Exhibit 289

Cancer Mortality Among Workers Exposed to Chemicals During Uranium Processing

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Data provided by the Comprehensive Epidemiology Data Resource allowed us to study patterns of cancer mortality as experienced by 3814 uranium-processing workers employed at the Fernald Feed Materials Production Center in Fernald, Ohio. Using risk-set analyses for cohorts, we estimated the effects of exposure to trichloroethylene, cutting fluids, and kerosene on cancer mortality. Our results suggest that workers who were exposed to trichloroethylene experienced an increase in mortality from cancers of the liver. Cutting-fluid exposure was found to be strongly associated with laryngeal cancers and, furthermore, with brain, hemato- and lymphopoietic system, bladder, and kidney cancer mortality. Kerosene exposure increased the rate of death from several digestive-tract cancers (esophageal, stomach, pancreatic, colon, and rectal cancers) and from prostate cancer. Effect estimates for these cancers increased with duration and level of exposure and were stronger when exposure was lagged.

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The US Department of Energy recently assembled the Comprehensive Epidemiology Data Resource (CEDR).[1] These epidemiologic data were collected at multiple nuclear facilities over the past 30 years and have been made available to the research community at large for the first time. Combining several independently collected data files included in CEDR provided us with the opportunity to examine the influence of chemical exposures in the work environment of the Fernald Feed Materials Production Center (FFMPC) in Fernald, Ohio, on cancer mortality. Workers at the FFMPC processed uranium-ore concentrate and uranium of low-enrichment grade into fabricated uranium metal products and, to a much lesser extent, produced thorium metal. Operations began in late 1951 and halted in July 1989. The uranium-processing work conducted at this facility involved the use of large amounts of nonradioactive industrial chemicals, many of which are potent respiratory irritants (hydrofluoric acid, ammonia, nitric and sulfuric acid, tributyl phosphate) or suspected carcinogens (trichloroethylene [TCE] and cutting fluids). Large-scale chemical operations consisted of dissolving ore concentrates in nitric acids to produce uranyl nitrate solution, which then was purified via solvent extraction, concentrated through evaporation, and thermally denitrated to uranium trioxide. Uranium trioxide was converted to uranium tetrafluoride and reduced to metal. Other chemical processes at the facility required fur-

nacing or wet chemical-hydrometallurgical processing.

In the early 1980s, the widespread use of chemicals prompted Wilson[2] to conduct an investigation of respiratory morbidity in FFMPC workers. The Wilson study provided historical measures of chemical use that, in combination with mortality data collected for all workers monitored for radiation exposure, allowed us to examine whether cancer mortality was associated with exposure to these chemicals while also allowing us to control for the effects of radiation exposures. In this report, we will focus our analyses on the effects of TCE, cutting fluids, and a combination of kerosene exposures with carbon (graphite) and other solvents. All of these chemicals were used in large quantities at the facility, and either these chemicals are suspected chemical carcinogens or carcinogens were likely to have been formed in the processes in which they were used. The Fernald cohort is characterized by an extremely long follow-up and by the fact that its workers were monitored for exposure to both internal and external radiation. This article is solely based on the data provided by the CEDR, and the description of this study's methods relies on the CEDR documentation[1] and the article by Wilson.[2]

Materials and Methods

Study Population

The study population consists of 3814 white male employees identified from company rosters and personnel records who were first hired at the facility between January 1, 1951, and December 31, 1972, were continuously employed for at least 3 months, and were monitored for radiation. For all workers, vital status was last ascertained on January 1, 1990. Thus follow-up began on January 1, 1951, or date of hire, whichever date was later, and ended either on the date of death or on December 31, 1989, whichever date came earlier. Mortality data for FFMPC workers are only available in the CEDR database for those workers who were radiation-monitored. Thus we had to exclude 287 workers for whom chemical-exposure data existed but who could not be matched to the records provided in the radiation files. Approximately 88% of all cohort members were hired at the facility before 1960. Employment at the facility peaked in 1956 and slowly decreased until all operations halted in July 1989. Vital-status searches were conducted using two record systems: the Social Security Administration, for the period before 1979, and the National Death Index, for the period 1979 to 1989. Workers not known to be alive and not identified by either system as dead were assumed to be alive at the end of follow-up. Death-certificate information was available for a total of 1045 workers who died during the follow-up period.

Exposure Assessment

In the late 1970s and early 1980s, plant experts—including industrial hygienists, a plant foreman, and an engineer—historically determined the likelihood of chemical exposure for each job title and plant area. All experts included in this rating procedure had been at the company for at least 20 years and were supervised by the medical director during this task. For the period 1952 to 1977, these experts classified workers into four main categories of chemical exposure, from none (level 0) to heavy (level 3). For the following analyses, measures of intensity (exposure level) and duration (exposure in years) were derived from the job-exposure matrix created by the plant expert to describe exposure to TCE, cutting fluids, and kerosene.

Approximately 62% of all workers held only one job title during employment at the Fernald facility, one quarter held two titles, and only 5% changed titles four times or more. Almost 45% of employees worked in one physical location of the plant, whereas one fifth moved between locations more than five times. Only 15% of the workforce was employed at the plant for less than 1 year, 31% between 1 and 5 years, and over half (54%) for more than 5 years (ie, this cohort constitutes a fairly stable workforce).

External radiation exposure was reported as annual deep doses derived from film badge dosimeters. Internal radiation exposure was reported as annual lung doses, based on individual urine bioassays and area sampling. Exposure to internal radiation-emitting particles at Fernald originated from airborne long-lived radioactive materials such as uranium, thorium, and radium compounds. Most of the exposures, however, were due to U-235 isotopes varying from depleted to slightly enriched. Workers were placed on an internal-exposure monitoring program for uranium when industrial hygiene surveys indicated high levels of radioactive substances in the work environment. The soluble and insoluble uranium and thorium compounds used at the facility may also have exhibited some chemical toxicity, primarily targeting kidneys and lungs. Although no independent measures for the chemical toxicity of these radioactive compounds exist, estimates of internal radiation dose might reflect chemical toxicity to some extent.

Smoking history was available on medical records for a small subsample of workers (approximately 20%) employed on or after January 1, 1968, when the company introduced pulmonary-function testing. Because information about smoking history was only available for approximately one fifth of all subjects, we were not able to adjust for smoking in our analyses. However, we examined the smoking distributions by chemical exposure and determined whether such exposure was related to smoking prevalence. The records also provided information on salary status (hourly vs salaried; Table 1).

TABLE 1
Characteristics of the All-Male Fernald Cohort

Number of employees	3,814
Average follow-up time, years	31.5
Average age at entry into cohort, years	30.5
Number of person-years of follow-up	120,237
Number of deaths	1,045
Total mortality rate, per 10^5/year	869
Total cancer mortality rate, per 10^5/year	273
Pay type	
Salaried	1,224
Hourly/union	2,590

Statistical Analyses

We used two different analytical approaches: (1) external comparisons of our monitored workers with the general US population and—for all-causes and total cancer mortality—with the NIOSH-CORPS cohort,[3] and (2) internal comparisons among monitored workers, according to level and duration of chemical exposure (dose-response analyses).

In external comparisons, the Monson[4] program was used to estimate standardized mortality ratios (SMRs; observed/expected deaths) for the monitored study population. Expected numbers of deaths were estimated from the mortality rates of the US white male population or NIOSH-CORPS data, stratified by age (5-year categories) and calendar year (5-year intervals). Estimation of 95% confidence intervals for the SMRs was based on a formula derived by Byar and recommended by Breslow and Day.[5]

For internal comparisons of workers exposed to chemicals at different levels, we examined cancers by site, concentrating on organ sites for which effects have previously been reported in the literature. The small numbers of many specific cancers made it necessary to group some sites in order to achieve a minimum of ten cases. Thus, for most analyses, sites with few cases were combined, based on the assumption that any carcinogenic effect of exposures should be similar at these sites because of anatomical proximity, tissue similarity, similarity of exposure routes, or similarity of diagnostic categories. The single cancers and cancer groups we examined were as follows: (1) all hemato- and lymphopoietic cancers (International Classification of Diseases, 9th revision [ICD-9][6] codes 200 to 208) and, in addition, lymphomas (excluding Hodgkin's lymphomas) and leukemias separately; (2) esophagus and stomach cancers (ICD-9 codes 150 and 151); (3) liver and biliary tract cancers (ICD-9 codes 155 and 156); (4) pancreatic cancers (ICD-9 code 157); (5) colon and rectal cancers (ICD-9 codes 153 and 154); (6) bladder and kidney cancers (ICD-9 codes 188 and 189); (7) prostate (ICD-9 code 185); (8) brain (ICD-9 codes 191 and 192), and (9) lung cancers (ICD-9 code 162). We also conducted separate analyses for two rare cancers for which we observed fewer than ten cases (ie, eight cancers of the liver and biliary tract [ICD-9 codes 156 and 157) and five cancers of the larynx [ICD-9 code 161]), because these cancers have consistently been linked to two of the chemicals in previous studies, in which liver cancers were found to be associated with TCE exposure[7] and laryngeal cancers with cutting fluid exposures.[8]

For internal comparisons, we utilized the risk-set approach for cohort analysis described by Breslow and Day,[5] a method basically equivalent to Cox proportional hazards modeling. When using risk sets, conditional logistic regression is used to compare individuals who have died of cancer with individuals still at risk of dying from cancer ("survivors"). We constructed risk sets of deaths and survivors by matching to each cancer death all cohort members who were still alive at the time of the index subject's death and who were within 3 years of the index case's age. This age-range specification helped us avoid constructing risk sets with fewer than five non-cases, ie, we based our analyses on risk sets that included between five and 830 survivors for each cancer death.

We used multiplicative rather than additive models because the limited size of our data set did not allow us to adequately distinguish between alternative models. We evaluated cumulative exposure duration (in years) as a set of binary variables (minimum of 2 and 5 years of exposure), as three categories of duration (<2 years, 2 to 10 years, >10 years of exposure), and as a continuous variable (in years). To allow for a period of cancer induction/latency after exposure and, additionally, to reduce possible selection bias, cumulative exposure duration was lagged.[9] Lagging entailed limiting the exposure duration for each individual in a risk set to the duration at the level achieved 15 years prior to the index death.

Results of the conditional logistic regression analyses were used to estimate rate ratios and 95% confidence intervals (95% CIs) for chemical effects. Individual exposure duration and other time-related variables, such as time since first hired, were treated as time-dependent. All models were adjusted for the same confounders: pay status, time since first hired, and cumulative time-dependent external- and internal-radiation doses (continuous). Time since first hired was used to control for the selective loss of less healthy workers.[10] Because of the small number of exposed cases, the number of variables that could be included in many of our models without causing convergence problems was limited. This limitation in numbers and the fact that some chemical exposures only occurred concomitantly (such as moderate kerosene, carbon, and other solvent exposures) meant that, for the most part, we only included one chemical at a time in our models (see also below). In addition, whenever possible, we report

TABLE 2
Exposure to Chemicals, by Exposure Level, for Fernald Workers

Exposure Level	No. of Workers Exposed to Trichloroethylene (TCE)	Cutting Fluids	Kerosene
1—Light	2,792*	1,792†	1,691‡
2—Moderate	179	82§	905‖
3—Heavy	0	405¶	0

* Approximately half of the workers were also exposed to cutting fluids.
† All workers were exposed to TCE and most were exposed to kerosene and carbon at level 1.
‡ All workers were exposed to cutting fluids, TCE, carbon, and all respiratory irritants at level 1.
§ All workers are also exposed to TCE at level 2.
‖ All workers were exposed to carbon at level 2 but to no other chemicals.
¶ Some workers were exposed to TCE at levels 1 but to no other chemicals.

results for models in which we adjusted for other chemicals.

Results

The Fernald cohort of white male workers is characterized by a long follow-up period (average, 31.5 years) and a high percentage of hourly employees (68%) (Table 1). During the study period, 26.5% of all cohort members died (1045 total deaths; Table 1). Of these deaths, 328 were due to cancer, yielding a total cancer-mortality rate of 273 per 10^5/year (Table 1).

Table 2 displays the exposure distribution of the three chemicals included in our internal comparisons of cohort members. Most notably, low-level exposure to all of the three chemicals of interest occurred in a large number of workers simultaneously (1691; 44%). In addition to being exposed to these three chemicals, these 1691 workers were also exposed to all of the respiratory irritants used at FFMPC. Low-level chemical exposure to cutting fluids and kerosene thus almost always represents exposure to a combination of all of the chemicals used at the facility. Moderate exposure (level 2) occurred either as a combination-type exposure or as a singular exposure, depending on the jobs and plant areas; moderate cutting fluid exposure always occurred in combination with moderate TCE exposure. The job titles for which such mixed exposure was documented were set-up workers, riggers, and degreasers, whereas electricians (n = 92) were exposed to TCE at moderate levels only. No exposure to TCE was rated as heavy (level 3). Heavy cutting fluids exposure (level 3) was attributed to machining tool operators and laboratory machinists, some of whom also experienced low-level TCE exposure. Moderate kerosene exposure was experienced by chemists and chemical operators (n = 905) all of whom were also exposed to moderate levels of carbon and all respiratory irritants. Thus, at the highest level at which kerosene exposure occurred (level 2), any effects on cancer outcome represent the combined effects of kerosene and other chemicals (carbon and solvents), but none of these workers was at the same time exposed to TCE or to cutting fluids.

The overall mortality rate was lower among Fernald workers than among US white males (SMR = 0.84, 95% CI, 0.79 to 0.90); however, the rate of deaths from all malignant neoplasms was slightly increased (SMR = 1.10; 95% CI, 0.99 to 1.23; Table 3). Similarly, when we compared this uranium-worker cohort with NIOSH-CORPS workers, we found that the SMR for all causes was still lower (SMR = 0.81; 95% CI, 0.76 to 0.86) but the cancer mortality rate was even higher (SMR = 1.24; 95% CI, 1.11 to 1.38) among the uranium workers. Thus the Fernald cohort is generally healthier than other worker cohorts, especially with respect to cardiovascular mortality, but exhibits a 24% increase in mortality due to cancers. Compared with the US population, the SMRs for the Fernald cohort were greater than one for cancers of all digestive system organs, the prostate, and the lymphopoietic system. Yet none of the CIs in these external comparisons excluded the null value.

TCE exposure was strongly associated with liver cancers (exposure duration, >5 years; 15-year lag rate ratio [RR] = 12.1; 95% CI, 1.03 to 144); Table 4). Furthermore, TCE exposure seemed to be associated with brain cancers in the analyses of single chemicals (Table 4); however, this effect completely disappeared when cutting-fluid exposure was added to the model. As shown in Table 5, cutting-fluid exposure at any level was associated with hemato- and lymphopoietic system, brain, bladder, and kidney cancer mortality, but the estimates for high-exposure levels were based on very small numbers of exposed cases. Cutting fluids were, furthermore, very strongly related to the rare cancers of the larynx (exposure duration, >5 years; 15-year lag RR = 236; 95% CI, 9.93 to 5630); Table 5).

Kerosene exposure at moderate levels (level 2) and of long duration (>5 years) increased the rate of prostate cancers, especially after adjustment for TCE exposure (for 15-year lag RR = 4.50; 95% CI, 0.98 to 20.8; Table 6). Furthermore, when we adjusted for the other two chemicals in the models, kerosene exposure at moderate levels (level 2) was strongly associated with esophageal and stomach cancers (exposure duration, >2 years; and 15-year lag RR = 9.22; 95% CI, 2.34 to 36.3; and exposure duration, >5 years; 15-year lag RR = 12.4; 95% CI, 2.53 to 60.8, respectively). Also, the results displayed in Table 6 suggest a

TABLE 3
Observed (Obs) and Expected (Exp) Numbers of Deaths for White Male Subjects for the Fernald Cohort and Estimated Standardized Mortality Ratios (SMRs) and 95% Confidence Intervals (CIs): Comparison With the US Population, by Cause of Death

Causes of Death*	Obs	Exp	SMR	95% CI
All causes (ICDA-8 001–998)	1045	1238.40	0.84	0.79–0.90
All malignant neoplasms	328	297.38	1.10	0.99–1.23
Cancers				
Buccal cavity and pharynx (ICDA-8 140–149)	9	8.75	1.05	0.48–1.99
Digestive organs and peritoneum (ICDA-8 150–159)	85	73.37	1.16	0.93–1.43
Esophagus (ICDA-8 150)	9	7.32	1.23	0.56–2.33
Stomach (ICDA-8 151)	15	10.97	1.37	0.76–2.26
Large intestine (ICDA-8 153)	26	26.07	1.00	0.65–1.46
Rectum (ICDA-8 154)	7	6.56	1.07	0.43–2.20
Liver (ICDA-8 155–156)	8	4.83	1.66	0.71–3.26
Pancreas (ICDA-8 157)	18	15.05	1.20	0.71–1.89
Respiratory system (ICDA-8 160–163)	120	113.92	1.05	0.87–1.26
Larynx (ICDA-8 161)	5	4.15	1.20	0.39–2.81
Lung—primary and secondary (ICDA-8 162)	112	108.72	1.03	0.85–1.24
Bone (ICDA-8 170)	0	0.97	0.00	0.00–3.78
Skin (ICDA-8 172–173)	4	6.28	0.64	0.17–1.63
Prostate (ICDA-8 185)	24	17.14	1.40	0.90–2.08
Testis (ICDA-8 186–187)	1	1.45	0.69	0.01–3.85
Bladder (ICDA-8 188)	8	6.83	1.17	0.50–2.31
Kidney (ICDA-8 189)	5	7.72	0.65	0.21–1.51
Brain and other central nervous system (ICDA-8 191–192)	12	9.43	1.27	0.66–2.22
Thyroid (ICDA-8 193)	0	0.53	0.00	0.00–6.90
Lymphosarcoma and reticulosarcoma (ICDA-8 200)	8	4.69	1.71	0.73–3.36
Hodgkin's disease (ICDA-8 201)	6	2.88	2.09	0.76–4.54
Leukemia and aleukemia (ICDA-8 204–207)	12	10.96	1.09	0.56–1.91
Lymphatic tissue (ICDA-8 202–203, 208)	10	9.72	1.03	0.49–1.89
Lymphopoietic cancer (ICDA-8 200–208)	37	28.85	1.28	0.90–1.77
Cancer residual†	23	22.11	1.04	
Other causes				
Benign neoplasms (ICDA-8 210)	1	3.39	0.29	0.00–1.64
Diseases of blood and blood-forming organs (ICDA-8 280–289)	2	2.60	0.77	0.09–2.78
All diseases of circulatory system (ICDA-8 390–458)	450	577.89	0.78	0.71–0.85
Arteriosclerotic heart disease, including CHD (ICDA-8 410–414)	332	417.67	0.79	0.71–0.89
All vascular lesions of CNS (ICDA-8 430–438)	47	58.50	0.80	0.59–1.07
All respiratory diseases (ICDA-8 460–519)	53	78.35	0.68	0.51–0.88
Emphysema (ICDA-8 492)	3	14.28	0.21	0.04–0.61
All diseases of digestive system (ICDA-8 520–577)	48	62.94	0.76	0.56–1.01
Cirrhosis of liver (ICDA-8 571)	33	36.07	0.91	0.63–1.28
All diseases of the genitourinary system (ICDA-8 580–629)	3	14.00	0.21	0.04–0.63
All external causes of death (ICDA-8 800–998)	110	122.89	0.90	0.74–1.08
Suicide (ICDA-8 950–959)	24	30.47	0.79	0.50–1.17
Total residual‡	15	2.61	5.76	

*ICDA, *International Classification of Diseases, Adapted 8th Revision;* CHD, coronary heart disease; CNS, central nervous system.
† Cancers of unspecified site.
‡ Including undetermined causes of death and missing causes of deaths due to missing death certificates.

twofold increase in the mortality rate from colon and rectal cancers; however, the 95% CI included the null value. Similarly, a two- to threefold increase in mortality was observed for two other digestive tract cancers: pancreatic cancers (low exposure, >5 years; 15-year lag RR = 1.33; 95% CI, 0.31 to 5.66; and moderate exposure, >5 years; 15-year lag RR = 2.78; 95% CI, 0.51 to 15.2) and oropharyngeal tract cancers (ICD-9 codes 140 to 149) (low exposure, >2 years; 15-year lag RR = 1.85; 95% CI, 0.37 to 9.36; and moderate exposure, >2 years, 15-year lag RR = 2.87; 95% CI, 0.43 to 19.2), but the confidence intervals for the estimates included the null value. When we combined the cancers at all digestive-tract sites, we estimated a consistent two- to threefold increased mortality rate for moderate-level kerosene exposure of more than 5 years (low exposure: 15-year lag RR = 1.80; 95% CI, 1.05 to 3.10; and moderate exposure: 15-year lag RR = 2.71; 95% CI, 1.37 to 5.34). These estimates for kerosene exposure remained stable when we

TABLE 4
Adjusted Rate Ratio (RR) Estimates (and 95% CI) for the Effects of TCE Exposure (Both Levels in Model) and Cancer Mortality, by Cancer Site and Level, 0 and 15 Years' Lag for Exposures: Results From Conditional Logistic Regression Analyses Matched on Time and Age (±3 Years)*

	TCE Light (level 1)						TCE Moderate (level 2)					
	Lag Zero			Lag 15 Years			Lag Zero			Lag 15 Years		
Exposure Duration, by Cancer Site	Case *n*	RR	95% CI	Case *n*	RR	95% CI	Case *n*	RR	95% CI	Case *n*	RR	95% CI
Hemato- and lymphopoietic cancers (*n* = 37)												
>2 Years	18	1.35	0.68–2.69	15	1.45	0.68–3.06	1	0.98	0.13–7.41	1	1.17	0.15–9.00
>5 Years	15	1.85	0.87–3.95	12	1.79	0.78–4.08	0	—		0	—	
Esophagus and stomach cancers (*n* = 24)												
>2 Years	15	2.21	0.91–5.33	12	2.61	0.99–6.88	0	—		0	—	
>5 Years	8	1.03	0.40–2.63	5	1.02	0.32–3.21	0	—		0	—	
Liver cancers (*n* = 8)												
>2 Years	3	0.93	0.19–4.53	3	1.16	0.24–5.60	1	4.97	0.48–51.1	1	5.53	0.54–56.9
>5 Years	3	1.90	0.35–10.3	3	2.86	0.48–17.3	1	8.82	0.79–98.6	1	12.1	1.03–144
Prostate cancers (*n* = 24)												
>2 Years	10	0.78	0.33–1.85	10	0.91	0.38–2.18	1	1.35	0.17–10.4	1	1.44	0.19–11.4
>5 Years	8	0.83	0.33–2.09	8	1.04	0.40–2.70	1	1.58	0.20–12.5	1	1.96	0.25–15.6
Brain cancers (*n* = 12)												
>2 Years	6	1.81	0.49–6.71	4	2.29	0.42–12.5	1	3.26	0.37–28.9	1	6.94	0.66–73.1
>5 Years	3	1.32	0.28–6.17	3	5.41	0.87–33.9	1	4.52	0.49–41.5	1	14.4	1.24–167

* Adjusted for time since first hired, pay type (salaried/hourly), external and internal radiation dose (continuous and lagged), and same chemical at a different level.

adjusted for the other chemicals in the model.

For all associations reported above, the effects were generally stronger at higher levels of exposure and increased with duration of exposure. Effect size furthermore increased when a 15-year lag was utilized.

Internal comparisons showed no or no consistent effect for any of the examined chemicals on cancers of the lung after we controlled for internal and external radiation doses and/or for other chemicals (Table 7).

Discussion

A previous study that examined cancer mortality due to internal and external radiation among Fernald workers found that mortality from lung and some other radiosensitive solid cancers was increased among workers who had experienced exposure to high levels of alpha and gamma radiation.[10a] The analyses presented here were conducted to examine whether chemical exposures occurring during uranium processing contributed to cancer mortality in workers when the radiation effects on cancer were taken into account. We concentrated our analyses on three potentially carcinogenic exposures: that is, TCE, cutting fluids, and kerosene, in combination with a mixture of several solvents and carbon.

According to the CEDR, approximately 60% of all Fernald workers were exposed to cutting fluids and/or the kerosene-solvent mixture at any level, and almost 80% were exposed to TCE. Moderate levels of exposure to TCE occurred among 5% of all workers, 11% of workers were exposed to high levels of cutting fluids (level 3), and 24% of all workers were exposed to the kerosene-solvent mixture at moderate levels (level 2). Although fewer workers were categorized as having had moderate or high levels of exposure to chemicals, it is important to note that the categories "light" to "heavy" reflect an ordinary rating scale used by plant experts to attribute the likelihood of exposure to workers according to job titles and plant areas and are not based on actual measurements from industrial hygiene surveys.

We found a strong effect of TCE exposure on liver and biliary tract cancers in this cohort. According to a recent review article,[8] TCE exposure has been most consistently linked to three types of cancer: liver and biliary tract cancers, non-Hodgkin's lymphoma, and kidney cancers. Thus, although our liver-cancer results are based on a small number of cases (eight cases, four of whom were exposed to TCE), they are consistent with previous study results. Furthermore, all previous studies examining the association between TCE and liver/biliary tract cancers

TABLE 5

Adjusted Rate Ratio (RR) Estimates (and 95% CI) for the Effects of Cutting-Fluid Exposure (Both Levels in Model) and Cancer Mortality, by Cancer Site and Level, 0 and 15 Years' Lag for Exposures: Results From Conditional Logistic Regression Analyses Matched on Time and Age (±3 Years)*

	Cutting Fluid, Light and Moderate Exposure (levels 1 and 2)						Cutting Fluid, Heavy Exposure (level 3)					
	Lag Zero			Lag 15 Years			Lag Zero			Lag 15 Years		
Exposure Duration, by Cancer Site	Case *n*	RR	95% CI	Case *n*	RR	95% CI	Case *n*	RR	95% CI	Case *n*	RR	95% CI
HLL (*n* = 37)												
>2 Years	16	1.97	0.96–4.08	14	2.18	1.00–4.76	4	2.94	0.96–9.01	3	2.87	0.80–10.3
>5 Years	15	3.26	1.48–7.20	12	2.95	1.25–6.95	3	4.76	1.28–17.7	2	4.14	0.87–19.8
Laryngeal cancer (*n* = 5)												
>2 Years	3	4.49	0.52–38.6	2	2.02	0.24–16.9	2	36.1	3.57–365	2	23.2	2.68–201
>5 Years	2	4.31	0.40–46.4	2	8.05	0.52–125	2	190	9.57–3758	2	236	9.93–5630
Esophagus and stomach cancers (*n* = 24)												
>2 Years	11	1.67	0.69–4.03	10	2.36	0.90–6.19	1	1.17	0.15–9.33	0	—	
>5 Years	6	0.86	0.32–2.34	4	0.97	0.29–3.24	0	—		0	—	
Pancreatic cancers (*n* = 18)												
>2 Years	9	1.90	0.70–5.11	7	1.81	0.62–5.33	1	1.09	0.14–8.69	0	—	
>5 Years	7	1.62	0.58–4.48	3	0.83	0.22–3.22	0	—		0	—	
Bladder and kidney cancers (*n* = 13)												
>2 Years	5	1.36	0.40–4.69	4	1.03	0.29–3.72	3	5.31	1.26–22.3	3	5.67	1.33–24.2
>5 Years	4	1.29	0.35–4.73	3	1.02	0.25–4.14	2	4.93	0.95–25.6	2	6.33	1.15–34.7
Prostate cancers (*n* = 24)												
>2 Years	7	0.53	0.21–1.33	7	0.59	0.23–1.49	0	—		0	—	
>5 Years	6	0.58	0.22–1.55	6	0.71	0.26–1.94	0	—		0	—	
Brain cancers (*n* = 12)												
>2 Years	7	4.70	1.26–17.5	5	8.45	1.50–47.6	1	3.18	0.33–30.5	1	6.52	0.54–79.4
>5 Years	4	3.11	0.70–13.6	4	12.5	1.80–87.4	0	—		0	—	

* Adjusted for time since first hired, pay type (salaried/hourly), external and internal radiation dose (continuous and lagged), and same chemical at a different level.

† HLL, hemato- and lymphopoietic cancers.

also based their conclusions on as few as two to six exposed cases ineach cohort studied. We did not observe an effect for kidney cancers, which, overall, was a rare occurrence in this cohort ($n = 5$). An effect for all hemato- and lymphopoietic system cancers was suggested for cases with long durations (>10 years) of TCE exposure; however, this excess was not solely attributable to non-Hodgkin's lymphomas, and the positive associations for TCE exposure disappeared when we adjusted our analysis for cutting-fluid exposures. The slightly increased rate of brain cancers observed at moderate levels of TCE exposure was based on only one case, with the job title "degreaser," who was exposed to a combination of cutting fluids and TCE, and the effect disappeared completely after adjustment for cutting-fluid exposure.

Cutting fluids comprise three classes of fluids: straight oils, soluble, and synthetic fluids, each of which is a complex and variable mixture of many substances, some of which are known or suspected carcinogens or co-carcinogens.[11] Furthermore, certain processes, such as high-speed grinding, may alter the composition of the fluids and their carcinogenic properties. The carcinogens contained to some degree in most cutting fluids prior to 1980 are polycyclic aromatic hydrocarbons and nitrosamines.[12,13] Because no information concerning the types of cutting fluids used in the operations at Fernald throughout the 30-year study period was documented, it was impossible to differentiate exposures with respect to the type of fluid. However, when we examined the overall effect of cutting-fluid exposure at different levels and duration, we found that exposure at this uranium-processing facility was associated with increased rates of hemato- and lymphopoietic system cancers, brain, bladder, and kidney cancers and was also very strongly related to the generally rare cancers of the larynx.

Machining or cutting fluids have previously been linked to excess mortality from laryngeal cancers,[11,12,14,15] and several researchers observed an association between bladder and urinary tract cancers and work as a machinist.[12,16,17] Thus the

TABLE 6

Adjusted Rate Ratio (RR) Estimates (and 95% CI) for the Effects of Kerosene Exposure (Levels 1 and 2 in Model) and Cancer Mortality, by Cancer Site and Level, 0 and 15 Years' Lag for Exposures: Results From Conditional Logistic Regression Analyses Matched on Time and Age (±3 Years)*

Exposure Duration, by Cancer Site	Kerosene, Light Exposure (level 1)						Kerosene, Moderate Exposure (level 2)					
	Lag Zero			Lag 15 Years			Lag Zero			Lag 15 Years		
	Case *n*	RR	95% CI	Case *n*	RR	95% CI	Case *n*	RR	95% CI	Case *n*	RR	95% CI
Esophagus and stomach cancers (*n* = 24)												
>2 Years	10	1.98	0.77–5.09	9	3.46	1.22–9.80	5	3.00	0.81–11.2	5	7.71	2.04–29.1
>5 Years	5	0.96	0.32–2.94	3	1.26	0.31–5.15	4	2.86	0.60–13.6	4	10.7	2.26–50.7
Colon and rectum cancers (*n* = 33)												
>2 Years	10	1.13	0.49–2.60	9	1.20	0.50–2.91	8	1.80	0.64–5.06	7	2.11	0.75–5.97
>5 Years	9	1.26	0.52–3.01	7	1.40	0.52–3.74	5	1.13	0.31–4.18	4	1.91	0.50–7.27
Bladder and kidney cancers (*n* = 13)												
>2 Years	3	0.63	0.16–2.54	3	0.71	0.18–2.89	3	2.27	0.47–11.0	3	1.13	0.23–5.47
>5 Years	3	0.87	0.21–3.55	2	0.61	0.12–3.10	2	1.63	0.24–11.1	2	0.91	0.13–6.32
Prostate cancers (*n* = 24)												
>2 Years	7	0.76	0.29–2.02	7	0.88	0.33–2.36	6	2.00	0.54–7.34	6	2.44	0.69–2.36
>5 Years	6	0.92	0.32–2.63	6	1.10	0.37–3.23	6	3.69	0.91–15.0	5	3.40	0.78–14.8

* Adjusted for time since first hired, pay type (salaried/hourly), external and internal radiation dose (continuous and lagged), and same chemical at different level.

findings for laryngeal and bladder cancers in the study presented here are supported by previous research investigating the effects of cutting fluid. The association between cutting fluids and brain cancer mortality suggests a possible contamination of fluids with nitrosamines, which have previously been linked to cancers of these organ systems.[18] However, the observed increase in mortality from blood and lymph system cancers in workers exposed to cutting fluids is not easily explainable by one of the more prevalent carcinogenic cutting-oil contaminants. Other comparable work environments for which increased rates of blood and lymph system cancers among workers have been reported are petroleum and chemical plants.[19,20]

Heavy cutting-fluid exposure at Fernald was attributed solely to workers with two job titles: machine tool operators, who used lathes and grinders for the machining of uranium metal pieces, and laboratory mechanics, who performed test machining of uranium metal. No other chemical exposures at more than light levels were reported for these workers. Low and moderate cutting-fluid exposure occurred in toolmakers, welders, millwrights, helpers, degreasers, and some other jobs, in combination with exposure to many other chemicals at low or moderate levels.

Cutting fluids have previously been found to increase the rates of digestive-tract cancers such as cancers of the stomach,[17,21,22] rectum,[12,22] and pancreas.[12,21] Surprisingly, we did not find an association between digestive-tract cancers and cutting fluids in this cohort as expected in the case of nitrosamine contamination of cutting fluids; rather, all digestive-tract cancers in this cohort were associated with kerosene/solvent-mixture exposures. Kerosene was used in the chemical refining process of uranyl nitrate that involved the use of an organic solvent mixture which included tributyl phosphates and kerosene. The group of workers who experienced exposures to the kerosene/solvent mixture and to most respiratory irritants used at the facility and, in addition, to carbon at moderate levels were called chemical operators. However, this group of moderately exposed workers was exposed to neither TCE nor to cutting fluids. Thus the effects observed for prostate and digestive-tract cancers in this cohort can be attributed to the combination of kerosene, carbon, and other non-TCE solvent exposures. The absence of lung cancer effects for this chemical mixture suggests that exposure might have involved the inhalation of aerosolized particles of nonrespirable size that were trapped in the upper respiratory tract and consequently swallowed. This reasoning is also supported by the fact that kerosene/solvent mixture exposures increased the risk of cancers along the entire gastrointestinal tract, ie, from the oral cavity to the rectum.

The results of our external comparisons suggest that the Fernald cohort of uranium-processing workers is healthier than the white male US population, and thus exhibits the well-known "healthy worker effect." A deficit is also apparent when other worker NIOSH-cohorts[3] replace the US as the reference population in the calculation of expected mortality rates. This deficit is primarily due to

TABLE 7

Adjusted Rate Ratio (RR) Estimates (and 95% CI) for the Effects of Chemical Exposure Cancer Mortality, by Cancer Site and Level, 0 Years Lag for Exposures: Results From Conditional Logistic Regression Analyses Matched on Time and Age (±3 Years)*

	Lung Cancers (*n* = 112)		Hemato- and Lymphopoietic Cancers (*n* = 37)		Esophagus and Stomach Cancers (*n* = 24)		Colon and Rectum (*n* = 33)		Pancreatic Cancers (*n* = 18)		Brain Cancers (*n* = 12)		Prostate Cancer (*n* = 24)		Bladder and Kidney Cancers (*n* = 13)	
Exposure (in years)	Case *n*	RR (95% CI)	Case *n*	RR (95% CI)	Case *n*	RR (95% CI)	Case *n*	RR (95% CI)	Case *n*	RR (95% CI)	Case *n*	RR (95% CI)	Case *n*	RR (95% CI)	Case *n*	RR (95% CI)
TCE (level 1)																
<2	68	1	19	1	9	1	21	1	8	1	6	1	14	1	6	1
2–10	22	0.72 (0.44–1.16)	8	0.98 (0.42–2.26)	9	2.34 (0.91–6.02)	5	0.54 (0.20–1.46)	8	2.11 (0.79–5.66)	5	1.80 (0.49–6.67)	4	0.68 (0.22–2.08)	5	1.94 (0.59–6.44)
>10	22	0.77 (0.47–1.29)	10	2.17 (0.88–5.33)	6	2.09 (0.66–6.67)	7	0.85 (0.33–2.16)	2	0.57 (0.12–2.85)	1	0.94 (0.09–9.36)	6	0.82 (0.29–2.32)	2	0.76 (0.14–400)
TCE (level 2)																
<2	110	1	36	1	24	1	33	1	17	1	11	1	23	1	13	1
2–10	2	4.19 (0.51–34.2)	1	1.67 (0.22–12.4)	0	—	0	—	1	3.54 (0.45–27.9)	1	4.20 (0.51–34.2)	0	—	0	—
>10	0	—	0	—	0	—	0	—	0	—	0	—	1	2.15 (0.28–16.6)	0	—
Cutting fluids (levels 1, 2)																
>2	80	1	21	1	13	1	22	1	9	1	5	1	17	1	8	1
2–10	14	0.61 (0.34–1.08)	6	1.11 (0.44–2.84)	7	1.85 (0.71–4.83)	4	0.62 (0.21–1.83)	7	2.83 (1.02–7.88)	6	4.85 (1.33–17.7)	2	0.38 (0.09–1.65)	3	1.32 (0.34–5.17)
>10	18	0.75 (0.44–1.29)	10	3.31 (1.32–8.28)	4	1.27 (0.37–4.35)	7	1.18 (0.46–3.01)	2	0.78 (0.16–3.84)	1	2.00 (0.19–21.1)	5	0.68 (0.23–2.02)	2	0.80 (0.15–4.07)
Cutting fluids (level 3)																
<2	105	1	33	1	23	1	31	1	17	1	11	1	24	1	10	1
2–10	4	0.85 (0.31–2.34)	2	1.60 (0.37–6.92)	1	1.49 (0.19–11.5)	1	0.84 (0.11–6.32)	1	1.23 (0.16–9.46)	1	2.08 (0.23–18.4)	0	—	2	4.56 (0.94–22.1)
>10	3	1.45 (0.45–4.64)	2	5.72 (1.18–27.8)	0	—	1	1.97 (0.25–15.4)	0	—	0	—	0	—	1	5.70 (0.63–52.0)
Kerosene (level 1)																
<2	84	1	23	1	14	1	23	1	9	1	6	1	17	1	10	1
2–10	13	0.67 (0.37–1.22)	5	1.02 (0.37–2.78)	6	1.77 (0.65–4.87)	4	0.81 (0.27–2.41)	7	3.62 (1.29–10.2)	5	5.38 (1.44–20.2)	2	0.46 (0.10–2.02)	1	0.43 (0.05–3.53)
>10	15	0.73 (0.41–1.30)	9	3.07 (1.22–7.71)	4	1.37 (0.40–4.67)	6	1.18 (0.44–3.16)	2	0.97 (0.20–4.78)	1	2.44 (0.23–26.0)	5	0.82 (0.26–2.43)	2	0.77 (0.15–3.85)
Kerosene (level 2)																
<2	86	1	33	1	19	1	25	1	14	1	12	1	18	1	10	1
2–10	8	0.87 (0.42–1.83)	3	0.97 (0.28–3.37)	2	1.85 (0.39–8.78)	4	2.01 (0.66–6.11)	2	1.40 (0.30–6.59)	0	—	1	1.02 (0.13–8.18)	2	1.83 (0.38–8.79)
>10	18	1.35 (0.65–2.79)	1	0.24 (0.02–2.52)	3	3.66 (0.59–22.8)	4	1.33 (0.31–5.65)	2	1.14 (0.15–8.66)	0	—	5	4.29 (0.89–20.5)	1	0.52 (0.04–7.64)

* Adjusted for time since first hired, pay type (salaried/hourly), external radiation dose (continuous), and internal radiation dose (continuous). Note that no other chemical exposures were included in these models.

TABLE 8
Smoking Prevalence for a Subgroup of 757 Fernald White Male Workers, by Chemical Exposure Level*

Exposure Level	No. (%) Smokers	No. (%) Ex-Smokers	No. (%) Non-Smokers	Total (%)
TCE				
0	75 (43.4)	37 (21.4)	61 (35.3)	173 (100)
1	236 (43.7)	135 (25.0)	169 (31.3)	540 (100)
2	24 (54.6)	11 (25.0)	9 (20.5)	44 (100)
Total	335 (44.3)	183 (24.2)	239 (31.6)	757 (100)
Cutting Fluids				
0	103 (41.2)	56 (22.4)	91 (36.4)	250 (100)
1	162 (42.1)	98 (25.5)	125 (32.5)	385 (100)
2	20 (66.7)	5 (16.7)	5 (16.7)	30 (100)
3	50 (54.4)	24 (26.1)	18 (19.6)	92 (100)
Total	335 (44.3)	183 (24.2)	239 (31.6)	757 (100)
Kerosene				
0	85 (49.4)	39 (22.7)	48 (27.9)	172 (100)
1	149 (40.8)	96 (26.3)	120 (32.9)	365 (100)
2	101 (45.9)	48 (21.8)	71 (32.3)	220 (100)
Total	335 (44.3)	183 (24.2)	239 (31.6)	757 (100)

* In 1965, 51.3% of the US white male population over the age of 20 were cigarette smokers.[23]

reduced rates of death from cardiovascular diseases. Fernald workers, however, died at higher rates from many cancers, when compared with either reference population. Furthermore, they were less likely to smoke than the US population (according to the Surgeon General,[23] during the 1960s, 51.3% of the white male US population over the age of 20 were cigarette smokers), which might partially explain the observed reduction in cardiovascular disease mortality. Because the Fernald cohort is, in general, healthier and engages in behavior that is less likely to cause many cancers, the observation of increased cancer rates points to causative agents in the work environment.

As mentioned previously, exposure to respiratory irritants was very common at this facility, prompting Wilson to conduct an exposure assessment and to examine nonmalignant respiratory morbidity.[2] He was, however, unable to find any association between the chemicals studied (ammonia, carbon, cutting fluids, kerosene, lime, nitric acid, sodium hydroxide, tributyl phosphate, TCE) and the occurrence of nonmalignant respiratory diseases. As listed in Table 3, significantly fewer Fernald workers died of respiratory diseases or emphysema, compared with the US population. Possible explanations for the lack of an increase in respiratory morbidity for workers heavily exposed to respiratory irritants could be either that the entire cohort represents a highly selected group of healthy workers or that the most heavily exposed workers were the healthiest. A selection of healthier workers into exposed jobs could also lead to a bias toward the null for the internal comparisons of cancer mortality performed in this study.

Table 8 shows that there are no clear patterns of association between smoking and general levels of chemical exposure, making it unlikely that smoking is an explanation for the observed relationships between chemicals and cancer mortality. Yet the comparisons in Table 8 represent a rather crude picture, because we did not base our conclusions for chemical-exposure effects on a simple comparison of exposure levels but rather on time-dependent and lagged-duration measures. If the effects observed for chemicals were really due to differences in smoking, one would expect to see an association with lung cancers, the most strongly smoking-related cancer. We found no association of any chemical exposure in this cohort with lung-cancer mortality, after adjustment for radiation effects.

Because chemical-exposure data in the CEDR was only available for the period 1952 to 1977, we lack exposure information for the remaining 12 years of the plant's operation (1978 to 1989). Yet this lack of data could be compared with a lack of postemployment exposure history. The resulting exposure misclassification would most likely be nondifferential with respect to case status and thus expected to bias our results toward the null.

Our results for the two rare cancers of the liver and larynx are quite strong and are corroborated by results from previous studies that linked TCE exposure to liver cancers and cutting-fluids exposure with laryngeal cancers. Furthermore, cutting-fluid exposure in this cohort was associated with brain cancers, hemato- and lymphopoietic cancers, and bladder and kidney cancers, whereas kerosene exposures increased the chances of death from all digestive-tract cancers and from prostate cancers. Causal inference is strengthened by the fact that the effect estimates for all reported associations increased with duration and level of exposure, were observed to be stronger when exposure was lagged, are biologically plausible, and/or have previously been observed among workers who experienced similar chemical exposures.

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Fat Cities

. . .Stay away from New Orleans; Columbus, Ohio; and Milwaukee. These cities have the highest rate of overweight men and, not surprisingly, the largest number of fast-food burger chains, *Men's Fitness* magazine reports. Not for nothing is Milwaukee's major league baseball team named the Brewers: Wisconsin has the highest per capita consumption of alcohol of any state.

—From Schogol M. Food Watch. *Philadelphia Inquirer*, January 6, 1999, p F2.