

# Exhibit 272



14352

## Risk of Cancer and Exposure to Gasoline Vapors

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Until the introduction of self-service around 1970, service station workers in the Nordic countries were exposed to gasoline vapors. Based on measurements reported in the literature, the 8-hour time-weighted average benzene exposure was estimated to be in the range of 0.5–1 mg/m<sup>3</sup>. We studied the cancer incidence in a cohort of 19,000 service station workers from Denmark, Norway, Sweden, and Finland. They were identified from the 1970 censuses and followed through 20 years, where 1,300 incident cancers were observed. National incidence rates were used for comparison. The incidence was not increased for leukemia (observed = 28, standardized incidence ratio (SIR) = 0.9, 95% confidence interval (CI) 0.6–1.3) nor for acute myeloid leukemia (observed = 13, SIR = 1.3, 95% CI 0.7–2.1). The incidence was slightly elevated for kidney cancer (observed = 57, SIR = 1.3, 95% CI 1.0–1.7) and for pharyngeal, laryngeal, and lung cancer. A 3.5-fold risk of nasal cancer was found (observed = 12, SIR = 3.5, 95% CI 1.8–6.1). This cohort exposed to gasoline vapors with benzene levels estimated to be 0.5–1 mg/m<sup>3</sup> showed no excess risk of leukemia or acute myeloid leukemia, a 30% elevated risk of kidney cancer, and a previously unnoticed risk of nasal cancer. *Am J Epidemiol* 1997;145:449–58.

gasoline; incidence; kidney neoplasms; leukemia; nose neoplasms

The possible risk of cancer following low dose exposure to petroleum products and, in particular, exposure to gasoline vapors containing benzene is an issue of public concern (1, 2). Until around 1970, service station workers in the Nordic countries were employed to fill customers' cars. Since then, self-service increased gradually and became predominant around 1990. Benzene has been used as an indicator of

exposure to gasoline. The volume percentage of benzene in the various gasoline blends ranged from 2 to 6 volume percent in the Nordic countries. The available measurements indicate that the 8-hour time-weighted average exposure to benzene for the Nordic service station workers was on average 0.5–1 mg/m<sup>3</sup>, as described below. Biologic monitoring data based on urine samples (3, 4) and peripheral lymphocytes (4, 5) from service station workers have indicated that early effects of exposures occur at such exposure levels.

A group of scientists and representatives from the petrochemical industry therefore met in December 1993 at the International Agency for Research on Cancer in Lyon, France, and decided to study the possible cancer risk associated with low dose exposure to gasoline vapors as a joint Nordic analysis of cancer incidence in service station workers. We report here on the outcome of this study.

## MATERIALS AND METHODS

### Population

The aim was to assess the cancer risk among persons occupationally exposed to gasoline and gasoline vapors. We did not focus on persons occupationally exposed to exhaust fumes and combustion products, although many of the people exposed to gasoline

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Abbreviations: CI, confidence interval; SIR, standardized incidence ratio.

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would unavoidably also have been exposed to exhaust fumes.

The service station workers were identified from the data files of the 1970 census in Denmark, Norway, Sweden, and Finland. They were followed up for deaths, emigrations, and incident cancer cases through a 15- to 20-year period. The use of personal identification numbers and central population registers in the Nordic countries ensured a virtually complete follow-up.

At the 1970 census, self-administered questionnaires were completed by each household in free text, where the education, job title, and name and address of the work place at the time of the census had to be listed for each member of the household. The questionnaires were checked by the municipalities in Denmark and Norway and centrally coded by the Central Bureau of Statistics in all four countries (6). The industry for a given person was coded according to nationally adapted versions of the International Standard Industrial Classification of 1958 (7). In Norway, Sweden, and Finland, the occupation was coded according to nationally adapted versions of the International Standard Occupational Classification (8). In Denmark, occupation was coded according to a national classification. Service station workers were identified from the census files using the combination of codes for industry and occupation, as shown in table 1.

In Denmark, 5,250 service station workers (4,055 men and 1,195 women) were registered at the census on November 9, 1970. They were followed up for deaths and emigrations through November 8, 1987, by linkage with the Central Population Register and for

incident cancer cases by linkage with the National Cancer Register. For each cancer site, person-years were counted from November 9, 1970, until the date of death, emigration, diagnosis of the studied cancer, or November 8, 1987, whichever came first. The observed number of cancer cases was thus equivalent to the number of observation periods terminated by a date of diagnosis. Person-years and observed cancer cases were counted in the same way for all persons who were economically active on the census date and used for the generation of cancer incidence rates by sex and 5-year age groups (defined as age at the time of the census). These rates were used for calculation of the expected number of cancer cases among the service station workers (9).

In Norway, 3,561 persons (3,181 men and 380 women) were service station workers on the census date of November 1, 1970. They were followed up for deaths and emigrations for 1971–1991 by linkage with the Central Population Register and for incident cancers by linkage with the National Cancer Register. Person-years were counted from January 1, 1971, until the date of death, emigration, or December 31, 1991, whichever came first. All cancer cases diagnosed within these periods were included as observed cases in the analysis. For calculation of expected numbers of cancer cases among service station workers, the national incidence rates for the years 1971–1991 by sex and 5-year age groups (defined by current age) were used (10).

In Sweden, 8,606 persons (7,901 men and 705 women) participated in both the 1960 and the 1970 censuses and were classified at the census on Novem-

TABLE 1. Service station workers aged 20–64 years in the Nordic countries in 1970

Country	Gasoline consumption, 1,000 tons, average annual			Census codes		Men (no.)	Women (no.)	Follow-up period	Person-years	
	1959– 1963 total	1969– 1973 total	Per capita*	Industry	Occupation				Men	Women
Denmark	1,036	1,555	0.32	661 (filling stations)	001–099 (self-employed)	1,988	60	1970–1987	31,367	937
					101–199, 501–599 (family workers)	4	871		68	14,357
					201–299 (salaried employees)	89	134		1,361	2,194
					301–399 (skilled workers)	325	0		5,281	0
					401–499 (unskilled workers)	1,649	130		25,953	2,099
					Total	4,055	1,195		64,030	19,587
Norway	489	979	0.25	657 (retail trade fuel and oil)	Self-employed	1,024	28	1971–1991	19,350	499
					Employees	2,157	352		41,268	7,233
					Total	3,181	380		60,618	7,732
Sweden	1,819	2,857	0.35	6242 (fuel retailing)	03 (self-employed)	2,503	342	1971–1989	NA†	NA
					06 (employees)	5,398	363		NA	NA
					338 (service station workers)	7,901	705		143,085	13,070
Finland	398	1,048	0.23	All codes	233 (service station workers)‡	1,387	165	1971–1985	20,800	2,500
Total						16,524	2,445		288,533	42,889

\* Annual consumption in 1969–1973 divided by population size in 1970.

† NA, not available.

‡ In the Finnish 1970 census, employees who performed practical work (e.g., shopkeepers or owners of shoemaker shops) were classified as their employees.

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## Exposure

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ber 1, 1970, as service station workers. They were followed up for deaths through December 31, 1989, by linkage with the annual death registers and for incident cancer cases by linkage with the National Cancer Register. Person-years were counted from November 1, 1970, until death or December 31, 1989, whichever came first. All cancer cases diagnosed within these periods were included as observed cases in the analysis. Person-years and observed cancer cases were counted in the same way for the total census population and used for generation of cancer incidence rates by sex and 5-year age groups (defined as age at the time of the census). These rates were used for calculation of the expected number of cancer cases among the service station workers (11).

In Finland, the 1,552 service station workers (1,387 men and 165 women) were identified at the census on December 31, 1970. They were followed up through December 31, 1985, for deaths by linkage with the annual death files of Statistics Finland and for incident cancer cases by linkage with the Finnish Cancer Register. Person-years were counted from January 1, 1971, until the date of death or December 31, 1985, whichever came first. All cancer cases diagnosed within these periods were included as observed cases in the analysis. Person-years and observed cancer cases were counted in the same way for all persons who were economically active on the census date and used for generation of cancer incidence rates by sex and 5-year age groups (defined as age at the time of the census). These rates were used for calculation of the expected number of cancer cases among the service station workers (12).

Standardized incidence ratios were calculated by dividing the observed number of cancer cases with the expected number. Ninety-five percent confidence intervals were calculated under the assumption that the observed number followed a Poisson distribution. For the period under study, the cancer incidence data were coded according to the *International Classification of Diseases*, Revision 7 (13).

### Exposure

The consumption of gasoline increased considerably in the Nordic countries during the 1960s. From 1959–1963 to 1969–1973, the average annual consumption more than doubled in Finland, doubled in Norway, and increased by around 50 percent in Sweden and Denmark (14).

The retail sale of gasoline was thus an expanding business in the Nordic countries in 1970 and, in the Danish cohort, half of the men were self-employed leaseholders of service stations owned by the oil companies. This group is likely to have stayed in the

industry for a long period beyond 1970. In Norway, 44 percent of those employed at service stations in 1960 still worked there in 1970; in Sweden, this percentage was 35 percent. In Finland, 81 percent of persons employed at service stations in 1980 also worked there in 1985 (15). The data thus indicate that a minimum of 35–50 percent of the service station workers stayed in the industry for at least 10 years. This work force was thus relatively stable compared with cohorts of factory workers from the Nordic countries (16, 17).

In Norway in 1972, all gasoline was sold at service stations with attendants. By 1983, this proportion had decreased to 50 percent and, by 1990, to 20 percent (18). In Sweden, most attendants operated the pumps until around 1970 (19). In Finland, car tanks were filled mostly by attendants until 1975 (20). Service station workers furthermore often used gasoline for cleaning their hands from oil and grease (19).

The concentration of benzene in gasoline in Norway (I. L. Nøstvik, Norwegian Petroleum Institute, personal communication, 1996) and Sweden (R. Jarsin, Swedish Petroleum Institute, personal communication, 1995) has varied between 3 and 5 volume percent since the 1950s. In Finland, the concentration in 99-octane gasoline decreased from 6 volume percent in 1977–1978 to 2–3 volume percent in 1981–1987, and it was 2–3 volume percent in 92-octane gasoline in 1977–1987 and in 95-octane from 1985 onward (P. Saikkonen and Neste Oy, personal communication, 1995). In Denmark, random samples of gasoline taken in the 1980s contained averages of 3–3.5 volume percent (E. Iversen, Danish Agency for Environmental Protection, personal communication, 1996).

In Sweden, the sale of unleaded gasoline exceeded that of leaded by 1990 (R. Jarsin, Swedish Petroleum Institute, personal communication, 1995), and a similar pattern was seen in the other Nordic countries. A major way to maintain the octane number in unleaded gasoline was to increase the amount of reformats with a high benzene content. This led to an increased benzene content in the gasoline in some countries (21, 22) but not exceeding 5 percent in Norway (I. L. Nøstvik, Norwegian Petroleum Institute, personal communication, 1996), Finland (23), and Denmark (24). In Finland, a city gasoline was launched in 1991 and a reformulated gasoline in 1994 with maximum benzene contents of 3 and 1 volume percent, respectively (P. Saikkonen and Neste Oy, personal communication, 1995).

Exposure to gasoline at service stations mainly occurs during the filling of the car tanks. During the pumping of 30 liters of gasoline containing 5 volume percent benzene into a car, about 700 mg of benzene are vaporized (25). Short-term measurements of ben-



zene during this process (at pumps without vapor recovery) in Finland in the early 1980s showed an average concentration of 1.6 mg/m<sup>3</sup> (20), in Sweden in 1989 of 2.3 mg/m<sup>3</sup> (26), and in Norway in 1995 of 3.3 mg/m<sup>3</sup> (13) (see table 2).

Measurements of 8-hour time-weighted average exposure to benzene for service station attendants are not available from the Nordic countries from 1970. Forty-five-minute measurements with silica gel tubes in Sweden in the late 1970s showed an average concentration of 0.27 mg/m<sup>3</sup> (27, 28). Measurements of 8-hour time-weighted average exposure in Norway in 1980–1981 showed 2.2 mg/m<sup>3</sup> (29). A considerable number of similar measurements in Germany in 1983 showed a range for service stations of <0.03–3.9 mg/m<sup>3</sup> (30). Other European measurements in 1986–1989 showed an overall level of 0.61 mg/m<sup>3</sup> (31), and recent measurements in Italy showed a level of 0.55 mg/m<sup>3</sup> (32) (see table 2). We assume on the basis of available data that the 8-hour time-weighted average exposure to benzene for service stations attendants in the Nordic countries in 1970 on the average was 0.5–1.0 mg/m<sup>3</sup>. It should be kept in mind, however, that the exposure level is influenced by workload, weather conditions, and work practices (33).

## RESULTS

The study included 16,524 men who contributed close to 300,000 person-years and 2,445 women with 43,000 person-years (table 1).

Table 3 shows the number of observed and expected cancer cases for male service station workers. To-

gether, they developed 1,130 cancer cases corresponding to a standardized incidence ratio of 1.1 (95 percent confidence interval (CI) 1.0–1.1).

An excess risk of lung cancer mortality has previously been observed among male service station workers in Denmark (34). This excess was also seen in the incidence data from Denmark, with 77 observed cases versus 49.79 expected (standardized incidence ratio (SIR) = 1.6, 95 percent CI 1.2–1.9), and to a minor extent in Norway (SIR = 1.2) and Sweden (SIR = 1.2). The standardized incidence ratio for men in the four countries together was 1.3 (95 percent CI 1.1–1.4). The contribution to this slightly elevated risk came primarily from squamous cell carcinomas (SIR = 1.4, 95 percent CI 1.1–1.7) (data not shown).

There was a consistent excess risk of nasal cancer among men across the Nordic countries; 10 cases were observed where 3.20 were expected (SIR = 3.1, 95 percent CI 1.5–5.7). An increased risk of pharyngeal cancer was indicated with 15 cases observed and 8.92 expected (SIR = 1.7, 95 percent CI 0.9–2.8), mainly from Denmark. For laryngeal cancer, 25 cases were observed and 17.06 expected (SIR = 1.5, 95 percent CI 0.9–2.2), mainly from Norway.

The risk of kidney cancer was elevated in Denmark, Norway, and Finland, and the standardized incidence ratio for the four countries together was at the borderline of statistical significance (observed = 53, expected = 40.46, SIR = 1.3, 95 percent CI 1.0–1.7) as was the standardized incidence ratio for renal pelvis cancer (observed = 10, expected = 5.00, SIR = 2.0, 95 percent CI 1.0–3.7).

TABLE 2. Concentration of exposure to benzene during work at service stations in Europe

Year	Country	Sampling duration	No. of samples	Arithmetic mean (mg/m <sup>3</sup> )	Range (mg/m <sup>3</sup> )	Reference
<i>Long-term sampling</i>						
1971	Great Britain	3, 5–14 hours	121	NA*	0.96–7.7 of means from nine stations	73
Early 1980s	Finland	8 hours estimated	36	0.64	NA	20
1980–1981	Norway	8 hours	39	2.2	0–18.2	29
Ca. 1980–1985†	Europe	8 hours	546	NA	0.03–18.2	30
1984–1985	Europe	8 hours	13	0.35	0.08–1.28	74
1986–1989	Europe	8 hours	82	0.61	<0.16–10.7	31
1990	France	8 hours	62	2.59	NA	75
1991–1992	Italy	8 hours	703	0.55	0.001–28.02	32
<i>Short-term sampling</i>						
Late 1970s	Sweden	45 minutes	ND*	0.27	0.06–0.99	27–28
Early 1980s	Finland	3–5 minutes	36	1.6	0.096–3.2	20
1989	Sweden	0.43–3.3 minutes	175	2.3	0.01–27.3	26
1995	Norway	2–3 minutes	17	3.26	0–19.94	18
1995	Norway	20–30 minutes	28	2.53	0–17.2	18

\* NA, not available; ND, not determined.

† Includes measurements from Norway, 1980–1981.

TABLE 3. Cancer incidence in male service station workers in the Nordic countries during the 15-20 years of follow-up from 1970-1971

ICD-7* code	Denmark			Norway			Sweden			Finland			Total		
	Observed	Expected	SIR*	Observed	Expected	SIR	Observed	Expected	SIR	Observed	Expected	SIR	Observed	Expected	SIR
140 (lip)	2	3.48	0.6	3	3.96	0.8	2	4.34	0.5	0	1.60	0.3	7	13.38	0.5
141 (tongue)	1	0.80	1.3	0	1.54	1.6	3	1.89	1.6	0	0.33	0.3	4	4.56	0.9
143-144 (mouth)	1	1.53	0.7	6	2.14	2.8	4	2.68	1.5	0	0.30	0.3	11	6.65	1.7
145-148 (pharynx)	6	2.06	2.9	4	2.60	1.5	5	3.79	1.3	0	0.47	0.8	15	8.92	1.7
150 (esophagus)	3	2.93	1.0	5	3.70	1.4	5	5.26	1.0	0	0.82	0.3	13	12.71	1.0
151 (stomach)	20	10.41	1.9	18	20.71	0.9	31	23.60	1.3	2	6.86	0.3	71	61.58	1.2
153 (colon)	17	15.95	1.1	27	25.02	1.1	35	30.00	1.2	3	3.11	1.0	82	74.08	1.1
154 (rectum)	13	13.13	1.0	14	17.48	0.8	26	21.70	1.2	1	2.82	0.4	54	55.13	1.0
155.0 (liver)	2	2.51	0.8	2	2.26	0.9	7	5.63	1.2	2	0.94	2.1	13	11.34	1.2
155.1 (gallbladder)	1	1.53	0.7	1	1.37	0.7	4	4.28	0.9	0	0.57	0.7	6	7.75	0.8
157 (pancreas)	4	7.62	0.5	11	10.69	1.0	15	14.90	1.0	2	2.94	0.7	32	36.15	0.9
160 (nose)	3	0.78	3.8	2	0.98	2.0	2	1.20	1.7	3	0.24	12.3	10	3.20	3.1
161 (larynx)	5	5.01	1.0	9	4.63	1.9	9	5.67	1.6	2	1.75	1.1	25	17.06	1.5
162.0, 1 (lung)	77	49.79	1.6	52	44.83	1.2	58	49.20	1.2	21	21.21	1.0	208	165.03	1.3
170 (breast)	0	0.41	0	0	0.45	0	0	0.72	0	0	0.08	0.8	0	1.66	0.9
177 (prostate)	18	17.22	1.0	35	48.28	0.7	65	73.00	0.9	9	5.96	1.5	127	144.46	0.9
180† (kidney)	10	6.50	1.5	17	11.69	1.5	22	19.30	1.1	4	2.97	1.4	53	40.46	1.3
180† (renal pelvis)	4	1.97	2.0	4	0.91	4.9	1	2.06	0.5	1	0.16	5.6	10	5.00	2.0
181 (bladder)	23	20.34	1.1	15	23.50	0.6	42	31.80	1.3	6	3.46	1.7	86	79.10	1.1
190 (melanoma)	5	6.55	0.8	10	13.30	0.8	17	20.40	0.8	1	2.47	0.4	33	42.82	0.8
191 (other skin)	28	32.74	0.9	6	8.93	0.7	10	12.80	0.8	0	1.30	0.9	44	55.77	0.8
193 (brain)	5	8.86	0.6	10	9.60	1.0	23	20.20	1.1	3	3.18	0.7	41	41.84	1.0
194 (thyroid)	1	0.89	1.1	1	1.93	0.5	4	3.55	1.1	0	0.65	4.0	6	7.02	0.9
196 (bone)	0	0.50	0	3	0.82	4.8	0	1.39	1.4	1	0.25	0.8	4	2.76	1.5
197 (connective tissue)	0	1.05	0	0	1.61	0	6	4.34	1.4	0	0.67	0.8	6	7.67	0.8
199 (other and unspecified)	0	1.74	1.7	19	11.06	1.7	26	18.00	1.5	0	1.27	1.5	48	32.07	1.5
200, 202 (non-Hodgkin's lymphoma)	8	5.98	1.3	9	9.25	1.0	18	16.90	1.1	2	2.47	0.8	37	34.60	1.1
201 (Hodgkin's disease)	3	2.86	1.3	2	2.00	1.0	5	4.85	1.0	0	1.03	1.1	10	10.24	1.0
203 (multiple myeloma)	2	2.60	0.8	3	5.35	0.6	3	7.13	0.4	1	0.91	0.6	9	15.99	0.6
204 (leukemia)	5	6.74	0.7	9	6.58	1.4	12	13.69	0.9	0	2.15	0.9	26	29.16	0.9
Acute myeloid leukemia	1	2.18	0.5	4	2.33	1.7	8	3.86	2.1	0	0.8	1.4	13	9.14	1.4
Chronic lymphatic leukemia	2	2.63	0.8	2	1.83	1.1	4	5.06	0.8	0	0.6	0.5	8	10.16	0.8
All other leukemia	2	1.93	1.0	3	2.42	1.2	0	4.77	1.2	0	0.8	0.5	5	9.87	0.5
140-205 (all malignant neoplasms)	279	240.76	1.2	307	306.88	1.0	477	447.0	1.1	67	75.73	0.9	1,130	1,070.37	1.1

\* ICD-7, International Classification of Diseases, Seventh Revision; SIR, standardized incidence ratio; CI, confidence interval.

† In Norway and Denmark, ureter included in ICD-7 code 181 (bladder); in Sweden and Finland, ureter and urethra included in ICD-7 code 181 (bladder).

An excess risk of acute myeloid leukemia has previously been observed among male service station workers in Sweden (13), and it was repeated here (observed = 8, expected = 3.86, SIR = 2.1, 95 percent CI 0.9–4.1), as the two studies overlapped. A similar pattern was seen in Norway but not in Denmark and Finland. In total, there were 13 observed cases of acute myeloid leukemia versus 9.14 expected among men (SIR = 1.4, 95 percent CI 0.8–2.4).

Table 4 shows the number of observed and expected cancer cases for female service station workers. Together, they developed 179 cancer cases, which was equivalent to the expected (SIR = 1.0). Noteworthy were two nasal cancer cases where 0.25 case was expected.

## DISCUSSION

Service stations are small work places scattered throughout every country. The collection of data for the present cohort of 19,000 workers was possible because the Nordic countries use the same personal identification numbers in the censuses, central population registers where deaths and migrations are recorded, and national cancer registers.

Persons included in the present study were recorded as service station workers at the 1970 census, where a careful procedure was used in the data collection. When questionnaires from the 1970 census in Denmark were retrieved for a nested case-control study (35), no coding error was found. In Norway, a control survey with personal interviews after the 1970 census showed identical distributions by occupational group (36), in line with results after the 1960 census in Sweden (37). In the Nordic countries, national cancer registration dates back to the 1940s and 1950s, and the registers cover virtually all incident cancer cases.

The main strengths of the present study are thus the national coverage and the accuracy of the data. The main weaknesses are that individual data are not available on length of employment and level of benzene exposure. The statistical data indicate, however, that the work force was relatively stable with a minimum of 35–50 percent staying for at least 10 years, and a considerable number of published long-term measurements was available for estimation of the exposure level.

Concerning possible confounding, it should be remembered that service station workers are also exposed to agents other than benzene in their work, both from the gasoline and from other sources. Gasoline is a mixture of hydrocarbons and additives. The total concentration of hydrocarbons in the air during the filling process may be 10-fold to 100-fold that of benzene (31). Lead gasoline contains organic lead

compounds as well as small quantities of dibromoethane and dichloroethane added as scavengers (38). Service station workers may also be exposed to exhaust emissions, including polycyclic aromatic hydrocarbons, aldehydes, and 1,3-butadiene (39). Exposure to diesel exhaust is limited by the fact that normally only one in 10 pumps will be a diesel pump. Ethene from vehicle exhaust may be transformed to ethylene oxide in the human body but, for service station workers, only in concentrations with a minimal impact on their leukemia risk (40).

As smoking is strictly forbidden in service stations, the smoking habits of service station workers are not expected to have exceeded the national average. In a survey of men in Sweden in 1963, 19 of 37 (51 percent) service station workers aged 18–49 years were smokers compared with 53 percent of all men (J. Carstensen, personal communication, 1996). A slightly higher smoking rate in 1963 among the 50- to 69-year-old men is hardly relevant for the present study including only persons aged 20–64 years in 1970. Data are not available on alcohol consumption among service station workers, but with the close police surveillance of drunken driving in the Nordic countries, service stations have not been a likely working environment for those with excessive alcohol consumption.

## Leukemia

An excess risk of leukemia (41), primarily acute non-lymphocytic leukemia (42), has been found in persons occupationally exposed to benzene. Low level exposure to benzene is widespread, and decisions on exposure limits are controversial. Extrapolations from persons with high exposure indicate that long-term low exposure entails a leukemia risk (43–45), though the inherent limitations should be remembered (46). Based on the algorithm by Crump and Allen (44) and the present consumption of gasoline, one extra leukemia case per 5–6 years would occur in Sweden because of the filling of cars (47). With the same exposure limited to service station workers, only four extra cases would be expected in the Swedish cohort.

Leukemia cases, representing an excess risk, have been found among garage workers who used gasoline to clean vehicle parts and hands and often syphoned gasoline by mouth from one vehicle tank to another (48, 49). Studies of oil distribution workers show some indication of risk of leukemia (50), primarily of acute myeloid or monocytic leukemia (51, 52), or of acute myeloid leukemia only (53). An increased mortality from leukemia was found among service station attendants in New Hampshire (54), while the risk of leukemia was not increased in an Italian cohort (two

TABLE 4. Cancer incidence in female service station workers in the Nordic countries during the 15-20 years of follow-up from 1970-1971

ICD-7*	Denmark			Norway			Sweden			Finland			Total		
	Observed	Expected	SIR*	Observed	Expected	SIR	Observed	Expected	SIR	Observed	Expected	SIR	Observed	Expected	SIR
	95% CI*														
140 (lip)	0	0.10		0	0.07		0	0.07		0	0.01		0	0.25	
141 (tongue)	0	0.12		0	0.09		0	0.10		0	0.02		0	0.33	
143-144 (mouth)	0	0.26		0	0.14		0	0.14		0	0.02		0	0.56	
145-148 (pharynx)	0	0.28		0	0.11		0	0.13		0	0.02		0	0.54	
150 (esophagus)	1	0.29	3.5	2	0.15	1.3	2	0.15	1.6	1	0.05	20.4	2	0.64	3.1
151 (stomach)	3	1.44	2.1	5	1.57	1.3	2	1.28	0.7	0	0.39		7	4.64	1.5
153 (colon)	9	4.89	1.8	2	3.72	1.3	4	2.98	0.7	1	0.34		16	11.93	1.3
154 (rectum)	1	2.55	0.4	2	1.86	1.1	4	1.71	2.3	1	0.23	4.4	8	6.35	1.3
155.0 (liver)	1	0.43	2.3	0	0.18		0	0.38		0	0.05		1	1.04	1.0
155.1 (gallbladder)	1	0.67	1.5	0	0.28		0	0.79		0	0.09		1	1.83	0.6
157 (pancreas)	1	1.64	0.6	0	1.10		0	1.22		0	0.18		1	4.14	0.2
157 (pancreas)	1	1.64	0.6	0	1.10		0	1.22		0	0.02		2	0.25	8.0
160 (nose)	1	0.10	10.0	1	0.07	14.3	0	0.06		0	0.01		0	0.50	
161 (larynx)	0	0.34		0	0.06		0	0.09		0	0.01		0	0.50	
162.0, 1 (lung)	4	6.06	0.7	5	1.99	2.5	1	2.13	0.5	3	2.82	3.7	11	10.45	1.1
170 (breast)	22	23.62	0.9	13	10.23	1.3	23	15.32	1.5	3	2.82	1.1	61	51.99	1.2
171 (cervix uteri)	10	7.32	1.4	4	2.61	1.5	3	2.42	1.2	0	0.32		17	12.67	1.3
172 (corpus uteri)	5	4.88	1.0	2	2.71	0.7	3	3.63	0.8	2	0.61	3.3	12	11.83	1.0
175 (ovary)	3	5.27	0.6	1	2.88	0.4	2	3.93	0.5	1	0.63	1.6	7	12.71	0.6
180† (kidney)	1	1.20	0.9	2	0.92	2.2	1	1.15	0.9	0	0.17		4	3.44	1.2
180† (renal pelvis)	0	0.37		0	0.05		0	0.12		0	0.01		0	0.55	
181 (bladder)	1	1.71	0.6	0	0.96		1	1.03	1.0	0	0.08		2	3.78	0.5
190 (melanoma)	2	3.02	0.7	1	1.90	0.5	3	1.92	1.6	0	0.27		6	7.11	0.8
191 (other skin)	6	8.03	0.8	1	0.79	1.3	0	0.68		0	0.08		7	9.58	0.7
193 (brain)	2	2.58	0.8	2	1.26	1.6	1	2.03	0.5	0	0.39		5	6.26	0.8
194 (thyroid)	0	0.46		0	0.59		1	0.81	1.2	0	0.23		1	2.19	0.5
196 (bone)	0	0.08		0	0.05		0	0.09		0	0.01		0	0.23	
197 (connective tissue)	0	0.22		0	0.19		0	0.32		0	0.06		0	0.79	
199 (other and unspecified)	0	0.50		0	1.34		2	2.07	1.0	0	1.11		2	4.02	0.5
200, 202 (non-Hodgkin's lymphoma)	1	1.31	0.8	1	1.02	1.0	0	1.11		0	0.18		2	3.62	0.6
201 (Hodgkin's disease)	0	0.41		0	0.15		0	0.23		0	0.05		0	0.85	
203 (multiple myeloma)	0	0.52		0	0.56		2	0.50	4.0	0	0.07		0	1.65	
204 (leukemia)	2	1.32	1.5	0	0.63		0	0.88		0	0.16		2	2.99	0.7
Acute myeloid leukemia	0	0.57		0	0.26		0	0.33		0	0.1		0	1.23	0.1-2.4
Chronic lymphatic leukemia	2	0.34	5.9	0	0.14		0	0.24		0	0.0		2	0.75	2.7
All other leukemia	0	0.41		0	0.23		0	0.33		0	0.1		0	1.04	0.3-9.6
140-205 (all malignant neoplasms)	75	81.43	0.9	42	41.25	1.0	53	51.76	1.0	9	8.21	1.1	179	182.65	1.0
															0.8-1.1

\* ICD-7, International Classification of Diseases, Seventh Revision; SIR, standardized incidence ratio; CI, confidence interval.

† In Norway and Denmark, ureter included in ICD-7 code 181 (bladder); in Sweden and Finland, ureter and urethra included in ICD-7 code 181 (bladder).



observed deaths vs. 3.6 expected (55)). Likewise, the risk of leukemia was not increased in the present Nordic cohort (28 deaths observed vs. 32.15 expected).

Two Swedish case-control studies found an excess risk of acute myeloid leukemia following exposure to gasoline (56, 57), but a third study (58) with small numbers found no association between acute leukemia and work as a service station worker. An excess of acute myeloid leukemia has previously been found in the cohort of male Swedish service station workers (occupational code 338) during the period 1971–1984 based on 10 observed and 2.8 expected cases (19). In the present study, only Swedish service station workers in fuel retailing were included, and the cohort was followed for 6 more years, resulting in eight observed cases of acute myeloid leukemia (six cases in 1971–1984 and two in 1985–1989) versus 3.9 expected. However, this observation was not supported by the data from the other Nordic countries, where a total of five acute myeloid leukemia cases were observed versus 6.54 expected.

The work practice among service station workers in 1970 probably did not differ among the Nordic countries. Further studies on acute myeloid leukemia and gasoline exposure should, to be informative, include persons with gasoline exposure above the level for Nordic service station workers in 1970.

### Kidney and renal pelvis cancer

Renal cell carcinoma was found in male rats exposed to unleaded gasoline vapor containing trimethylpentane (59, 60). However, the epidemiologic data refer to the era of leaded gasoline with a low content of trimethylpentane. An association between kidney cancer and exposure to gasoline (50, 51, 61, 62) or aviation gasoline (63) has been suggested in some studies but not in all (64). A recent international case-control study of renal cell carcinoma showed a relative risk of 1.6 (95 percent CI 1.2–2.0) for exposure to gasoline accounted for mainly by concomitant exposure to other petroleum products (65). No death from kidney cancer was observed versus 2.4 expected in a recent cohort study of service station attendants from Italy (55). The present study showed a slightly elevated risk of kidney cancer, with a standardized incidence ratio of 1.3 (95 percent CI 1.0–1.7) for men and women. In a Finnish case-control study (62), persons with high exposure to gasoline had a sevenfold risk of renal cell carcinoma, and it is possible that the slight excess risk of kidney cancer in the present cohort came from a subgroup with high exposure. Smoking is a risk factor for kidney cancer (66), but with the available data on smoking habits and no marked excess risk of

lung cancer, smoking is unlikely to explain the slightly elevated kidney cancer risk among the service station workers. To shed further light on this question, a nested case-control study in the cohort would be needed.

The doubled risk of renal pelvis cancer among men in the present study was based on small numbers with no cases among women. A previous case-control study of renal pelvis cancer in Denmark found a relative risk of 5.6 among persons exposed to vapors in the chemical, petrochemical, or plastic industries or from exposure to gasoline or petroleum products (67).

### Cancer of the nose, pharynx, larynx, and lung

The 3.5-fold risk of nasal cancer among the service station workers (observed = 12, expected = 3.45, SIR = 3.5, 95 percent CI 1.8–6.1) is not likely to be a chance finding as it appears across four countries and both sexes.

A large number of person-years is needed before a possible excess risk of nasal cancer is observed, and data on nasal cancer have not been tabulated in the previous studies of service station workers (54, 55) or distribution workers (50, 51, 53). Only two case-control studies on nasal cancer report data related to gasoline exposure. The relative risks were 0.71 for exposure to "petroleum products" in a study from the United States (68) and 0.7 for occupation as "dealers in asphalt, oil, or other petroleum substances" in a study from Japan (69). Only one death from nasal cancer was found among gas station/garage owners and attendants from Washington State in 1950–1979 (70), none was found among petrol pump forecourt attendants in the United Kingdom around 1980 (71), and no elevation in nasal cancer was found in petrol pump attendants in the United Kingdom around 1990 (72).

The excess risk of nasal cancer among service station attendants in the Nordic countries thus raises a flag that should be heeded in future studies of gasoline-exposed persons.

Given this excess risk of nasal cancer, it is interesting that somewhat elevated risks were found also for pharyngeal, laryngeal, and lung cancer, with standardized incidence ratios of 1.6, 1.4, and 1.2, respectively, when the data for men and women were combined. Data on pharyngeal cancer have not been tabulated in the previous cohort studies (50, 51, 53–55). Mortality from laryngeal cancer was slightly elevated (standardized mortality ratio = 1.4) among distribution workers in the United Kingdom (51) but not among gasoline service station workers in New Hampshire (54) and Italy (55), and data on this cancer were not reported for the two remaining cohorts (49, 53).

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The 20 percent elevated risk of lung cancer in the Nordic cohort originates mainly from the Danish men, where the risk was elevated by 60 percent. Only marginally increased risks were seen in the other Nordic countries, and the mortality from lung cancer was not elevated in the other cohorts of service station workers (54, 55) or distribution workers (50, 51, 53).

## Conclusion

This cohort of 19,000 persons exposed to gasoline vapors with an estimated, average level of exposure to benzene below  $1 \text{ mg/m}^3$  showed no excess risk of leukemia or specifically of acute myeloid leukemia. Further studies on leukemia and gasoline exposure should, to be informative, include persons with exposure above the level of Nordic service station workers in 1970. The Nordic service station workers had a 30 percent elevated risk of kidney cancer. The risks for pharyngeal, laryngeal, and lung cancer were elevated by 60 percent, 40 percent, and 20 percent, respectively. Although moderate, these excesses are noteworthy because this large cohort of Nordic service station workers also revealed a previously unnoticed 3.5-fold excess risk of nasal cancer in gasoline-exposed persons. This topic should be given attention in future studies.

## ACKNOWLEDGMENTS

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