Lymphohematopoietic Malignancies and Oil Exploitation in Koprivnica–Krizevci County, Croatia

DAVORKA GAZDEK, MD, MSC, MARIJA STRNAD, MD, PHD, JADRANKA MUSTAJBEGOVIC, MD, PHD, ZLATKA NEMET-LOJAN, MD

To determine lymphohematopoietic malignancy incidence rates between populations living near oil–gas fields (two regions) compared with those living in areas free from oil-gas exploitation (one region) in Koprivnica–Krizevci County, Croatia, 803 new cases of lymphohematopoietic malignancies were studied for two time periods: 1971–1980 (prior to oil–gas exploitation) and 1981–2000 (during oil–gas exploitation). The results showed considerable geographic differences in the incidences of chronic myeloid leukemia and multiple myeloma. The authors conclude that proximity to oil or gas fields represents an increased population risk of developing lymphohematopoietic cancers. *Key words*: crude oil; natural gas; hematopoietic malignancies; leukemia; lymphoma; Croatia.

INT J OCCUP ENVIRON HEALTH 2007;13:258–267

The oldest and largest crude oil and natural gas field in Croatia is in Koprivnica–Krizevci County (Figure 1). Although gas and oil deposits were discovered in 1960s, major exploitation (drilling, extracting, and hydrocarbon production) started in February 1981.[1,2] There are 90 production wells in the county, half of which are in the Djurdjevac region, and the other half in the Koprivnica region (Figure 2; Table 1). The Djurdjevac region alone produces around 50% of Croatian gas, which is about 30% of primary source of Croatian energy.[1–3]

The oil–gas fields in Koprivnica–Krizevci County are situated at depths between 3,500 and 4,000 m, under extremely high pressure (500 bars), at temperatures of 180–200°C, and contain high concentrations of carbon dioxide (10–24%), as well as hydrogen sulfide (0.007–0.01%) and mercury (100–1500 μg/m^3).[2,3] As Figure 3 shows, production fluid is brought in from all wells to the Central Gas Treatment Plant in the Djurdjevac region for separation of the liquid phase (oil and formation water) from the gaseous phase, gas dehydration, and removal of carbon dioxide, hydrogen sulfide, and mercury. Hydrogen sulfide, partially transformed into elementary sulfur in form of sulfide mud, is partially released into atmosphere with carbon dioxide. From the Central Gas Treatment Plant to refineries, crude oil is transported by the Adriatic Oil Pipeline (JANAF).[1–3]

Drilling and extraction of crude oil and natural gas, separation, and dehydration take place in an enclosed system with only a small possibility for human exposure. However, the production process also creates harmful components such as mercury, carbon dioxide, sulfide compounds (hydrogen sulfide and mercaptene–RSH) and formation water.[2,3] In order to control and improve the efficiency of an industrial facility, a comprehensive environmental monitoring program was established (1990, 1995/1996, and annually beginning in 1999).[4] Monitoring included measurements of the main pollutants in ambient air (mercury, carbon dioxide, hydrogen sulfide, mercaptene–RSH), as well as metals such as cadmium, molybdenum, cobalt, lead,

Figure 1—Map of Croatia with Koprivnica–Krizevci County marked.

Received from the Institute of Public Health, Koprivnica–Krizevci County, Koprivnica, Croatia (DG); the Croatian National Institute of Public Health, Zagreb, Croatia (MS); the School of Public Health "Andrija Stampar," Medical Faculty University of Zagreb, Zagreb, Croatia (JM); and General Hospital "Dr. Tomislav Bardek," Koprivnica, Croatia (ZN-L).

Address correspondence and reprint requests to: Davorka Gazdek, MD, Institute of Public Health, Koprivnica–Krizevci County, Florijanski trg 4, 48 000 Koprivnica, Croatia; telephone: +385 48 221 875; fax: + 385 48 622 994; e-mail: <szjz@kc.htnet.hr>.

zinc, copper, vanadium, chrome, and barium in soil. In order to determine the level of mercury present, the National Petroleum Company constructed appropriate process units at the Central Gas Treatment Plant, which became operative in February 1992.[2,3] Mercury removal has been accomplished by the use of sulfur-impregnated activated carbon. The efficiency of mercury adsorption from gas has been found to be 89–99%.[5]

The desulfurization unit (conversion of hydrogen sulfide into elemental sulfur) at the Central Gas Treatment Plant was put into operation in the early 1990s. Until the concentration of hydrogen sulfide released at the plant outlet into the atmosphere was reduced, the mercaptene–RSH concentration remained high. Dehydration is accomplished by glycol, which absorbs benzene and other organic components.[6] This process also emits organic compounds.[7] Drilling wastes (drilling mud and formation water) are deposited into pits until wastewater spills directly into nearby streams. Geochemical and mineralogical assessments of materials from two already closed pits showed higher than normal concentrations of mercury, lead, total hydrocarbons, BTEX, and polycyclic aromatic hydrocarbons in spite of lime stabilizzation of the waste.[9] These byproducts of oil–gas exploitation represent potential problems that affect the environment and the health of local populations. Inhabitants of rural areas of Koprivnica–Krizevci County drink only well water because only towns and their surrounding areas have piped-in drinking water.[8] A special facility for treatment of liquid waste from oil–gas production is being built and will be finished in 2007.[6]

There have been few studies done on the effects of exposures to oil and gas on human health. The IARC/WHO found that carcinogenic effects of exposures to crude oil and natural gas are few, but that possible hematologic carcinogens in oil and gas, benzene being the most familiar, but also 1,3-butadiene and polycyclic aromatic hydrocarbons, might be related to environmentally induced cancers.[10] Most of the available research has been done on workers who have had contact with benzene during production, processing, or transport.[11–16] Those studies show that exposure to benzene increases the risk for developing myeloid leukemia, especially acute myeloid leukemia, while relationships with other subtypes of lymphohematopoietic malignancies are questionable. Only a few studies mention the effect of proximity to oil fields on the emergence of cancer in general populations. Most of these studies show that living near oil fields increases the risk for developing lymphohematopoietic malignancies, and particularly myeloid leukemia.[11,17–19]

Figure 2—Map of Koprivnica–Krizevci County with Djurdjevac, Koprivnica, and Krizevci regions marked, as well as oil fields (vertical lines), gas fields (horizontal lines), and Central Gas Treatment Plant (CGP).

TABLE 1 Oil–Gas Fields in Koprivnica–Krizevci County, Croatia

	Year Beginning Exploitation	Number of Wells (12/31/01)	Production in 2001		
			Oil (t)	Gas (1,000m^3)	Condensate (t)
Djurdjevac					
Field 1	1981	19 gas		987,402	48,475
Field 2	1985	13 gas		375,847	127,600
Field 3	1987	4 gas		827	
Field 4	1970	7 (3 gas + 4 oil)	3,387	4,480	
Total		43	3,387	1,368,556	176,075
Koprivnica					
Field 5	1966	19 (18 oil+1 gas)	10,691	3,216	
Field 6	1971	6 oil	870		
Field 7	1987	3 gas		15,657	150
Field 7	2000	2 gas		154,565	21,876
Field 8	1988	1 gas		954	
Field 9	1985	6 gas		19,091	666
Total		37	11,561	193,483	22,692

*Oil–gas fields (see Figure 2).

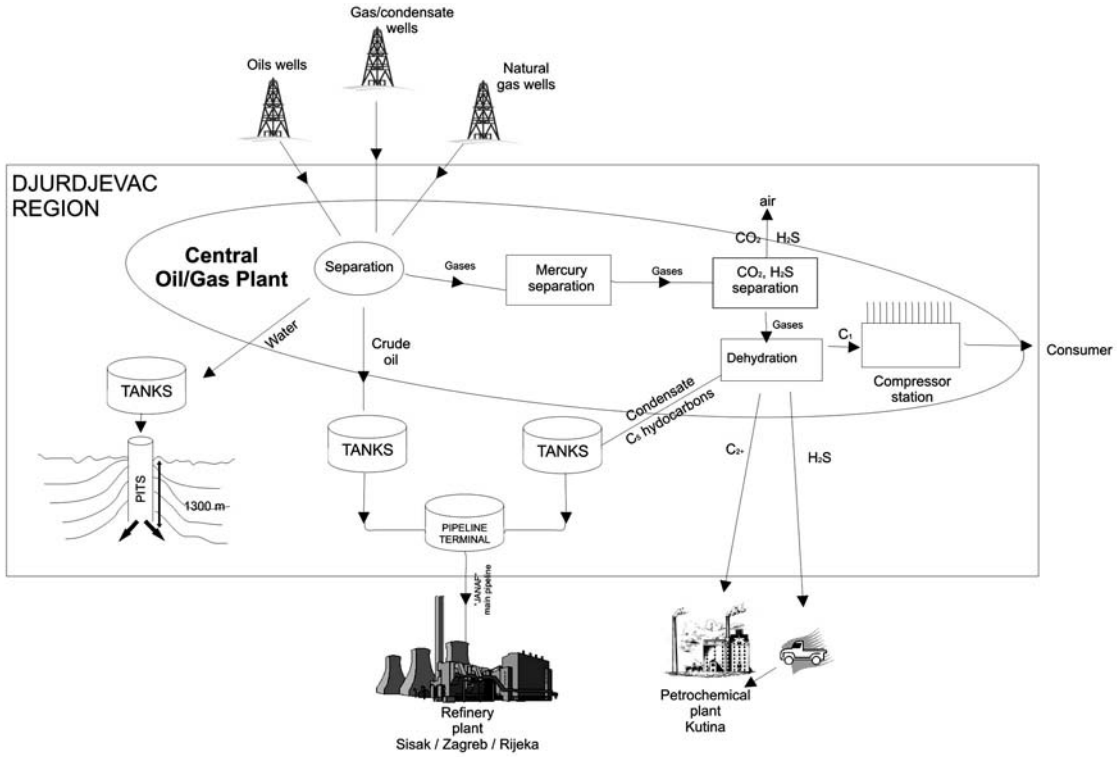

Figure 3—Oil-gas recovery from wells, Koprivnica-Krizevci County.

The effect of natural gas and crude oil exploitation on the population's health in Koprivnica–Krizevci County had not previously been studied, the exception being the study of mercury levels in urine of workers in oil and gas facilities, inhabitants of a village in the Djurdjevac region and a village in the Krizevci region. The results of that research indicated that the mercury levels were within normal limits, but also that the inhabitants of the village in the Krizevci region had lower levels of mercury than did those in the Djurdjevac region.[20]

The objective of this study was to determine whether there were any differences in incidence rates of lymphohematopoietic malignancies, all cases of leukemia, Hodgkin's and non-Hodgkin's lymphomas, multiple myeloma, acute and chronic lymphoid leukemia, and acute and chronic myeloid leukemia between populations living in the proximity of oil–gas fields and those living in region free from oil–gas exploitation in Koprivnica–Krizevci County.

METHODS

Study Area

Koprivnica–Krizevci County is situated in the north of Croatia, on the border with Hungary (Figure 1). According to the 2001 Census, there are 124,467 inhabitants in the County. It consists of three regions: Djurdjevac, Koprivnica and Krizevci. The Djurdjevac region covers an area of 509.41 km^2 and has 27,063 inhabitants, the Koprivnica region covers an area of 742.90 km^2, with 60,669 inhabitants, and the Krizevci region covers an area of 494.09 km^2 and has 36,735 inhabitants. There are three main towns, with 50% of the County population.[8] Piped-in drinking water is supplied to the town areas, while the rural population has wells. The main industries are food and pharmaceutical manufacturers (Koprivnica), as well as the petroleum industry (Djurdjevac). Most people work in trade (56%), service (11%), and industry (8%). Only 5% of the people are agricultural workers, with small family farms (average 0.16–0.24 ha). Because the food industry has been active in the area for 60 years, and the petroleum industry for more than 35 years, the county belongs among the most developed counties in Croatia, with equal and free medical care for all inhabitants. Each region has health centers. A general hospital, with approximately 400 beds, is situated in Koprivnica, about 30 km from other towns, and has existed for more than a hundred years. The hospital offers histopathology and has access to chemotherapy.[21]

Data Collection

Data for determining the incidences of lymphohematopoietic malignancies for the three regions were obtained from the Croatian Cancer Registry of the Croatian National Institute of Public Health in Zagreb.

The Croatian Cancer Registry has compiled cancer incidence and mortality data since 1959 from population-based cancer registries in the whole of Croatia. Electronic data processing was introduced in 1968. Under the Statistical Research Program promulgated by the Parliament, the data are routinely collected from hospitals and inpatient reports, reports of cancer mortalities, and histology and cytology reports. Histopathologic confirmation of the diagnoses is available for 97% of lymphoma cases and more than 70% of leukemia cases. Only less than 6% of lymphohematopoietic malignancies are registered on death certificates. The cancer data include personal identification, gender, age at diagnosis, cancer site, histology, year of diagnoses, residence and education.[22] The National Cancer Registry has been affiliated with the IARC since 1994, and the first published cancer-incidence data relate to the 1993–97 period.[23]

Lymphohematopoietic cancer data are classified according to the Ninth Revision of the International Classification of Diseases (ICD-9)[24] and are categorized according to the latest World Health Organization classification of pathologic and genetic features of tumors of the hematopoietic and lymphoid tissues[25]: lymphohematopoietic malignancies (total 200–208 and polycythemia vera 238.4 and idiopathic myelofibrosis 289.8), acute lymphoid leukemia (204.0), chronic lymphoid leukemia (204.1, and hairy-cell leukemia 202.4), acute myeloid leukemia (205.0, 205.3, 206.0, 207.0, and 207.2), chronic myeloid leukemia (205.1), all types of leukemia (204–208 and 202.4), multiple myeloma (203), Hodgkin's lymphoma (201), non-Hodgkin's lymphoma (200 and 202 except 202.4).

Statistical Analysis

New cases of subtype-specific lymphohematopoietic malignancies were accumulated by sex and divided into five-year age groups (0–4, 5–9, up to 70-74, 75+) for the Djurdjevac, Koprivnica, and Krizevci regions, respectively, for two time periods: 1971–1980 (the period prior to oil–gas exploitation) and 1981–2000 (the period of full oil–gas exploitation). Incidence rates are expressed as new cases per 100,000 person-years and then directly age-standardized to European standard populations.[26] Populations at risk were obtained by mid-period population censuses (1971, 1981, 1991, and 2001) obtained from the Central Croatian Bureau of Statistics.[8]

Relative risks along with 95% confidence intervals (CIs) were calculated as standardized rate ratios (SRRs) for all regions both prior to oil–gas exploitation (1971–1980) and during oil–gas exploitation (1981–2000).

In addition to those measures, research also compared age-standardized rates between the different regions for the period of full oil–gas exploitation (1981–2000). Statistically significant differences were registered as 95% CI of SRR in the studied time periods. The incidence rates in the Krizevci region were used for reference because this area does not have any oil or gas wells.

RESULTS

From 1971 to 2000 there were 803 new cases of lymphohematopoietic malignancies registered with the Croatian Cancer Registry. Those new cases had permanent residence in Koprivnica–Krizevci County, with 212 being registered in the Djurdjevac region, 358 in the Koprivnica region, and 233 in the Krizevci region, which does not have any oil or gas wells.

Table 2 shows the incidence rates of total and individual types of lymphohematopoietic malignancies in each region for the two time periods (1971–1980 and 1981–2000). It also shows grouped data of the exposed regions for the two time periods. All three regions showed increases in total lymphohematopoietic malignancies and all subtypes of lymphohematopoietic malignancies, except non-Hodgkin's lymphoma. A decrease was seen only in the Djurdjevac region in the second time period, which is marked by oil–gas exploitation. In all three regions there were statistically significant increases in total lymphohematopoietic malignancies, total leukemias, and chronic lymphoid leukemias. Furthermore, in the Djurdjevac region there was a significant ninefold increase of chronic myeloid leukemia. In the Koprivnica region acute lymphoid leukemias rose fivefold, whereas acute myeloid leukemia increased fourfold. Group data analysis of data from the exposed regions for the two time periods also showed significant increases of all lymphohematopoietic malignancies except Hodgkin's lymphoma.

Increased incidences for all lymphohematopoietic malignancies and all leukemias by age were observed in both men and women for all studied regions for the period 1981–2000, the period of full oil–gas exploitation (Figures 4 and 5).

The incidences of lymphohematopoietic malignancies in particular regions for the time period of full oil–gas exploitation (1981–2000) are shown in Table 3. Incidence rates of total leukemia, acute and chronic myeloid leukemia, chronic lymphoid leukemia, and multiple myeloma were higher in the Djurdjevac and Koprivnica regions than in the Krizevci region. Differences in the incidence rates of chronic myeloid leukemia were statistically significant, with the highest in the Djurdjevac region, and the lowest in the Krizevci region. Furthermore, significantly elevated relative risks were observed for chronic myeloid leukemia and multiple myeloma for grouped data from the exposed regions, while data analysis for the period 1971–1980 do not show a statistically significant difference for any lymphohematopoietic cancer.

TABLE 2 Incidences and Age-standardized Rates of Lymphohematopoietic Malignancies by Sex, Type, Regions

	Djurdjevac + Koprivnica					Djurdjevac				
	1971–1980		1981–2000		Rate Ratio	1971–1980		1981–2000		Rate Ratio
	Cases	ASR	Cases	ASR	(95%CI)	Cases	ASR	Cases	ASR	(CI)
HL										
Pooled	18	1.7	45	2.4	1.4 (0.86–2.44)	9	2.2	20	3.4	1,6 (0.73–3.35)
Male	9	1.8	17	1.9	1.1 (0.48–2.38)	6	1.4	5	1.8	0.6 (0.16–1.96)
Female	9	1.6	28	3.0	1.8 (0.92–3.72)	3	2.2	15	5.2	3.7 (1.24–10.67)
NHL										
Pooled	34	3.4	103	4.9	1.5 (1.02–2.11)	18	4.8	30	4.5	0.9 (0.51–1.70)
Male	20	4.4	51	5.6	1.3 (0.78–2.10)	13	7.8	14	5.0	0.6 (0.29–1.42)
Female	14	2.5	52	4.1	1.6 (0.94–2.82)	5	2.7	16	3.7	1.4 (0.53–3.68)
MM										
Pooled	21	2.0	69	3.2	1.6 (1.01–2.47)	9	2.6	25	3.3	1.3 (0.60–2.63)
Male	7	1.7	38	4.1	2.4 (1.22–4.66)	3	2.0	17	5.6	2.8 (1.01–7.62)
Female	14	2.3	31	2.4	1.0 (0.53–1.93)	6	3.3	8	1.6	0.5 (0.14–1.71)
ALL										
Pooled	6	0.6	25	1.5	2.5 (1.14–5.58)	4	1.3	7	1.5	1.2 (0.36–4.13)
Male	5	1.1	17	2.2	2.0 (0.81–4.91)	3	2.0	5	2,2	1.1 (0.26–4.55)
Female	1	0.2	8	0.9	4.3 (0.84–22.36)	1	0.6	2	0.9	1.5 (0.14–14.64)
CLL										
Pooled	12	1.2	77	3.4	2.9 (1.86–4.60)	5	1.3	30	3.7	2.9 (1.32–6.22)
Male	10	2.3	38	4.3	1.9 (1.00–3.49)	4	2.6	17	5.7	2.2 (0.84–5.59)
Female	2	0.4	39	2.9	8.3 (3.39–10.09)	1	0.3	13	2.6	8.7 (1.81–32–54)
AML										
Pooled	6	0.6	33	1.6	2.7 (1.28–5.55)	3	0.9	11	1.6	1.8 (0.56–5.63)
Male	3	0.6	14	1.6	2.7 (0.92–7.66)	1	0.6	5	1.8	3.0 (0.49–18.30)
Female	3	0.6	19	1.6	2.6 (0.95–6.94)	2	1.1	6	1.3	1.2 (0.23–5.61)
CML										
Pooled	8	0.7	39	1.9	2.7 (1.41–5.05)	1	0.2	15	2.1	9.7 (2.38–39.78)
Male	4	0.8	20	2.2	2.8 (1.15–6.91)	0	—	7	2.4	—
Female	4	0.7	19	1.7	2.4 (0.93–6.15)	1	0.4	8	1.8	4.5 (0.89–26.87)
All leukemias										
Pooled	46	4.5	219	10.5	2.3 (1.76–3.05)	19	5.6	77	10.8	1.9 (1.23–3.03)
Male	32	7.1	117	13.4	1.9 (1.34–2.70)	13	8.6	42	14.8	1.7 (0.98–3.06)
Female	14	2.5	102	8.4	3.4 (2.17–5.32)	6	2.9	35	7.8	1.4 (1.20–5.06)
All lymphohemato–poietic malignancies										
Pooled	124	12.0	446	21.4	1.8 (1.49–2.13)	57	15.8	155	22.4	1.4 (1.06–1.91)
Male	71	15.6	230	25.9	1.7 (1.30–2.12)	36	22.1	81	28.3	1.3 (0.87–1.88)
Female	53	9.3	216	18.0	1.9 (1.47–2.53)	21	10.9	74	18.4	1.7 (1.07–2.67)

ASR = age-standardized incidence rate per 100,000 person-years relative to Europe standard population; rate ratio between 1980–2000 and 1971–1980; CI = 95% confidence interval. HL = Hodgkin's lymphoma; NHL = non-Hodgkin's lymphoma; MM = multiple myeloma, ALL = acute lymphoid leukemia; CLL = chronic lymphoid leukemia; AML = acute myeloid leukemia; CML = chronic myeloid leukemia.

and Periods (Ages: 0–75 Years)

Koprivnica					Krizevci				
1971–1980		1981–2000		Rate Ratio	1971–1980		1981–2000		Rate Ratio
Cases	ASR	Cases	ASR	(95%CI)	Cases	ASR	Cases	ASR	(CI)
9	1.3	25	2.0	1.5 (0.71–2.98)	11	2.5	20	2.5	1.0 (0.47–2.05)
3	1.0	12	2.0	2.0 (0.64–5.96)	6	3.0	15	4.0	1.3 (0.55–3.33)
6	1.7	13	2.0	1.2 (0.44–3.05)	5	2.2	5	1.0	0.5 (0.11–1.90)
16	2.5	73	5.2	2.1 (1.28–3.28)	14	3.3	43	4.9	1.5 (0.86–2.64)
7	2.4	37	6.0	2.5 (1.26–4.86)	10	5.8	19	5.2	0.9 (0.40–2.00)
9	2.5	36	4.3	1.7 (0.90–3.40)	4	1.6	24	4.9	3.1 (1.25–7.13)
12	1.7	44	3.1	1.8 (1.01–3.19)	5	1.2	17	1.9	1.7 (0.68–4.17)
4	1.6	21	3.4	2.1 (0.85–5.18)	0	—	9	2.5	—
8	1.9	23	2.7	1.4 (0.67–3.10)	5	2.1	8	1.4	0.7 (0.21–2.33)
2	0.3	18	1.6	5.5 (1.78–16.70)	5	1.2	16	2.3	2.0 (0.81–5.05)
2	0.6	12	2.2	3.7 (1.01–11.52)	4	1.8	10	2.9	1.6 (0.54–4.81)
0	—	6	0.9	—	1	0.4	6	1.6	4.0 (0.69–23.55)
7	1.1	47	3.2	3.0 (1.61–5.63)	4	0.8	21	2.4	2.9 (1.18–6.98)
6	2.1	21	3.6	1.7 (0.75–3.93)	2	1.0	12	3.3	3.3 (0.99–11.27)
1	0.3	26	3.0	10.0 (2.92–26.91)	2	0.7	9	1.8	2.6 (0.67–9.38)
3	0.4	22	1.6	4.0 (1.38–9.01)	3	0.7	10	1.3	1.9 (0.58–6.08)
2	0.6	9	1.5	2.5 (0.66–9.22)	1	0.5	3	1.0	2.0 (0.25–15.57)
1	0.4	13	1.7	4.3 (1.23–19.37)	2	0.7	7	1.3	1.6 (0.41–7.08)
7	1.0	24	1.8	1.9 (0.86–3.97)	2	0.5	5	0.6	1.3 (0.26–6.15)
4	1.2	13	2.1	1.8 (0.63–4.83)	1	0.4	3	0.7	1.8 (0.22–13.97)
3	0.8	11	1.6	2.0 (0.59–5.94)	1	0.5	2	0.4	1.8 (0.07–9.95)
27	4.0	142	10.3	2.6 (1.82–3.63)	17	3.9	72	8.9	2.3 (1.46–3.68)
19	6.3	75	12.6	2.0 (1.28–3.12)	10	4.8	38	10.6	2.2 (1.18–4.07)
8	2.2	67	8.6	3.9 (2.22–6.87)	7	2.9	34	7.2	2.5 (1.24–4.05)
67	10.0	291	20.9	2.1 (1.65–2.63)	57	13.1	176	21.0	1.6 (1.21–2.11)
35	12.1	149	24.7	2.0 (1.48–2.82)	29	15.1	95	26.2	1.7 (1.19–2.55)
32	8.6	142	17.9	2.1 (1.49–2.93)	28	12.0	81	16.8	1.4 (0.92–2.10)

TABLE 3 Age-standardized Rates of Lymphohematopoietic Malignancies by Type and Regions, 1981-2000 (Ages:

	All Lymphohematopoietic Malignancies		Hodgkin's Lymphoma		Non-Hodgkin's Lymphoma		Multiple Myeloma	
	ASR	Rate Ratio (CI)	ASR	Rate Ratio (CI)	ASR	Rate Ratio (CI)	ASR	Rate Ratio (CI)
Krizevci	21.0	1.0 (referent)	2.5	1,0 (referent)	4.9	1.0 (referent)	1.9	1.0 (referent)
Koprivnica	20.9	1.0 (0.82–1.20)	2.0	0.8 (0.43–1.44)	5.2	1.1 (0.72–1.54)	3.1	1.6 (0.93–2.69)
Djurdjevac	22.4	1.1 (0.86–1.33)	3.4	1.4 (0.73–2.62)	4.5	0.9 (0.57–1.46)	3.3	1.7 (0.91–3.20)
Djurdjevac + Koprivnica	21.4	1.0 (0.85–1.21)	2.4	1.0 (0.57–1.65)	4.9	1.0 (0.70–1.43)	3.2	1.6 (1.01–2.63)

ASR = age-standardized incidence rate per 100,000 person-years relative to Europe standard population; CI = 95% confidence interval.

DISCUSSION

The aim of this study was to assess possible effects of exposures to crude oil and natural gas exploitation on the occurrence of lymphohematopoietic malignancies in certain regions of Koprivnica–Krizevci County. The results showed considerable increases in the incidences of chronic myeloid leukemia and multiple myeloma. Some epidemiologic studies have shown associations of the same types of lymphohematopoietic malignancies with exposures to benzene, crude oil, or petroleum refinery waste dumps.[11,15,27–29]

Crude oil and natural gas are mixtures of many chemical compounds, mostly hydrocarbons, but also metals, nitrogen, and oxygen and sulfide compounds.[10] Benzene can be found during the crude oil and natural gas production.[7,30,31] Although the presence of benzene or other organic pollutants in the vicinity of oil–gas fields in Koprivnica–Krizevci County has not been demonstrated (a reason could be politics of the National Petroleum Company as well as the Government[32]), geochemical and mineralogic assessments showed higher than normal concentrations of lead, mercury, total hydrocarbons, BTEX, and polycyclic

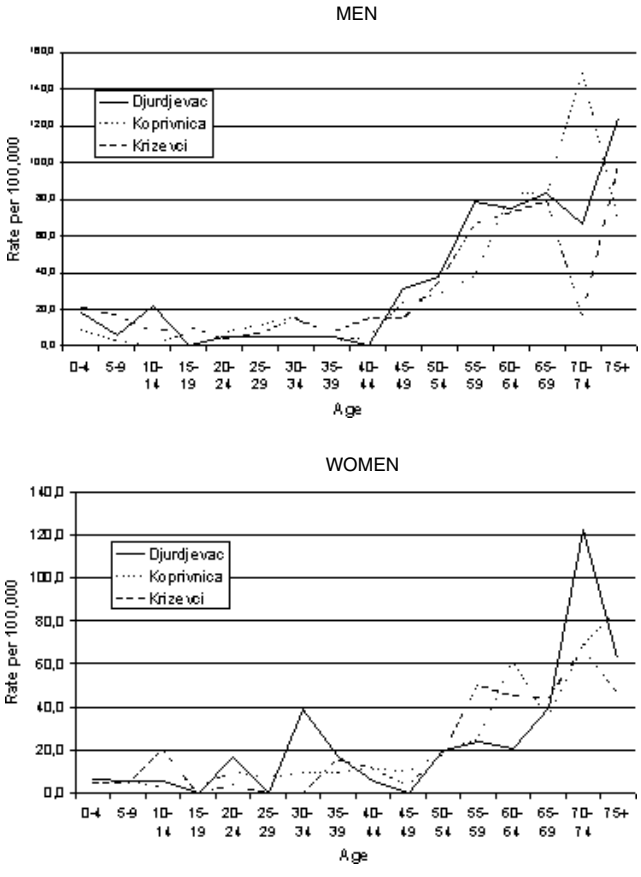

Figure 4—Total lymphohematopoietic malignancies, incidences in regions by age group for men and women, 1981–2000.

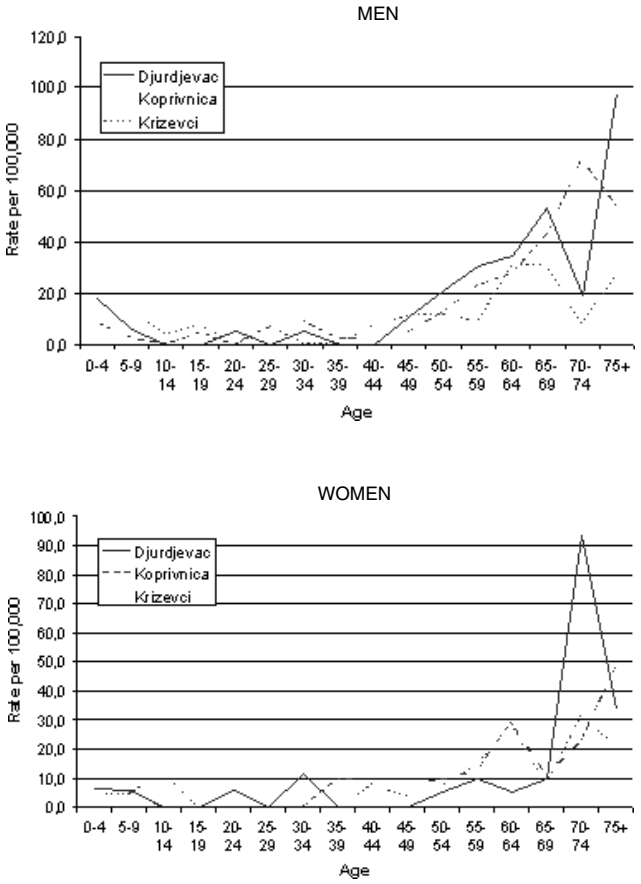

Figure 5—Total leukemia incidences in regions by age group in men and women, 1981–2000.

0–75 Years, Sexes Combined)

All Leukemias		Acute Lymphoid Leukemia		Chronic Lymphoid Leukemia		Acute Myeloid Leukemia		Chronic Myeloid Leukemia	
ASR	Rate Ratio (CI)	ASR	Rate Ratio (CI)	ASR	Rate Ratio (CI)	ASR	Rate Ratio (CI)	ASR	Rate Ratio (CI)
8.9	1.0 (referent)	2.3	1.0 (referent)	2.4	1.0 (referent)	1.3	1.0 (referent)	0.6	1,0 (referent)
10.3	1.2 (0.87–1.53)	1.5	0.7 (0.33–1.36)	3.2	1.3 (0.82–2.16)	1.6	1.2 (0.59–2.59)	1.8	3.0 (1.40–7.33)
10.8	1.2 (0.87–1.69)	1.6	0.7 (0.28–1.56)	3.7	1.5 (0.88–2.73)	1.6	1.2 (0.53–3.08)	2.1	3.5 (1.32–10.08)
10.5	1.2 (0.91–1.53)	1.5	0.7 (0.33–1.32)	3.4	1.4 (0.93–2.18)	1.6	1.3 (0.63–2.51)	1.9	3.4 (1.65–6.87)

aromatic hydrocarbons in materials from two already closed pits, in spite of lime stabilization of the waste from the petroleum industry.[9] Benzene is the most familiar leukemogen,[10] as well as 1,3-butadiene in the tire-manufacturing industry,[33] but not in petrochemical industry,[34] although exposures to polycyclic aromatic hydrocarbons might be related to leukemias in children[35] and esophageal, pancreatic, prostate, and lung cancers in adults.[36] Exposure to benzene from oil and gas fields can occur through fume inhalation or dermal contact or by drinking water contaminated by oil.[10] It is possible to contaminate the environment and people during oil and gas exploitation by exposures to large quantities of drill mud and liquid waste. Such liquid waste, together with drill mud, contains hydrocarbons and nitrogenous and sulfide compounds, as well as various metals. This waste can penetrate the surrounding soil and water, causing contamination,[10] as evidenced by research that connects cancer increases in populations living near oil fields with drinking water contaminated with oil substances.[19]

In Koprivnica–Krizevci County, drilling wastes (drilling mud and formation water) are deposited into pits, and waterwaste is spilled directly into nearby streams. Construction of a facility for treatment of liquid waste from oil–gas production will be completed in 2007.[6] Inhabitants of rural areas in the Djurdjevac and Koprivnica regions (where the oil–gas operations are situated) drink only well water because only towns and their surrounding areas have piped-in drinking water.[21]

There have been few studies of residents living near oil fields or petrochemical industries. It has been shown that living near oil fields increases the risk for total cancers as well as cancers of the stomach, rectum, skin (melanoma) and kidney.[18] An increase in hematopoietic cancers in children less than 10 years old was also found.[18] By contrast, a study from China did not find an association between residential petrochemical exposures and leukemia risk in children.[37] However, residential petrochemical exposure was a significant risk factor for leukemia for the older age group.[37] Our study showed a higher incidence rate of leukemias in children less than 10 in the unexposed region and higher incidence rates of leukemias in adults in the exposed regions.

Although our study showed the strongest associations between residential oil–gas exploitation exposures and chronic myeloid leukemia, as well as multiple myeloma, we could not ignore the fact that except for Hodgkin's lymphoma, all lymphohematopoietic cancers had occurred more frequently in the exposed regions since the beginning of full oil–gas exploitation. All those cancers are associated with exposures to benzene or benzene-related industry.[16,38–40]

Our data suggested that long exposure to oil–gas exploitation elevates the risks for chronic myeloid leukemia and multiple myeloma. Most research done on oil and gas field workers indicates that the risk of getting myeloid leukemia, especially acute myeloid leukemia, is higher among workers who have worked in the fields for more than 30 years.[11,13,14] Although there are no data on concentrations of hydrocarbons or benzene for the County, some studies have confirmed the presence of benzene in crude petroleum production or waste,[7,9,30,31] while others suggest that concentrations of benzene in oil increase the occurrence of leukemia from 0.01 to 1%.[10] The higher the concentration and duration of benzene exposure, the greater the risk of leukemia.[12,41]

Also, studies have been done on air pollution, water, soil, and vegetation used for human and animal consumption, as well as forest vegetation, in Koprivnica–Krizevci County from 1990, 1995/1996 and every year since 1999.[4] Those studies have monitored sulfide compounds (especially mercaptene-RSH and hydrogen sulfide) and levels of mercury, nitrate and nitrite, which were occasionally found to be higher than legally allowed, while levels of cadmium, molybdenum, cobalt, lead, zinc, copper, vanadium, chrome, and barium were below the legal maximums. Radioactive levels of uranium, radium, thorium, caesium, and natural potassium showed normal yearly variations. Although it is well known that some of the above-mentioned metals and compounds are carcinogenic,[42–44] no connection with hematopoietic malignancies was found in literature, nor were their effects on certain subtypes of lymphohematopoietic malignancies in Koprivnica–Krizevci County evident.

During more than 30 years of crude oil and natural gas exploitation in Koprivnica–Krizevci County, there have been a few changes in production processes that could have had adverse effects on the environment and people's health. The most important of these changes was the installation of a mercury-absorption machine and a machine for desulfurization.[2,3] Those changes in production were done in order to decrease emissions of mercury and sulfuric compounds, which are not related to lymphohematopoietic malignancies.[43,45–47]

The major limitation of the present study is that it was ecological. While reliable estimates of presumed exposures were available for the regions included, individual burdens through internal and external exposures were not considered. However, other ecological factors that need to be considered are other sources of benzene, which is mostly associated with lymphohematopoietic malignancies. Motor vehicle exhaust and tobacco smoke are other main sources of benzene. Information from the Central Croatian Bureau of Statistics showed that every second resident of Koprivnica–Krizevci County has a vehicle, and there are no differences between regions.[8,21] The latest smoking research (2003) showed that 28% (ratio between men and women is 1:1) in Koprivnica–Krizevci County were smokers, which is 1% more than the Croatian average. Also, differences in smoking habits between regions were not found.[48]

Our findings indicate evidence of a causative relationship between exposures to oil–gas exploitation and increased incidences of chronic myeloid leukemia and multiple myeloma. Considering this is the first study of effects of oil and natural gas exploration on people's health in Croatia and Koprivnica–Krizevci County, further research may be useful to confirm our observations.

References

1. Karasalihovic D, Maurovic L, Sunjerga S. Natural gas in Croatian energy future. Applied Energ. 2003;75:9-22.
2. Technical documentation, "Project Podravina." Zagreb, Croatia: INA–Naftaplin,1992.
3. Technological report of Podravina for 2005. Publication 2662-018/06. Zagreb, Croatia: INA–Naftaplin, 2006.
4. Public Health Institute of Koprivnica–Križevci County. Environment Monitoring CPS Molve 1999–2005. Summary reports. Koprivnica, Croatia: Public Health Institute of Koprivnica–Križevci County, 2001—2006.
5. Spiric Z, Horvat M. Biomonitoring in petroleum industry. The 7th International Petroleum Environmental Conference, Paris, France, 2003. <http://chem.unep.ch/mercury/report/1st-draft-comments/gov/7%20IPEC.pdf>.
6. Ferencic M. Primijenjene tehnologije u obradi prirodnog plina u cilju zastite okolisa. EGE. 2006;4:89-92. [In Croatian]
7. Verma DK, Joohnson DM, McLean JD. Benzene and total hydrocarbon exposures in the upstream petroleum oil and gas industry. Am Ind Hyg Assoc J. 2000;61:255-63.
8. Central Croatian Bureau of Statistics. Statistical Yearbook. Bulletin No.24-37. Zagreb, Croatia: Central Croatian Bureau of Statistics, 1993–2005.
9. Durn G, Gaurina-Medjimurec, Fröschl H, Meandzija I, Veronek B, Mesic S. The geochemical and mineralogical assessment of lime stabilized waste from the petroleum industry in Croatia. J Energ Resour–ASCE. 2004;126:112-8.
10. World Health Organization. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Occupational Exposures in Petroleum Refining: Crude Oil and Major Petroleum Fuels. Volume 45. Lyon, France: WHO, 1989.
11. Sathiakumar N, Delzell E, Cole P, et al. A case–control study of leukemia among petroleum workers. J Occup Environ Med. 1995;37:1267-77.
12. Glass DC, Gray CN, Jolley DJ, Gibbons C, Sim MR. The health watch case–control study of leukemia and benzene: the story so far. Ann NY Acad Sci. 2006;1976:80-9.
13. Divine BJ, Hartman CM. Update of a study of crude oil production workers 1946–94. Occup Environ Med. 2000;57:411-7.
14. Divine BJ, Hartman CM, Wendt JK. Update of the Texaco mortality study 1947–93: Part II. Analyses of specific causes of death for white men employed in refining, research, and petrochemicals. Occup Environ Med. 2000;57:143-4.
15. Lewis RJ, Schnatter AR, Katz AM, et al. Updated mortality among diverse operating segments of a petroleum company. Occup Environ Med. 2000;57:595-604.
16. Schnatter AR. Rosamilia K, Wojcik NC. Review of the literature on benzene exposure and leukemia subtypes. Chem Biol Interact. 2005;153-154:9-21.
17. Yang C, Zhang X. Incidence survey of leukemia in China. Chin Med Sci J. 1991;6:65-70.
18. Hurtig AK, San Sebastian M. Geographical differences in cancer incidence in the Amazon basin of Ecuador in relation to residence near oil fields. Int J Epidemiol. 2002;31:1021-7.
19. San Sebastian M, Armstrong B, Cordoba JA, et al. Exposures and cancer incidence near oil fields in the Amazon basin of Ecuador. Occup Environ Med. 2001;58:517-22.
20. Report on determining mercury levels in urine of workers of INA-CPS Molve and inhabitants of villages Kalnik and Molve. Zagreb, Croatia: Institute for Medical Research and Occupational Health, 2000–2005.
21. Physical plan for Koprivnica-Krizevci County. Koprivnica, Croatia: The County Institute of Physical Planning of Koprivnica–Krizevci County, 2001.
22. Cancer incidence in Croatia. Bulletin No.1-28. Zagreb, Croatia: Croatian National Institute of Public Health, 1986–2005.
23. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB (eds). Cancer Incidence in Five Continents. Volume VIII. IARC Scientific Publications No. 155. Lyon, France: IARC; 2002.
24. International Classification of Diseases, 9th Revision. Geneva, Switzerland: World Health Organization, 1977.
25. Jaffe ES, Harris NL, Stein H, Vardiman JW (eds). Pathology and Genetics of Tumors of Haematopoetic and Lymphoid Tissues. WHO Classification of Tumors. Lyon, France: IARC, 2001.
26. dos Santos Silva I. Cancer Epidemiology: Principles and Methods. Lyon, France: IARC, 1999.
27. Mehlman MA. Dangerous and cancer-causing properties of products and chemicals in the oil refining and petrochemical industries. Part XXX: Causal relationship between chronic myelogenous leukemia and benzene-containing solvents. Ann NY Acad Sci. 2006;1076:110-9.
28. Infante PF. Benzene exposure and multiple myeloma: a detailed meta-analysis of benzene cohort studies. Ann NY Acad Sci. 2006;1076:90-109.
29. Speer SA, Semenza JC, Kurosaki T, Anton-Culver H. Risk factors for acute myeloid leukemia and multiple myeloma: a combination of GIS and case–control studies. J Environ Health. 2002; 64:9-16.
30. van Wijngaarden E, Stewart PA. Critical literature review of Determinants and levels of occupational benzene exposure for United States community case–control studies. Appl Occup Environ Hyg. 2003;18:678-93.
31. Kirkeleit J, Riise T, Bratvein M, Moen BE. Benzene exposure on a crude oil production vessel. Ann Occup Hyg. 2006;50:123-9.
32. Infante PF. The past suppresion of industry knowledge of the toxicity of benzene to humans and potential bias in future benzene Research. Int J Occup Environ Health. 2006;12:268-72.
33. Cheng H, Sathiakumar N, Graff J, Matthews R, Delzell E. 1,3-Butadiene and leukemia among synthetic rubber industry workers: exposure–response relationships. Chem Biol Interact. 2006 Oct 13; [Epub ahead of print]
34. Tsai SP, Wendt JK, Ransdell JD. A mortality, morbidity, and hematology study of petrochemical employees potentially

exposed to 1,3-butadiene monomer. Chem Biol Interact. 2001:135-6:555-67.
35. Lagorio S, Forastiere F, Lipsett M, Menichini E. Air pollution from traffic and the risk of tumors. Ann Ist Super Sanita. 2000;36:311-29.
36. Nadon L, Siemiatycki J, Dewar R, Krewski D, Gerin M. Cancer risk due to occupational exposure to polycyclic aromatic hydrocarbons. Am J Ind Med. 1995;28:303-24.
37. Yu CL, Wang SF, Pan PC, et al. Residential exposure to petrochemical and the risk of leukemia: using geographic information system tools to estimate individual-level residential exposure. Am J Epidemiol. 2006;164:200-7.
38. Mehlman MA. Causal relationship between non-Hodgkin's lymphoma and exposure to benzene and benzene-containing solvents. Ann NY Acad Sci. 2006;1076:120-8.
39. Hayes RB, Songnian Y, Dosemeci M, et al. Benzene and lymphohaematopoietic malignancies in humans. Am J Ind Med. 2001;40:117-26.
40. Savitz DA, Andrews KW. Review of epidemiologic evidence on benzene and lymphatic and hematopoietic cancers. Am J Ind Med. 1997;31:287-95.
41. Hayes RB, Yin S-N, Dosemeci M, et al. Benzene and the dose-related incidence of hematologic neoplasms in China. J Natl Cancer Inst. 1997;89:1065-71.
42. Hayes RB. The carcinogenicity of metals in humans. Cancer Causes Control. 1997;8:371-85.
43. Jarup L. Hazards of heavy metal contamination. Br Med Bull. 2003;68:167-82.
44. Pyszel A, Wrobel T, Szuba A, et al. Effect of metals, benzene, pesticides and ethylene oxide on the haematopoietic system. Med Pract. 2005;56:249-55.
45. Baughman TA. Elemental mercury spills. Environ Health Perspect. 2006;114:147-52.
46. Hessel PA, Herbert FA, Melenka LS, et al. Lung health in relation to hydrogen sulfide exposure in oil and gas workers in Alberta, Canada. Am J Ind Med. 1997;31:554-7.
47. Costigan MG. Hydrogen sulfide: UK occupational exposure limits. Occup Environ Med. 2003;60:308-12.
48. Kovacic L. Gazdek D. Samardjic S. Croatian health survey—smoking. Acta Medica Croatica. 2007;61:281-5.