures (asbestos, solvents) was calculated for each study subject.

For some study subjects, there were gaps in the work histories abstracted from company records. If more than 25% of a subject's work history was missing, that subject was not included in the analysis. For remaining study subjects with missing work history, exposure to a given agent during years for which work history was missing was imputed from the mean exposure to that agent among all study subjects from the same plant during that year.

Statistical Methods

Conditional logistic regression was used to evaluate the relationship between esophageal cancer and cumulative exposure to total particulate for three types of MWF, grinding, or machining operations, and several agents that were components, additives, or contaminants of the MWF, or were present elsewhere in the work environment (for example, asbestos, which was used in brake, axle, and transmission assembly operations). Models were fit for each continuous predictor variable. Odds ratios for a continuous predictor quantify the increase in risk of esophageal cancer mortality associated with a one unit change in exposure (either 1 mg/m^3-year or 1 year). The number of years since hire was included as a variable in all models to control for the healthy worker (survivor) effect sometimes observed after workers whose health is impaired selectively leave employment.

To account for cancer latency, lagged exposure variables were constructed to include only those exposures occurring during hypothesized biologically relevant time periods. Exposure lag periods of 10 and 20 yr were evaluated. Choice of the best exposure lag period was based on goodness of fit as measured by the score statistic.

A SAS program was written to construct categorical exposure groups using quartiles of the exposure distribution in the cases [SAS, 1990]. This method of categorizing exposure variables yielded the most efficient categorical estimators, as demonstrated in analyses of simulated data structured similarly to this case-control data set [Sullivan et al., 1996]. For each exposure, odds in categorical exposure groups were compared with the lowest exposure category. The SAS PHREG procedure [SAS, 1990] and EGRET software [SERC, 1993] were used to estimate odds ratios (ORs) and 95% confidence limits. Tests for linear trend using mean exposure (for all study subjects in the categorical exposure group) were weighted by the proportion of cases and controls in each exposure category [Rothman, 1986].

Potential confounding was assessed for each exposure (main effect) for which the preceding analyses suggested elevated risk of esophageal cancer. Confounding was evaluated by fitting models using each main effect, controlling in succession for each other continuous exposure covariate. A variable was treated as a confounder and included in the model in subsequent analyses if its inclusion in the model resulted in an improvement in fit as measured by the P value (to enter) for the score statistic ($P < 0.2$).

We examined correlation coefficients for evidence of collinearity between exposure variables. Two variables with a correlation coefficient of 0.75 or greater were not included together in the same model because of concern that collinearity between the exposure variables would make interpretation difficult.

RESULTS

Of the 60 study subjects identified with esophageal cancer, 7 cases (and their matched controls) were removed from analysis because more than 25% of their work history was missing; an additional 58 controls were also excluded

TABLE I. Characteristics of Esophageal Cancer Cases and Controls With Potential Exposure to Metalworking Fluids in the Automobile Manufacturing Industry

Characteristic	Cases (n = 53)	Controls (n = 971)
Race[a]		
White (%)	47.2	49.8
Black (%)	15.1	16.6
Unknown (%)	37.7	33.6
Gender[a]		
Male (%)	96.2	96.0
Female (%)	3.8	4.0
Year of birth[a]	1910	1910
Age in risk year[ab]	63.3	63.6
Age started work	33.1	33.2
Year started work	1943	1943
Years worked	17.8	17.2

[a]Matched.
[b]For a case, risk year is the year in which the case subject died; for a control, risk year is the year in which the matched control subject reached the age at which the case subject died. Controls were selected from among co-workers who remained at risk by the age of death of the case.

because of missing data. Demographic characteristics of the 53 remaining cases and their matched controls are compared in Table I. As expected, the means of the matching variables were similar. Race was unknown for 38% of cases. Cases with unknown race were matched with controls of unknown race. For some cases, fewer than 20 controls meeting the matching criteria were available. The average year of birth for case-control study subjects was 1910, and the mean year of hire was 1943. Only 9% of study subjects were hired after 1960; less than 1% were hired after 1970. Both cases and controls worked an average of approximately 17.5 yr.

Overall, 93% of study subjects had been exposed to soluble MWF, 54% to straight fluids and 23% to synthetic MWF (Table II). Average cumulative exposure was greater for soluble MWF than for straight or synthetic metalworking fluid. There was no difference between cases and controls in average cumulative lifetime exposure to synthetic MWF, although cases had somewhat higher cumulative exposure to grinding operations using synthetic MWF. Seventy-eight percent of study subjects were involved in grinding operations at some time during their work experience. Grinding operations typically involved either soluble or synthetic fluids. Although these water-soluble fluids are more effective with high-speed grinding operations, some grinding was also done dry or with straight fluids. Machining operations generally used soluble or straight MWF.

The metalworking environment is characterized by multiple exposures, both concurrently and sequentially, making it difficult to isolate the effect of any one agent. Most workers were exposed to more than one type of metalworking fluid or operation. For example, among 781 study subjects exposed to soluble MWF in grinding operations, 97% also had experience working with soluble fluids in machining operations. There were 153 workers exposed to synthetic fluids in grinding operations; 95% of these also had experience grinding with soluble MWF. Exposure to metals was ubiquitous: 91% of study subjects were exposed to steel, and 70% were exposed to cast-iron in metalworking operations.

TABLE II. Exposure Characteristics Among Case-Control Study Subjects

	All study subjects		Mean lifetime exposure[a]	
Exposure	% Ever exposed	Range[b]	Cases	Controls
MWF type (mg/m^3-years)				
Straight	54	0.0–143.3	5.1	7.4
Synthetic	23	0.0–43.7	2.6	2.7
Soluble	93	0.0–271.0	34.1	31.1
Operation (mg/m^3-years)				
Grinding with synthetic MWF[c]	15	0.0–43.7	3.2	2.6
Grinding with soluble MWF	76	0.0–266.4	19.7	18.0
Machining with soluble MWF	91	0.0–121.3	15.5	16.9
Metals (years)				
Steel	91	0.0–41.0	11.5	10.9
Iron	70	0.0–41.2	8.7	8.2
Aluminum[c]	12	0.0–20.3	3.0	3.7
Sulfur (years)	25	0.0–39.0	5.5	5.8
Biocide (years)	13	0.0–26.2	3.4	5.8
Nitrosamine[c] (years)	15	0.0–32.8	5.7	5.7
Asbestos[d] (years)	66	0.0–36.3	5.6	5.9
Solvent[d] (years)	37	0.0–30.7	4.0	3.7

[a]Among ever exposed study subjects.
[b]Zero exposure values result from rounding.
[c]Exposure occurred in plants II and III only.
[d]Based on 582 study subjects (34 cases) in a limited number of jobs/departments in plants I and II for which data on exposure to asbestos and solvents are available.

Exposure-Response Modeling

Continuous exposure variables

Results of modeling based on continuous measures of exposure are presented for unlagged exposure variables as well as for exposure variables with 10-yr and 20-yr lags in Table III. For a 20-yr lag, exposure is cumulated to 20 yr before the risk date (the date of death of the case, or the date on which a control reached the age of death of the matched case). The ORs and 95% confidence intervals (CIs) in Table

TABLE III. Adjusted Odds Ratios (OR) for Esophageal Cancer with Increasing Exposure Lag Period: Analysis of Continuous Exposure Variables with Odds Ratios and 95% Confidence Intervals (CI) Calculated Assuming 5 Years or 5 mg/m^3-years of Exposure[a]

	Lag 0		Lag 10 yr		Lag 20 yr[b]	
Exposure	OR	95% CI	OR	95% CI	OR	95% CI
MWF type						
Straight						
mg/m^3-years	1.0	0.9–1.1	1.0	0.8–1.1	0.9	0.8–1.2
years	1.0	0.8–1.3	1.1	0.8–1.3	1.1	0.8–1.5
Synthetic						
mg/m^3-years	1.2	0.8–1.8	1.5	0.9–2.6	2.8	1.1–7.5
years	1.1	0.8–1.7	1.5	0.9–2.7	3.3	1.1–9.6
Soluble						
mg/m^3-years	1.0	1.0–1.0	1.0	1.0–1.1	1.0	1.0–1.1
years	1.1	0.9–1.2	1.1	0.9–1.3	1.1	0.9–1.4
Operation						
Grinding with synthetic MWF[c]						
mg/m^3-years	1.2	0.8–1.8	1.5	0.9–2.7	2.8	1.0–7.5
years	1.1	0.8–1.7	1.5	0.9–2.7	3.3	1.1–9.5
Grinding with soluble MWF						
mg/m^3-years	1.0	1.0–1.1	1.0	1.0–1.1	1.0	1.0–1.1
years	1.0	1.0–1.4	1.0	1.0–1.4	1.2	1.0–1.5
Machining with soluble MWF						
mg/m^3-years	1.0	0.9–1.1	1.0	0.9–1.1	1.0	0.9–1.1
years	1.0	0.9–1.2	1.1	0.9–1.3	1.1	0.9–1.4
Metals						
Steel years	1.0	0.9–1.2	1.1	0.9–1.3	1.1	0.8–1.4
Iron years	1.0	0.9–1.2	1.1	0.9–1.3	1.1	0.8–1.4
Aluminum years[c]	0.6	0.2–2.1	—[e]	—[e]	—[e]	—[e]
Sulfur years	0.9	0.6–1.4	1.1	0.7–1.7	1.2	0.7–2.1
Biocide years	0.9	0.5–1.6	1.3	0.6–3.0	16.0	1.8–143.2
Nitrosamine years[c]	1.2	0.8–1.8	1.7	1.0–2.9	3.7	1.2–11.1
Asbestos years[d]	0.8	0.6–1.2	0.8	0.5–1.2	0.7	0.4–1.4
Solvent years[d]	1.1	0.8–1.5	1.0	0.6–1.6	1.0	0.4–2.3

[a]All models include time since hire as a covariate.
[b]With a 20-yr lag, exposure is cumulated to 20 yr before the risk date (the date of death for a case, or the date on which a control reached the age of death of the matched case).
[c]Exposure occurred in plants II and III only.
[d]Exposure data available for 582 study subjects (34 cases) in a limited number of jobs/departments in plants I and II only.
[e]Insufficient number in exposure category.

III were calculated assuming 5 yr or 5 mg/m^3-years of exposure [Hosmer and Lemeshow].

Among the MWF types, there was no notable pattern of increasing risk with increasing exposure to straight or soluble MWF. For synthetic MWF, there was a dose-related increase in risk of esophageal cancer when exposure was measured either as cumulative exposure (mg/m^3-years) or as duration. Risk associated with synthetic MWF increased with increasing exposure lag period; odds ratios were statistically significant with a 20-yr lag.

Examining the effect of operation revealed increased risk from grinding operations, but no significant increased risk from machining operations. Those grinding with synthetic MWF were at increased risk when exposure was measured both as duration and as cumulative exposure. Risk increased with increasing exposure lag period, and was statistically significant among those with a 20-yr lag between exposure and outcome. With a 20-yr lag, the odds ratio (OR) for a 5 mg/m^3-years increase in lifetime cumulative exposure to grinding with synthetic MWF was 2.8 (95% CI = 1.0–7.5). For a 5-yr increase in duration of exposure, the OR was 3.3 after a 20-yr lag period (95% CI = 1.1–9.5). The similarity between these odds ratios and those observed for synthetic MWF (regardless of operation) reflects that most synthetic exposure among these workers occurred during grinding operations. Only one case and eight controls were exposed to synthetic MWF in machining operations. There was also increased risk associated with increasing duration of exposure to soluble MWF in grinding operations. Those grinding with soluble MWF for 5 yr experienced a 1.2-fold risk of esophageal cancer mortality (95% CI = 1.0–1.5) after a 20-yr exposure lag.

There was no significantly increased risk for any metal. Among MWF constituents, when duration of exposure was lagged, there was elevated risk for biocides, although the confidence intervals were wide. After accounting for a 20-yr lag period, exposure to biocides for 5 yr was associated with a statistically significant 16-fold risk of esophageal cancer (95% CI = 1.8–143.2). For nitrosamines, risk increased with increasing exposure lag period. With a 20-yr exposure lag, a 5-yr increase in exposure to nitrosamine was associated with a statistically significant odds ratio of 3.7 (95% CI = 1.2–11.1). Asbestos and aluminum exposure seemed to be inversely related to esophageal cancer risk. Exposure to asbestos among these workers occurred in assembly operations where there was little MWF exposure.

Models using continuous exposure variables lagged 20 yr generally provided a better fit, as evidenced by the *P* value associated with the score statistic (not shown). Therefore, exposure variables constructed with a 20-yr lag period were used in subsequent analyses.

Categorical exposure variables

Categorical variables were used in conditional logistic regression models to evaluate the dose-response relationship between esophageal cancer and each 20-yr lagged cumulative exposure. Initially each exposure was considered alone, without taking account of potential confounding by other exposures (models not shown). These initial results suggested that esophageal cancer was associated with each of the primary types of MWF, as well as with biocides and

TABLE IV. Adjusted Odds Ratios (OR) from a Single Model for Esophageal Cancer Risk by Operation (Exposure Measured as mg/m^3-Years with a 20-yr Lag)[a]

Exposure (mg/m^3-years)	No. cases	OR	95% confidence interval
Grinding with synthetic MWF			
0	46	1.0	
>0	7	4.1	1.1–15.3
Grinding with soluble MWF[b]			
0	18	1.0	
>0 and <1.75	9	2.5	0.8–7.7
>1.75 and <4.5	9	5.9	1.9–18.8
>4.5 and <15.0	9	3.6	1.1–11.4
15.0+	8	3.1	0.9–10.2
Machining with soluble MWF[c]			
0	15	1.0	
>0 and <2.33	9	1.3	0.4–4.4
≥2.33 and <7.0	10	1.1	0.3–4.2
≥7.0 and <15.0	9	1.4	0.4–5.7
15.0+	10	1.3	0.3–5.1

[a]Model also adjusted for time since hire. Likelihood ratio statistic = 21.99, 12 df, $P < 0.04$.
[b]Trend test for the ORs for grinding with soluble MWF: $P = 0.36$.
[c]Trend test for the ORs for machining with soluble MWF: $P = 0.25$.

TABLE V. Adjusted Odds Ratios (OR) from a Single Model for Esophageal Cancer Risk by Operation (Exposure Measured in Years with a 20-yr Lag)[a]

Exposure (years)	No. cases	OR	95% confidence interval
Grinding with synthetic MWF			
0	46	1.0	
>0	7	3.8	1.0–14.1
Grinding with soluble MWF[b]			
0	18	1.0	
>0 and <1.25	9	3.2	1.1–9.5
>1.25 and <3.8	8	3.0	1.0–9.8
>3.8 and <12.0	9	2.3	0.7–7.9
12.0+	9	9.3	2.1–42.1
Machining with soluble MWF[c]			
0	15	1.0	
>0 and <2.0	9	1.3	0.4–4.2
≥2.0 and <5.5	10	1.0	0.3–3.8
≥5.5 and <11.0	10	2.3	0.6–9.2
11.0+	9	0.9	0.2–4.3

[a]Model also adjusted for time since hire. Likelihood ratio statistic = 24.41, 12 df, $P = 0.02$.
[b]Trend test for the ORs for grinding with soluble MWF: $P < 0.04$.
[c]Trend test for the ORs for machining with soluble MWF: $P = 0.95$.

nitrosamine. There seemed to be risk associated with both machining and grinding operations, although the evidence was stronger for grinding. To further evaluate these associations, confounding was assessed for each exposure that appeared related to esophageal cancer in the preceding analyses.

There was evidence of confounding between exposure to soluble MWF and exposure to grinding (with any MWF type). However, the inclusion of these collinear variables (r = 0.86) in the same model resulted in unstable estimates of risk, reflected in large standard errors and wide confidence intervals [Sullivan et al., 1994]. Although there were only six subjects with grinding exposure who had no soluble exposure at any time, there were many grinding operations that used synthetic fluids rather than soluble fluids. To more effectively separate out the risk associated with fluid type from that associated with operation, composite variables were defined to measure concurrent exposure, i.e., grinding with soluble MWF, grinding with synthetic MWF, and machining with soluble metalworking fluid.

Table IV presents results for a single model that includes cumulative exposure (mg/m^3-years) to grinding with soluble MWF, along with the other two operation/MWF type variables. After controlling for exposure to soluble MWF in both grinding and machining operations, a 4.1-fold risk of esophageal cancer was observed among those who had used synthetic metalworking fluid in grinding operations (95% CI = 1.1–15.3). After controlling for the effect of grinding with synthetic MWF and machining with soluble MWF, we observed increased risk associated with exposure to soluble MWF in grinding operations. The risk was elevated at 2.5 or greater in all exposure categories, but rose to 5.9 (95% CI = 1.9–18.8) in the middle category of exposure. Although risk estimates were significant in two categories of exposure, the trend test was not statistically significant ($P = 0.36$). However, when the model was constructed using duration of exposure (Table V) rather than cumulative exposure, the trend test was statistically significant ($P < 0.04$); those with 12 or more years exposure to soluble MWF in grinding operations experienced a 9.3-fold risk of esophageal cancer (95% CI = 2.1–42.1). After controlling for grinding with soluble MWF and grinding with synthetic MWF, machining with soluble MWF was no longer associated with increased risk (trend $P = 0.25$; Table IV).

Table VI presents results for cumulative exposure (mg/m^3-years) to each of the three primary fluid types (in separate models), adjusted for confounding by other exposures. When nitrosamine and grinding with soluble MWF were included in the model, there was no longer evidence of an association with straight MWF. Ever working with synthetic MWF was associated with a 3.9-fold risk of esophageal cancer mortality (95% CI = 1.1–14.3) after controlling for cumulative exposure to soluble MWF in grinding operations. The average cumulative lifetime exposure to synthetic MWF was 2.6 mg/m^3-years; most exposure

TABLE VI. Adjusted Odds Ratios (OR) for Esophageal Cancer and Cumulative Metalworking Fluid Particulate (mg/m^3-years) in Separate Models for Each Exposure (20-yr Lag)

	Exposure (mg/m^3-years)	No. cases	OR	95% confidence interval
Model 1	Straight MWF[a]			
	0	29	1.0	
	>0 and <0.17	6	2.2	0.7–6.7
	≥0.17 and <0.6	6	1.4	0.5–4.0
	≥0.6 and <2.75	6	1.3	0.5–3.6
	2.75+	6	1.3	0.4–3.8
Model 2	Synthetic MWF[b]			
	0	46	1.0	
	>0	7	3.9	1.1–14.3
Model 3	Soluble MWF[c]			
	0	14	1.0	
	>0 and <3.3	10	2.1	0.7–6.7
	≥3.3 and <12.0	10	2.1	0.6–7.8
	≥12.0 and <22.5	9	3.5	0.9–13.1
	22.5+	10	1.7	0.4–6.7

[a]Model adjusted for time since hire, years of nitrosamine exposure, and cumulative exposure to soluble MWF (mg/m^3-years) in grinding operations. Likelihood ratio statistic 25.51, 12 df, $P < 0.02$; trend test for the ORs for straight MWF exposure: $P = 0.58$.
[b]Model adjusted for time since hire and cumulative exposure to soluble MWF (mg/m^3-years) in grinding operations. Likelihood ratio statistic 21.32, 8 df, $P = 0.006$.
[c]Model adjusted for time since hire and years of nitrosamine exposure. Likelihood ratio statistic 15.79, 8 df, $P < 0.05$; trend test for the ORs for soluble MWF exposure: $P = 0.68$.

TABLE VII. Adjusted Odds Ratios (OR) for Esophageal Cancer and Duration of Exposure to Metalworking Fluid Components (Years) in Separate Models for Each Exposure (20-yr Lag)

	Exposure (years)	No. cases	OR	95% confidence interval
Model 1	Steel[a]			
	0	15	1.0	
	>0 and <3.0	9	0.8	0.2–2.8
	≥3.0 and <5.5	10	1.5	0.4–6.4
	≥5.5 and <11.0	10	1.8	0.4–7.5
	11.0+	9	1.1	0.2–5.3
Model 2	Iron[b]			
	0	25	1.0	
	>0 and <1.3	7	0.9	0.3–2.4
	≥1.3 and <4.0	7	0.8	0.3–2.4
	≥4.0 and <7.0	7	1.9	0.6–5.6
	7.0+	7	0.6	0.2–1.8
Model 3	Sulfur[c]			
	0	45	1.0	
	>0	8	0.5	0.2–1.6

[a]Model adjusted for time since hire, years of nitrosamine exposure, and years of exposure to soluble MWF in grinding operations. Likelihood ratio statistic 26.36, 12 df, $P < 0.01$; trend test for the ORs for steel exposure: $P = 0.56$.
[b]Model adjusted for time since hire, years of nitrosamine exposure, and years of exposure to soluble MWF in grinding operations. Likelihood ratio statistic 27.01, 12 df, $P = 0.008$; trend test for the ORs for iron exposure: $P = 0.37$.
[c]Model adjusted for time since hire, years of nitrosamine exposure, and years of exposure to soluble MWF in grinding operations. Likelihood ratio statistic 24.71, 9 df, $P = 0.003$.

to synthetics occurred during grinding operations, in which average cumulative exposures were somewhat higher for cases (Table II). After controlling for nitrosamine, the OR for soluble MWF rose to 3.5 in the third quartile of exposure, but the trend was not monotonic and the confidence intervals were wide.

Although there was a borderline exposure-response association with steel (not shown) when no other exposure variable was taken into account (trend test for the ORs: $P = 0.08$), the ORs dropped substantially after controlling for years of exposure to nitrosamine and grinding with soluble metalworking fluids (Table VII). Exposure to cast iron was not associated with increased risk of esophageal cancer. Although confidence intervals were wide, those with sulfur exposure appeared to be at decreased risk of esophageal cancer. Sulfur exposure generally occurred in operations using straight or semisynthetic MWF.

Analysis of both continuous and categorical variables described above suggested that the strongest risk factors for esophageal cancer were grinding with either soluble or synthetic MWF, as well as nitrosamine exposure, and biocides. It should be noted that workers grinding with synthetic MWF were also exposed to nitrosamines and biocides. In fact, there were no study subjects exposed to either biocides or grinding with synthetic MWF who were not also exposed to nitrosamines. Because duration of exposure to nitrosamines, biocides, and grinding with synthetics were highly correlated (r ≥ 0.9), these exposure variables could not be entered into the same model.

Evaluation of confounding suggested that the relationships between esophageal cancer and all three of these exposures (nitrosamines, biocides, and grinding with synthetic MWF) might be confounded by exposure to soluble MWF in grinding operations. Therefore, a model was fit that included cumulative exposure to soluble MWF particulate in grinding operations (and, as always, years since hire). This model was then extended to include each of the three correlated exposures (nitrosamines, biocides, and grinding with synthetic MWF) successively (Table VIII).

The model with the best fit based on the significance of the likelihood ratio statistic (to enter) included nitrosamines (model 1). Automobile manufacturing workers (ever) exposed to nitrosamines experienced a 5.4-fold (95% CI = 1.5–19.9) risk of esophageal cancer after allowing for a

TABLE VIII. Adjusted Odds Ratios (OR) for Esophageal Cancer in Three Separate Models: Each Model Includes Grinding with Soluble MWF (mg/m^3-years) and One Additional Exposure (20-yr Lag)[a]

Exposure	No. of cases	Model 1[b] OR	Model 1[b] 95% CI	Model 2[c] OR	Model 2[c] 95% CI	Model 3[d] OR	Model 3[d] 95% CI
Grinding with Soluble MWF (mg/m^3-years)							
0	18	1.0		1.0		1.0	
>0 and <1.75	9	2.6	0.9–7.6	2.6	0.9–7.6	2.7	0.9–7.7
≥1.75 and <4.5	9	6.1	2.1–18.0	6.2	2.1–18.1	6.2	2.1–18.3
≥4.5 and <15.0	9	3.9	1.3–11.7	4.0	1.4–11.8	3.9	1.3–11.7
15.0+	8	3.2	1.0–10.3	3.3	1.1–10.6	3.2	1.0–10.2
Nitrosamines (years)							
0	45	1.0					
>0	8	5.4	1.5–19.9				
Biocides (years)							
0	48			1.0			
>0	5			3.8	0.8–18.9		
Grinding with synthetic MWF (mg/m^3-years)							
0	46					1.0	
>0	7					4.1	1.1–15.0

[a]Models also include time since hire. CI, confidence interval.
[b]Model likelihood ratio statistic 23.59, 8 df, $P = 0.003$; trend test for the ORs for grinding with soluble MWF: $P = 0.37$.
[c]Model likelihood ratio statistic 19.67, 8 df, $P = 0.01$; trend test for the ORs for grinding with soluble MWF: $P = 0.35$.
[d]Model likelihood ratio statistic 21.62, 8 df, $P = 0.006$; trend test for the ORs for grinding with soluble MWF: $P = 0.38$.

20-yr exposure lag (Table VIII). Biocide exposure (model 2) was associated with a nonsignificant increased risk of esophageal cancer when exposure was lagged 20 yr (OR 3.8; 95% CI = 0.8–18.9). Grinding with synthetic MWF (model 3) was associated with a 4.1-fold excess risk of esophageal cancer (95% CI = 1.1–15.0). Although statistical criteria suggest that nitrosamines in the MWF may account for at least part of the observed increased risk of esophageal cancer, the true causal agent (assuming a workplace exposure is causal) may have been biocides or some other factor intrinsic to grinding with synthetic MWF, for example, heat, speed, pressure, or particle size.

To evaluate potential confounding due to asbestos, this variable was added to the model including grinding with soluble MWF and nitrosamine. Recall that data on asbestos was only available for a subset of the study population. Analysis including duration of exposure to asbestos (Table IX) provides no evidence that this exposure is causal.

TABLE IX. Adjusted Odds Ratios (OR) from a Single Model for Esophageal Cancer Among 582 Study Subjects from Plants I and II (20-yr Exposure Lag)[a,b,c]

Exposure	No. of cases	OR	95% confidence interval
Grinding with Soluble MWF (mg/m^3-years)[d]			
0	13	1.0	
>0 and <2.5	6	1.8	0.5–7.1
≥2.5 and <6.0	5	3.5	0.9–13.9
≥6.0 and <29.0	5	2.2	0.5–9.1
29.0+	5	5.7	1.3–25.6
Nitrosamine (years)			
0	30	1.0	
>0	4	6.8	1.0–49.1
Asbestos (years)[e]			
0	22	1.0	
>0 and <1.0	7	0.8	0.3–2.3
1.0+	5	0.3	0.1–1.0

[a]Based on 582 study subjects (34 cases) in a limited number of jobs/departments in plants I and II for whom exposure data on asbestos are available.
[b]Model also includes time since hire.
[c]Likelihood ratio statistic 17.66, 10 df, $P = 0.06$.
[d]Trend test for the ORs for grinding with soluble MWF: $P < 0.11$.
[e]Trend test for the ORs for asbestos exposure: $P < 0.08$.

DISCUSSION

Several closely related MWF exposures were found to be associated with increased risk of esophageal cancer mortality in this study. The strongest evidence was observed for exposure to the water-soluble fluids (synthetic or soluble MWF) in grinding operations, and duration of exposure to biocides (a component or additive) and nitrosamines (a contaminant) in the water-based fluids (most common in synthetic MWF).

Metalworking Operation Versus Fluid Type

The odds ratio for any exposure to synthetic MWF (regardless of operation) was 3.9 (95% CI = 1.1–14.3) after controlling for exposure to soluble MWF in grinding operations (Table VI; model 2). Synthetic fluids are most effective in high-speed grinding operations. The mist resulting from the speed of these operations may increase the risk of respiratory exposure. Digestive exposure may occur after mucociliary clearance of larger particles from the respiratory system into the digestive system, or with direct oral contact while smoking or eating in the workplace.

Most exposure to synthetic fluids in this study population occurred during grinding operations. Compared with those who did not use synthetic MWF in grinding operations, those who did experienced a 4.1-fold risk of esophageal cancer (95% CI = 1.1–15.0) after controlling for exposure to soluble MWF in grinding operations (Table VIII; model 3). The small number of cases grinding with synthetics did not allow further categorization of exposure to examine a dose-response relationship. Similarly, we were not able to look specifically at risk associated with machining with synthetic MWF because such exposures occurred infrequently.

Those working in grinding operations were at significantly increased risk of esophageal cancer regardless of fluid type. Among those grinding with soluble MWF, the OR was uniformly elevated above 2.5, and rose to 6.1 (95% CI = 2.1–18.0) among those with between 1.75 and 4.5 mg/m^3-years exposure to grinding with soluble fluids (Table VIII; model 1). When duration of exposure (rather than cumulative exposure) was considered, a dose-response relationship was apparent (trend $P < 0.04$). The odds ratio rose to 9.3 (95% CI = 2.1–42.1) among those grinding with soluble MWF for 12 or more years (Table V).

Although we found increased risk of esophageal cancer associated with grinding with soluble MWF, exposures to soluble MWF in machining operations was not associated with such significantly increased risk. Those grinding with solubles had slightly higher average cumulative exposure than those machining with solubles (18.1 vs. 17.0 mg/m^3-years), but shorter average duration of exposure (9.9 vs. 11.1 yr), suggesting that intensity of exposure may be a factor. Based on data from the full UAW-GM cohort study, Hallock et al. [1994] reported that average MWF aerosol concentrations are lower in machining than in grinding operations. Another possible explanation for the increased risk observed for grinding with solubles is that exposure to larger size particles while using soluble MWF in grinding operations (compared with machining with solubles) [Woskie et al., 1994b] may increase gastrointestinal tract absorption of carcinogenic components of the MWF. D'Arcy et al. [1996] also reported larger particle size for soluble MWF, but did not evaluate grinding operations. We hypothesize that the speed of the grinding operations and heat associated with them may change the composition and carcinogenic potential of the MWF aerosol. There is some evidence that pressure and heat generated by high-speed grinding operations may increase nitrosamine formation in MWF containing ethanolamines [Kipling and Waldron, 1976; NIOSH, 1976; Fan et al., 1977].

In the analysis reported here, we found linear trends for grinding with soluble MWF only when exposure was measured as duration (Table IV compared with Table V). There are several possible explanations for why risk was more linear with years than with cumulative exposure. This pattern of response could result if estimating exposure retrospectively resulted in some misclassification of exposure level. Such misclassification might have led to an overestimate of exposure intensity in the more distant past, such that cumulative exposure might have been overestimated for workers with brief duration of exposure in the past. Or, changes in fluid formulations over calendar time may have resulted in a more hazardous exposure to a MWF component (for example, to nitrosamines) during a time period when lower exposure to soluble MWF in grinding operations occurred. If this were the case, then total MWF particulate would not be an adequate summary measure of exposure. Alternatively, grinding with soluble MWF may be a marker for an unmeasured causal agent to which grinders were concurrently exposed.

Nitrosamines and Ethanolamines

Study subjects exposed to nitrosamines experienced a 5.4-fold risk of esophageal cancer mortality (95% CI = 1.5–19.9; Table VIII; model 1). Nitrosamines are formed in MWF containing both ethanolamines and nitrites [Keefer et al., 1990; Kenyon et al., 1993]. Ethanolamines are used to balance pH and inhibit corrosion in all synthetic and semi-synthetic (and some soluble) MWF. Metalworking fluids containing ethanolamines and nitrites have been shown to form the potentially carcinogenic nitrosamine N-nitrosodiethanolamine (NDELA) [Fan et al., 1977; IARC, 1978; NIOSH, 1996]. Fuchs et al. [1995] demonstrated a statistically significant difference in DNA strand breaks related to intensity and duration of exposure to NDELA among synthetic MWF-exposed workers. The National Toxicology Program [NTP, 1991] considers several N-nitrosamines to be animal carcinogens. OSHA has regulated N-nitrosodiethylamine (NDEA) as an occupational carcinogen [29 Fed Reg 1910.1016, 1994]. IARC [1987] has classified various nitrosamines as probable (2A) and possible (2B) human carcinogens based on sufficient animal evidence but on limited human data.

Exposures in this study occurred prior to the 1984 EPA regulation restricting the use of nitrosating agents in MWFs containing ethanolamine [49 Fed Reg 2762, 1984]. However, it should be noted that Keefer et al. [1990] demonstrated the presence of NDELA as a contaminant of synthetic MWF in the absence of nitrosating agent additives. Challis et al. [1978] have shown that nitrosamines may be formed in water-soluble MWF by nitrogen oxides, accelerated by formaldehyde and metal salts in the MWF [NIOSH, 1996]. In addition, there is evidence from animal models that secondary amines react with nitrogen dioxide in vivo to form N-nitrosamines, resulting in tumor formation [Ewetz, 1993]. Both animal and human studies have documented endogenous formation of nitrite by bacterial reduction of ingested nitrate in the gastrointestinal tract [Ewetz, 1993].

Biocides

Risk estimates for biocides varied depending on the exposure lagging period used in the analysis. When exposure was lagged 20 yr, biocides were associated with an OR of 3.8 (95% CI = 0.8–18.9; Table VIII; model 2). When exposure variables were not lagged, biocides appeared to be protective. The OR for biocides in the unlagged analysis was 0.9 for a continuous exposure variable assuming 5 yr of exposure (Table III).

Biocides are MWF components or additives used to control microbial growth in water-based soluble, semisynthetic, and synthetic MWF reservoirs. Some biocides release formaldehyde, and have the same carcinogenic potential as other formaldehyde-containing aerosols [Swenberg et al., 1980; Albert et al., 1982; Kerns et al., 1983; Howell et al., 1996; NIOSH, 1996]. Formaldehyde is regulated as a carcinogen by OSHA [29 Fed Reg 1910.1048, 1994]. In addition, nitrated biocides can release nitrite, which may react with amines in alkanolamines to form nitrosamines [Mackerer, 1989].

Alternatively, biocides may be a marker for conditions that increase exposure to bacteria, endotoxin, fungi, and fungal mycotoxins that grow on water-soluble MWF. Known dietary risk factors for esophageal cancer (pickled vegetables, mycotoxin-contaminated grains) [Yang, 1980; IARC, 1993] suggest that MWF associated bacterial and fungal exposures could increase esophageal cancer risk. Mycotoxins are secondary metabolites secreted by fungi that may be inhaled, ingested, or absorbed through the skin [NIOSH, 1996]. Mycotoxins are immunosuppressive under conditions of chronic exposure [Lacey et al., 1994], and may inhibit protein synthesis, with resulting genetic alteration potentially affecting cell division and carcinogenesis, as well as DNA repair mechanisms.

Metals

Metalworking processes using any fluid type result in contamination of the MWF with metal salts. Workers involved in machining and grinding operations are also exposed to the particulate generated from the base metal of the part being machined or ground (steel, iron, or aluminum). In a population-based case-control study, Yu et al. [1988] found that those in metalworking occupations seemed to be at increased risk of esophageal cancer. This risk from metal dust and particulate exposure (nickel, stainless steel, beryllium, lead, iron, chromium, and chromates) appeared to be greatest for the anatomical lower third of the esophagus, to increase with duration of exposure, and to be independent of asbestos exposure. In contrast, after controlling for the confounding effects of other workplace exposure, we found no evidence that esophageal cancer mortality was related to exposure to metal dust (steel, iron).

Asbestos

Asbestos was used between 1950 and 1985 in brake and axle assembly at plant I and in transmission assembly at plant II [Eisen et al., 1994a]. No association was observed between asbestos exposure and esophageal cancer in the analyses reported here (although the study was not designed to evaluate asbestos exposure as a main effect). The existing literature is inconsistent regarding this potential risk factor. Some investigators have found no association [Yu et al., 1988], whereas others have implicated asbestos as an occupational risk factor for esophageal and other digestive cancers [Neuget and Wylie, 1987; Frank-Stromborg, 1989; Selikoff and Seidman, 1991]. In interpreting the significance of these negative findings, the reader should recall that analysis for asbestos was based on only 34 cases that occurred among 582 study subjects in a limited number of jobs/departments in two of the plants for whom exposure data on asbestos were available.

Unmeasured Risk Factors

The increased risk of esophageal cancer observed in this study may result from confounding by unmeasured risk factors. Diet is a strong risk factor for esophageal cancer. Hypothesized dietary risk factors for esophageal cancer for which data were not available in this study include chronic irritation of the esophageal mucosa and several dietary exposures or deficiencies such as low intake of vitamin C, vitamin A, and riboflavin; dietary deficiency of trace metals (zinc) and essential amino acids; exposure to opium and tobacco pyrolysates through chewing and other regional practices in ethnic populations; thermal irritation from hot drinks; tannin in food and beverages; salted foods; contamination of foods with fungi or their mycotoxin; and dietary nitrosamine [Yang, 1980; Day and Munoz, 1982; Neuget and Wylie, 1987; Yu et al., 1988; Frank-Stromborg, 1989; Li et al., 1989; Cheng et al., 1992; Wang et al., 1992; IARC, 1993].

Alcohol consumption is a strong risk factor for esophageal cancer in low incidence populations, and seems to act as a promotor [Day and Munoz, 1982; Yu et al., 1988; Frank-Stromborg, 1989]. Relative risk is dose-dependent and has been estimated to increase from 2.9 to 10.3 as daily alcohol consumption increases from less than 40 grams to more than 120 grams of alcohol per day [Yu et al., 1988]. Tuyns [1983] made somewhat higher risk estimates. Alcohol and tobacco are independent risk factors for esophageal cancer [Tuyns, 1983; Yu et al., 1988]. Cigarette smoking is associated with a 5- to 9-fold risk of esophageal cancer [Tuyns, 1983; Yu et al., 1988] and may act as an initiator [Day and Munoz, 1982; Frank-Stromborg, 1989; Yu et al., 1988].

Although data on nonoccupational risk factors were not available for this study, we have no reason to believe that there is any difference in diet or prevalence of smoking or alcohol use based on job assignment. Previously reported Poisson regression results from plants I and II found no dose-related increase in risk of lung cancer mortality among those exposed to either soluble or synthetic MWF, or grinding operations, suggesting that prevalence of cigarette smoking did not increase with increasing MWF exposure [Monson et al., 1992; Eisen et al., 1994a]. Similarly, a MWF dose-related difference in alcohol consumption would be expected to result in a MWF dose-related difference in cirrhosis mortality. Previously reported Poisson regression analysis based on plants I and II found no dose-related increase in cirrhosis mortality for either grinding operations or synthetic MWF exposure. There was, however, an approximate twofold elevated cirrhosis mortality among soluble MWF exposed workers [Monson et al., 1992], although there was no linear trend in cirrhosis mortality with increasing soluble MWF exposure (unweighted trend $P = 0.86$). An increase in liver disease in soluble MWF exposed workers would be consistent with National Toxicology Program (NTP) findings that ethanolamines are a liver toxin in animal studies [NTP, 1994; Mathews, 1996]. These findings are also consistent with results previously reported by Silverstein et al. [1988] of increased risk of nonmalignant liver disease among MWF-exposed workers; this increased risk of nonmalignant liver disease may be related to exposure to ethanolamines and nitrosamines, or to exposure to fungal mycotoxins produced in water-soluble MWF, or to alcohol. There was no indication in SMR analysis of the UAW/GM cohort of an overall increased risk of other alcohol-related causes of death such as suicide, accidents, or cardiovascular disease [Monson et al., 1992].

Race was one of the matching factors used in control selection because of the well-known racial differences in esophageal cancer incidence and mortality. The mortality rate for esophageal cancer is three times greater in black males than in white males in the United States. Race was unknown for 38% of esophageal cancer cases. Cases of unknown race were matched with controls of unknown race. If by chance, a large proportion of the cases with unknown race were black, and a large proportion of their matched controls were white, then race might partially explain the elevated risks observed; but to fully explain the results, these racial disparities would have to be distributed differentially by exposure type and level. This explanation seems unlikely.

CONCLUSIONS

The principal occupational risk factors for esophageal cancer observed in this case-control study are grinding with soluble or synthetic MWF, and exposure to nitrosamines and biocides that are components of these water-soluble MWF. Asbestos exposure does not explain the increased risk of esophageal cancer observed in relation to grinding with water-soluble MWF in this study.

Results of this study suggest the need for engineering controls to limit occupational exposure to MWF particulate in grinding operations. The observed relationship between esophageal cancer mortality and nitrosamine exposure highlights the importance of limiting both occupational and dietary exposure to nitrosamine and its precursors. These results also suggest that limiting bacterial and fungal growth by frequent replacement of MWF supplies to the machines might be preventive. The high risk associated with biocide use when exposure was lagged 20 yr to account for cancer latency suggests the need for caution in recommending increased biocide application as a control strategy. As a supplementary measure, administrative controls limiting gastrointestinal exposure resulting from smoking and eating in the workplace seem indicated.

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