



## ORIGINAL CONTRIBUTIONS

### Health Effects of Dioxin Exposure: A 20-Year Mortality Study

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Follow-up of the population exposed to dioxin after the 1976 accident in Seveso, Italy, was extended to 1996. During the entire observation period, all-cause and all-cancer mortality did not increase. Fifteen years after the accident, mortality among men in high-exposure zones A (804 inhabitants) and B (5,941 inhabitants) increased from all cancers (rate ratio (RR) = 1.3, 95% confidence interval (CI): 1.0, 1.7), rectal cancer (RR = 2.4, 95% CI: 1.2, 4.6), and lung cancer (RR = 1.3, 95% CI: 1.0, 1.7), with no latency-related pattern for rectal or lung cancer. An excess of lymphohemopoietic neoplasms was found in both genders (RR = 1.7, 95% CI: 1.2, 2.5). Hodgkin's disease risk was elevated in the first 10-year observation period (RR = 4.9, 95% CI: 1.5, 16.4), whereas the highest increase for non-Hodgkin's lymphoma (RR = 2.8, 95% CI: 1.1, 7.0) and myeloid leukemia (RR = 3.8, 95% CI: 1.2, 12.5) occurred after 15 years. No soft tissue sarcoma cases were found in these zones (0.8 expected). An overall increase in diabetes was reported, notably among women (RR = 2.4, 95% CI: 1.2, 4.6). Chronic circulatory and respiratory diseases were moderately increased, suggesting a link with accident-related stressors and chemical exposure. Results support evaluation of dioxin as carcinogenic to humans and corroborate the hypotheses of its association with other health outcomes, including cardiovascular- and endocrine-related effects. *Am J Epidemiol* 2001;153:1031–44.

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**Editor's note:** An invited commentary on this paper appears on page 1045, and the authors' response is on page 1048.

The health effects associated with exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, or simply "dioxin") have not yet been fully characterized. Uncertainty exists

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Abbreviations: CI, confidence interval; RR, rate ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

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about whether the extremely potent toxicity of TCDD in experimental animals, including carcinogenicity (1, 2), also applies to humans (3). In addition, the possible risk, if any, to human health of widespread, low-level dioxin contamination of the environment has still to be assessed (4).

One relevant data source that bridges these gaps in knowledge is the study of the Seveso, Italy, industrial accident (5, 6) that exposed several thousand people to substantial quantities of TCDD. The accident took place in the summer of 1976, when the temperature and pressure surged in an improperly maintained reaction vessel in the trichlorophenol production department of a chemical plant near the town of Seveso, 25 km north of Milan; given the concomitant failure of a safety device, the contents of the reactor were vented directly into the atmosphere (7).

The level and extent of the environmental contamination were documented by dioxin soil measurements in a wide area along the direction of the prevailing winds. Three contamination zones were delimited. The most heavily contaminated was called zone A, zone B was its natural continuation along the fallout path of the chemical cloud, and zone R, with

low-level and patchy contamination, represented a gray, circular strip between the highly contaminated zones and the surrounding territory (8).

The earliest accident-related health effect was chloracne in children who were outdoors and in the path of the toxic cloud (9). In the following years, under the supervision of an international steering committee, other health outcomes possibly linked to TCDD exposure were investigated, including spontaneous abortions (10), cytogenetic abnormalities (11, 12), congenital malformations (13, 14), impaired liver function and lipid metabolism (15, 16), and immunologic (17) and neurologic (18, 19) impairment. In 1984, the committee concluded their work and stated that the only ascertained effect of dioxin exposure was chloracne but that long-term studies were needed (20).

The mortality and the cancer incidence studies we designed were implemented in 1985. Results for mortality (1976–1986 and 1976–1991 (21–23)) and for cancer incidence (1977–1986 (24)) have been published. In this paper, we report on extension of the mortality study to the end of 1996. Although other populations with known TCDD exposure have been investigated (e.g., chemical workers (25–28), pesticide manufacturers and applicators (29, 30), and Vietnam War veterans (31)), Seveso remains unique because of several characteristics, including residents' exposure to "pure" TCDD and the presence of persons of both genders and all ages in the exposed populations.

## MATERIALS AND METHODS

Methodological aspects of the mortality study have been reported in detail previously (7, 21, 32). The three contaminated zones (A, B, and R) covered parts of the territory that included two health districts encompassing 11 municipalities, with a total population of nearly 300,000. The study population was comprised of all people, both sexes and all ages, residing in on the date of the accident or entering in the 10-year period after the accident, the districts in any of the study zones or in the surrounding noncontaminated area. The population living in this latter territory was adopted as the reference group. In addition to geographic proximity, all available indicators documented the close comparability of the reference population with the exposed one in terms of environmental, social, educational, cultural, and occupational characteristics. Its size (some 250,000 subjects) was also deemed reasonably large. Nevertheless, mortality rates for the reference population were compared with those for the entire Region of Lombardy (nearly 9 million inhabitants) to evaluate their stability (21).

Exposure classification was based on the address of the residence on the date of the accident or when the person first entered the area, if later. The extent and level of soil contamination in zones A and B were measured systematically by using a tight sampling grid, whereas analyses in zone R were scanty (7). Biologic data were also available. TCDD blood levels were measured in small plasma samples, stored immediately after the accident, from subjects living in zones A, B, and R who were reportedly exposed to high levels of dioxin (33) and in the plasma of subjects randomly selected

**TABLE 1. TCDD\* concentrations in soil and in the blood of selected residents in the zones contaminated after the Seveso, Italy, industrial accident in 1976**

Study area	Soil concentration†		Lipid-adjusted plasma concentration	
	Minimum	Maximum	No. of subjects	Median‡
Zone A	15.5	580.4	296§	447.0
			7¶	73.3
Zone B	1.7	4.3	80§	94.0
			51¶	12.4
Zone R	0.9	1.4	48§	48.0
Reference zone	NA*	NA	52¶	5.5

\* TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; NA, not available.

† Mean value ( $\mu\text{g}/\text{m}^2$ ); reference 8.

‡ Parts per trillion.

§ Samples collected in 1976–1977; reference 33.

¶ Samples collected in 1993–1994; reference 34.

from zone A, zone B, and the reference area who were enrolled in a current molecular epidemiology study (34). Table 1 shows exposure information by zone.

The search for vital status, and cause-of-death ascertainment for the deceased subjects, was performed on an individual basis by contacting the vital statistics offices of the 11 study towns and of thousands of municipalities throughout the country to reach those subjects who had migrated. The per-year migration rate from the 11 municipalities to other locations within Lombardy was 5.0 per 1,000 in the exposed and 11.5 per 1,000 in the reference population; the migration rates outside Lombardy were 6.2 and 6.3 per 1,000, respectively. Exposed and reference subjects were followed concurrently, as a unique cohort, by using the same means, methods, and criteria. Exposure status was ignored in this research phase.

In successive follow-ups, causes of death were coded by the same trained nosologist, who was unaware of the exposure status of the subjects. Coding accuracy and consistency were evaluated on the basis of criteria from the Italian Central Statistics Institute, located in Rome.

We also compared death rates in the pre- and postaccident periods to identify unusual risks possibly present even before the accident occurred in the exposed population and to highlight possible changes in the background death registration system in the area (35). Each study subject contributed person-time of observation from the date of the accident (July 10, 1976) or, if later, the date of first residence in the study area through the end of follow-up (December 31, 1996) or through the date of death, if earlier. All person-years of follow-up for each person were attributed to the zone of residence on the accident date or later, when he or she first moved to the area. Person-time was computed by stratifying on age, zone, residence on the day of the accident, gender, calendar time, duration of residence, and number of years elapsed since first exposure. For each contaminated zone, age-, gender-, and period-adjusted rate ratios and approximate 95 percent confidence intervals were estimated for each

cause of death by means of Poisson regression techniques (36) in Stata software (37). The expected number of deaths was obtained by multiplying the fitted reference rates (specific period, age, and gender) by the number of stratum-specific person-years in the exposed zones. Data also were analyzed separately by number of years since first exposure ("latency"), gender, age category, calendar time, duration of residence (surrogate for duration of exposure), and residence on the day of the accident.

## RESULTS

Information on the study population at the end of follow-up is shown in table 2. Tracing was virtually complete for those in the 11 study municipalities and was approximately 99 percent for those who had moved out of the area.

The person-years accrued during the 20.5-year follow-up period are reported in table 3. The 5-year (1992–1996) extension of the follow-up added to the entire study population, including the reference area, 1,225,644 person-years of observation and 9,570 deaths (26 in zone A, 180 in zone B, 1,203 in zone R, and 8,161 in the reference

zone). Distribution by age and gender was fairly uniform across zones, as expected. People in zone B were slightly younger.

Table 4 presents detailed results for the population living in high-exposure zones A and B, including observed and expected numbers of deaths; age-, gender-, and calendar-period-adjusted point estimates of the rate ratios; and 95 percent confidence intervals for the main causes of death in each zone and in both zones combined. All-cause and all-cancer mortality was similar to that in the reference population. Deaths from rectal cancer were elevated, with a nearly twofold increase in zone B. No liver cancer deaths were observed in zone A. An excess of "other" digestive cancer was found in both zones; however, it did not reach statistical significance. Lung cancer also was moderately in excess, but the increase was statistically nonsignificant. One melanoma death in zone A yielded a remarkable increase in the rate ratio estimate. Among lymphohemopoietic neoplasms, two deaths from non-Hodgkin's lymphoma were observed in zone A, which represented a higher-than-three-fold excess above expectations. In zone B, nearly twice as many as expected lymphohemopoietic neoplasms occurred, a significant increase that in particular included Hodgkin's disease, multiple myeloma, and myeloid leukemia. No deaths from soft tissue sarcoma were observed in zones A or B (0.1 and 0.7 expected, respectively).

Regarding nonmalignant causes of death, hypertension was nonsignificantly in excess in zone A. Chronic obstructive pulmonary disease increased significantly in zone A and less evidently in zone B. The zone B population also exhibited moderate increases in diabetes and chronic ischemic heart disease.

Zone A results by latency are available on the *Journal* website ([www.jhsph.edu/Publications/JEPI/bertazzi.htm](http://www.jhsph.edu/Publications/JEPI/bertazzi.htm) (table 1)). Increased mortality was found in the 5–9-year

**TABLE 2. Sample size and completeness of follow-up of the study population in the dioxin-contaminated and reference areas, Seveso, Italy, 1976–1996**

Study area	No. of subjects		No. of deaths	Not traced	
	Female	Male		No.	%
Zone A	414	390	96	5	0.6
Zone B	2,924	3,017	649	30	0.5
Zone R	19,424	19,200	4,937	202	0.5
Reference zone	118,775	113,970	32,128	1,616	0.7

**TABLE 3. Distribution of person-years of observation, by exposure zone, gender, age, and latency, for the population exposed to dioxin after the Seveso, Italy, industrial accident, 1976–1996**

Variable	Exposure zone			Reference zone	Total
	A	B	R		
Gender					
Male	7,270	55,648	349,480	2,032,871	2,445,269
Female	7,866	54,861	358,797	2,150,048	2,571,572
Age (years)					
<20	4,946	40,452	243,325	1,354,246	1,642,969
20–29	2,524	20,100	121,936	707,941	852,500
30–39	2,354	17,264	109,845	668,879	798,342
40–49	2,354	14,343	96,151	577,324	690,172
50–59	1,720	10,045	71,259	432,911	515,936
60–69	864	5,487	43,081	279,235	328,667
70–79	321	2,394	19,243	135,726	157,685
≥80	53	424	3,436	26,657	30,569
Latency (years)					
≤4	3,962	29,323	189,774	1,142,625	1,365,684
5–9	3,834	28,562	183,806	1,102,945	1,319,147
10–14	3,634	26,940	171,669	1,008,725	1,210,968
15–20	3,706	25,684	163,028	928,532	1,120,950

**TABLE 4. Observed and expected numbers of deaths, rate ratios,\* and 95% confidence intervals for selected causes of death in high-exposure zones A and B for the population exposed to dioxin after the Seveso, Italy, industrial accident, 1976–1996**

Cause of death (ICD-9† codes)	Zone A				Zone B				Total			
	Obs†	Exp†	RR†	95% CI†	Obs	Exp	RR	95% CI	Obs	Exp	RR	95% CI
All causes (001–999)	96	91.9	1.0	0.9, 1.3	649	654.6	1.0	0.9, 1.1	745	746.5	1.0	0.9, 1.1
All cancers (140–208)	27	31.4	0.9	0.6, 1.3	222	208.9	1.1	0.9, 1.2	249	240.2	1.0	0.9, 1.2
Digestive (150–159)	9	12.0	0.7	0.4, 1.4	75	81.7	0.9	0.7, 1.2	84	93.7	0.9	0.7, 1.1
Stomach (151)	3	3.6	0.8	0.3, 2.6	24	24.9	1.0	0.6, 1.4	27	28.5	0.9	0.6, 1.4
Colon (153)	2	2.3	0.9	0.2, 3.4	13	15.8	0.8	0.5, 1.4	15	18.1	0.8	0.5, 1.4
Rectum (154)	1	0.8	1.2	0.2, 8.6	11	5.7	1.9	1.1, 3.5	12	6.5	1.8	1.0, 3.3
Hepatobiliary (155–156)	0	2.6			13	17.3	0.8	0.4, 1.3	13	19.9	0.7	0.4, 1.1
Liver (155)	0	2.2			12	14.7	0.8	0.5, 1.4	12	16.9	0.7	0.4, 1.3
Pancreas (157)	1	1.2	0.8	0.1, 5.9	4	8.1	0.5	0.2, 1.3	5	9.3	0.5	0.2, 1.3
Other digestive (159)	2	0.6	3.2	0.8, 12.9	7	4.3	1.6	0.8, 3.5	9	4.9	1.8	0.9, 3.6
Respiratory (160–165)	9	7.7	1.2	0.6, 2.3	60	49.9	1.2	0.9, 1.6	69	57.6	1.2	0.9, 1.5
Lung (162)	9	6.7	1.3	0.7, 2.6	52	43.4	1.2	0.9, 1.6	61	50.1	1.2	0.9, 1.6
Soft tissue sarcoma (171)	0	0.1			0	0.7			0	0.8		
Melanoma (172)	1	0.2	4.2	0.6, 30.2	2	1.6	1.3	0.3, 5.2	3	1.8	1.7	0.5, 5.3
Breast (174)	2	2.6	0.8	0.2, 3.1	12	16.5	0.7	0.4, 1.3	14	19.1	0.7	0.4, 1.2
Genitourinary (179–189)	2	3.7	0.5	0.1, 2.2	24	24.8	1.0	0.6, 1.4	26	28.5	0.9	0.6, 1.3
Uterus (179–182)	0	0.6			2	3.8	0.5	0.1, 2.1	2	4.4	0.5	0.1, 1.8
Ovary (183)	1	0.6	1.6	0.2, 11.2	2	3.9	0.5	0.1, 2.0	3	4.6	0.7	0.2, 2.0
Prostate (185)	0	0.8			8	6.7	1.2	0.6, 2.4	8	7.5	1.1	0.5, 2.2
Bladder (188)	1	0.8	1.3	0.2, 9.4	5	5.5	0.9	0.4, 2.2	6	6.2	1.0	0.4, 2.2
Kidney (189)	0	0.7			6	4.6	1.3	0.6, 2.9	6	5.3	1.1	0.5, 2.6
Brain (191)	0	0.5			4	3.5	1.2	0.4, 3.1	4	4.0	1.0	0.4, 2.7
Lymphatic and hemo- poietic (200–208)	2	2.1	1.0	0.2, 3.9	26	14.0	1.9	1.3, 2.7	28	16.1	1.7	1.2, 2.5
Hodgkin's disease (201)	0	0.2			4	1.1	3.5	1.3, 9.8	4	1.3	3.1	1.1, 8.6
Non-Hodgkin's lymphoma (200, 202)	2	0.6	3.3	0.8, 13.1	5	4.0	1.2	0.5, 3.0	7	4.7	1.5	0.7, 3.2
Multiple myeloma (203)	0	0.4			5	2.5	2.0	0.8, 4.8	5	2.9	1.7	0.7, 4.2
Leukemia (204–208)	0	0.9			12	6.4	1.9	1.0, 3.3	12	7.4	1.6	0.9, 2.9
Lymphatic leukemia (204)	0	0.3			2	1.8	1.1	0.3, 4.4	2	2.1	1.0	0.2, 3.9
Myeloid leukemia (205)	0	0.4			6	2.5	2.4	1.0, 5.4	6	2.9	2.1	0.9, 4.7
Leukemia, unspecified (208)	0	0.3			4	2.0	2.0	0.7, 5.4	4	2.3	1.8	0.6, 4.8
Diabetes mellitus (250)	2	2.4	0.8	0.2, 3.3	24	16.9	1.4	0.9, 2.1	26	19.3	1.3	0.9, 2.0
All circulatory diseases (390–459)	37	33.3	1.1	0.8, 1.5	228	242.7	0.9	0.8, 1.1	265	276.0	1.0	0.8, 1.1
Chronic rheumatic heart disease (393–398)	3	0.4	7.0	2.2, 21.9	0	2.8			3	3.2	0.9	0.3, 3.0
Hypertension (400–405)	4	1.8	2.3	0.8, 6.1	5	12.6	0.4	0.2, 1.0	9	14.3	0.6	0.3, 1.2
Ischemic heart disease (410–414)	10	12.4	0.8	0.4, 1.5	87	89.5	1.0	0.8, 1.2	97	102.0	1.0	0.8, 1.2
Myocardial infarction (410)	5	7.9	0.6	0.3, 1.5	45	54.3	0.8	0.6, 1.1	50	62.3	0.8	0.6, 1.1
Chronic ischemic heart disease (412, 414)	5	4.6	1.1	0.5, 2.6	41	34.8	1.2	0.9, 1.6	46	39.4	1.2	0.9, 1.6
Cerebrovascular disease (430–438)	8	9.8	0.8	0.4, 1.6	80	71.0	1.1	0.9, 1.4	88	80.7	1.1	0.9, 1.3
Respiratory disease (460–519)	9	4.8	1.9	1.0, 3.6	35	37.7	0.9	0.7, 1.3	44	42.5	1.0	0.8, 1.4
Chronic obstructive pul- monary disease (490–493)	7	2.1	3.3	1.6, 6.9	22	16.9	1.3	0.9, 2.0	29	19.1	1.5	1.1, 2.2
Digestive disease (520–579)	5	5.8	0.9	0.4, 2.1	38	39.3	1.0	0.7, 1.3	43	45.2	1.0	0.7, 1.3
Cirrhosis of the liver (571)	2	3.9	0.5	0.1, 2.1	19	25.0	0.8	0.5, 1.2	21	28.8	0.7	0.5, 1.1
Unknown (799.9)	3	1.6	1.9	0.6, 5.9	11	11.2	1.0	0.5, 1.8	14	12.8	1.1	0.6, 1.9
Accidents (800–999)	7	5.7	1.2	0.6, 2.6	45	41.5	1.1	0.8, 1.5	52	47.1	1.1	0.8, 1.5

\* Adjusted for age, calendar period, and gender.

† ICD-9, *International Classification of Diseases and Causes of Death*, Ninth Revision; Obs, observed no.; Exp, expected no.; RR, rate ratio; CI, confidence interval.

period only, sustained mainly by suggestive increases in a number of cancer types and sites (including digestive, lung, melanoma, and bladder) and by deaths due to circulatory dis-

ease. Lung cancer and non-Hodgkin's lymphoma increased steeply after 15 years. Increased circulatory disease mortality characterized the first 10-year period, with the exception of

hypertension, which peaked between 10 and 15 years. Mortality from respiratory disease, predominantly chronic obstructive pulmonary disease, was elevated immediately after the incident and in the latest observation period.

In zone B (table 2, website), neither all-cause nor all-cancer mortality notably departed from expectations throughout the study period. The increased rectal cancer mortality failed to exhibit a consistent latency-related pattern. Other digestive cancers and lung cancer increased in the 5–9-year period, as they did in zone A. Two melanoma deaths in the 15–20-year period yielded a remarkably high risk ratio estimate. Lymphatic and hemopoietic neoplasms were fairly consistently elevated throughout the observation period. Hodgkin's disease increased in the early period, significantly so in the 5–9-year period, whereas non-Hodgkin's lymphoma showed a later, modest increase. The risk of multiple myeloma was increased in the categories 5–9 and 10–14 years. The numbers of deaths from leukemia were steadily above expectations, and the myeloid leukemia increase was highest in the longest latency period. Among nonmalignant causes, the increase in diabetes was most evident immediately after the accident and for chronic ischemic heart disease and chronic obstructive pulmonary disease in the 5–9-year period.

The results by latency for zones A and B combined (table 5) failed to reveal clear, definite, time-related mortality patterns. Only suggestive was the trend for lymphatic and hemopoietic neoplasms as a whole. As to specific causes, the rate of Hodgkin's disease was high in the early postaccident period: the rate ratio estimate for 0–10 years since first exposure was 4.9 (95 percent confidence interval (CI): 1.5, 16.4). The rates for non-Hodgkin's lymphoma and myeloid leukemia were instead high in the longest latency period and for multiple myeloma in the period between 5 and 15 years. The moderately increased diabetes mortality exhibited no regular time-related pattern. Rates of chronic ischemic heart disease and chronic obstructive pulmonary disease were high in the 5–9-year latency period.

This study provided an almost unique opportunity to examine the health experience of a large female population exposed to dioxin. Therefore, we considered it useful to report results separately by gender.

Among females in zone A (table 3, website), mortality from all causes and all cancers was as expected, with the exception of the 5–9-year latency period, which showed an excess of colon and other digestive cancers and of melanoma. Stomach cancer was increased in the second decade. The single observed case of non-Hodgkin's lymphoma occurred in the 15–20-year period. The risk ratios for hypertension and for chronic obstructive pulmonary disease were elevated. Definite patterns or trends could not be observed, but the population size was small and few events were observed. Among males in zone A (table 4, website), cancer mortality was slightly elevated after 15 years. Lung cancer showed a clear, significant increase, whereas the increases for rectal cancer and non-Hodgkin's lymphoma were significant but only suggestive. The highest mortality pattern from circulatory disease was found in the first postaccident periods; respiratory disease was elevated in the earliest period and after 15 years.

Regarding results by years since first exposure for females in zone B (table 5, website), all-cause and all-cancer mortality overall was as expected. In the 10–14-year period, digestive cancer mortality was elevated, and stomach and liver cancer showed statistically significant increases. Twelve cases of lymphatic and hemopoietic neoplasms made up a twofold statistically significant excess, with a suggestively increasing pattern by latency. The increase involved Hodgkin's disease, non-Hodgkin's lymphoma (significantly increased, as in zone A, in the latest latency period), and multiple myeloma. An excess of leukemia deaths was found, although not significantly so, 15 or more years after first exposure. With respect to nonmalignant causes, diabetes showed an excess that was significant after 15 years, and chronic obstructive pulmonary disease exhibited a pattern of moderately increased mortality with a peak between 10 and 15 years.

In total, males in zone B had moderately increased mortality from cancer causes (table 6, website). Rectal cancer increased significantly, but there was no definite latency pattern. In contrast to women, liver cancer was not increased, five "other" digestive cancer deaths represented a borderline significant excess, and lung cancer exhibited a slight, persistent elevation 5 or more years after first exposure. Lymphatic and hemopoietic neoplasms showed a nearly twofold borderline significant increase: Hodgkin's disease and leukemia mainly contributed to this finding. Most prominent was the increase in myeloid leukemia in the longest latency categories. No increased mortality from diabetes was noted, and no major departures from expectations were found for other nonmalignant causes of death.

When we examined the pooled experience of the highly exposed Seveso population (zone A plus zone B), no obvious departure of all-cause and all-cancer mortality from reference population rates was found for females (table 6). Ten to 14 years after the accident, mortality from digestive cancer (stomach and liver in particular) was borderline significantly increased. Lymphatic and hemopoietic neoplasms were significantly increased, with monotonically increasing risk ratio estimates. The highest risk ratio values were found for Hodgkin's disease, multiple myeloma, and non-Hodgkin's lymphoma in the latest latency category. Leukemia mortality was not elevated. Among nonmalignant diseases, the rate of diabetes was high, with a significant increase in the longest latency period, whereas the elevated mortality from chronic obstructive pulmonary disease peaked in the 10–15-year period. Results for males (table 7) showed an elevated cancer mortality for three sites. Rectal cancer was significantly increased, without a definite latency pattern. Lung cancer showed a moderate increase, which was borderline significant in the second and latest latency periods. The increased mortality from lymphatic and hemopoietic neoplasms was statistically borderline significant, but no particular trend or pattern was evident. The increase for leukemia, most notably myeloid leukemia, was significant. Among nonmalignant causes, an excess of chronic ischemic heart disease and chronic obstructive respiratory disease was found in the 5–9-year category.

In zone R, for none of the cancer sites considered was a mortality rate notably different from that expected found.

**TABLE 5. Observed and expected numbers of deaths, rate ratios,\* and 95% confidence intervals, by cause of death and years since first exposure (latency), for the population in zones A and B exposed to dioxin after the Seveso, Italy, industrial accident, 1976–1996**

Cause of death (ICD-9† codes)	No. of years since first exposure															
	0–4				5–9				10–14				15–20			
	Obs†	Exp†	RR†	95% CI†	Obs	Exp	RR	95% CI	Obs	Exp	RR	95% CI	Obs	Exp	RR	95% CI
All causes (001–999)	170	181.9	0.9	0.8, 1.1	187	177.2	1.1	0.9, 1.2	171	178.0	1.0	0.8, 1.1	217	209.7	1.0	0.9, 1.2
All cancers (140–208)	38	48.2	0.8	0.6, 1.1	63	55.8	1.1	0.9, 1.4	65	63.3	1.0	0.8, 1.3	83	73.9	1.1	0.9, 1.4
Digestive (150–159)	10	19.2	0.5	0.3, 1.0	22	21.1	1.0	0.7, 1.6	26	24.7	1.1	0.7, 1.6	26	29.5	0.9	0.6, 1.3
Stomach (151)	4	6.8	0.6	0.2, 1.6	4	7.1	0.6	0.2, 1.5	10	7.5	1.3	0.7, 2.5	9	7.4	1.2	0.6, 2.4
Colon (153)	0	3.9			5	4.1	1.2	0.5, 2.9	5	4.3	1.2	0.5, 2.8	5	6.0	0.8	0.3, 2.0
Rectum (154)	3	1.5	2.0	0.6, 6.5	1	1.3	0.7	0.1, 5.4	4	1.8	2.2	0.8, 6.1	4	2.0	2.0	0.7, 5.5
Hepatobiliary (155–156)	1	3.0	0.3	0.05, 2.4	5	3.7	1.3	0.6, 3.3	4	6.1	0.7	0.2, 1.8	3	7.0	0.4	0.1, 1.3
Liver (155)	1	2.4	0.4	0.1, 3.0	4	3.2	1.3	0.5, 3.4	4	5.2	0.8	0.3, 2.1	3	6.0	0.5	0.2, 1.6
Pancreas (157)	1	1.7	0.6	0.1, 4.3	2	1.9	1.1	0.3, 4.3	1	2.3	0.4	0.1, 3.1	1	3.4	0.3	0.04, 2.1
Other digestive (159)	1	0.6	1.6	0.2, 11.7	4	1.2	3.4	1.2, 9.3	1	1.3	0.8	0.1, 5.7	3	1.9	1.6	0.5, 5.0
Respiratory (160–165)	10	11.7	0.9	0.5, 1.6	19	13.0	1.5	0.9, 2.3	17	16.0	1.1	0.7, 1.7	23	16.7	1.4	0.9, 2.1
Lung (162)	9	10.0	0.9	0.5, 1.7	16	10.8	1.5	0.9, 2.4	15	14.4	1.0	0.6, 1.7	21	14.9	1.4	0.9, 2.2
Melanoma (172)	0	0.3			1	0.4	2.7	0.4, 20.4	0	0.6			2	0.7	3.1	0.7, 13.0
Breast (174)	3	3.4	0.9	0.3, 2.8	3	5.0	0.6	0.2, 1.9	3	4.5	0.7	0.2, 2.1	5	6.2	0.8	0.3, 2.0
Genitourinary (179–189)	4	5.6	0.7	0.3, 1.9	7	6.9	1.0	0.5, 2.2	5	7.6	0.7	0.3, 1.6	10	8.4	1.2	0.6, 2.2
Bladder (188)	1	1.2	0.8	0.1, 6.1	3	1.3	2.3	0.7, 7.2	0	1.8			2	1.8	1.1	0.3, 4.5
Kidney (189)	0	0.9			0	1.3			3	1.5	2.0	0.6, 6.5	3	1.7	1.8	0.6, 5.7
Brain (191)	0	0.5			2	1.2	1.7	0.4, 7.0	2	1.0	1.0	0.5, 8.1	0	1.3		
Lymphatic and hemo- poietic (200–208)	5	3.5	1.4	0.6, 3.5	6	3.6	1.7	0.7, 3.8	8	4.0	2.0	1.0, 4.1	9	5.2	1.7	0.9, 3.4
Hodgkin's disease (201)	1	0.3	3.4	0.4, 26.0	2	0.3	6.1	1.4, 27.5	1	0.4	2.6	0.3, 19.6	0	0.3		
Non-Hodgkin's lymphoma (200, 202)	0	0.6			0	1.0			2	1.4	1.5	0.4, 6.0	5	1.8	2.8	1.1, 7.0
Multiple myeloma (203)	0	0.6			2	0.5	3.8	0.9, 16.2	3	0.5	5.5	1.7, 18.4	0	1.2		
Leukemia (204–208)	4	2.0	2.0	0.7, 5.5	2	1.8	1.1	0.3, 4.6	2	1.7	1.2	0.3, 4.8	4	1.9	2.1	0.8, 5.8
Lymphatic leukemia (204)	1	0.4	2.5	0.3, 18.8	1	0.4	2.6	0.3, 19.8	0	0.6			0	0.7		
Myeloid leukemia (205)	1	0.7	1.5	0.2, 11.3	0	0.7			2	0.8	2.6	0.6, 10.9	3	0.8	3.8	1.1, 12.5
Leukemia, unspecified (208)	2	0.9	2.1	0.5, 8.8	1	0.6	1.6	0.2, 11.5	0	0.3			1	0.3	3.0	0.4, 23.1
Diabetes mellitus (250)	7	3.6	2.0	0.9, 4.2	3	4.7	0.6	0.2, 2.0	8	5.0	1.6	0.8, 3.2	8	5.8	1.4	0.7, 2.8
All circulatory diseases (390–459)	71	70.5	1.0	0.8, 1.3	81	69.7	1.2	0.9, 1.4	52	64.0	0.8	0.6, 1.1	61	71.9	0.8	0.7, 1.1
Hypertension (400–405)	3	3.7	0.8	0.3, 2.5	1	3.3	0.3	0.04, 2.1	3	3.5	0.9	0.3, 2.7	2	3.7	0.5	0.1, 2.2
Ischemic heart disease (410–414)	21	25.0	0.8	0.5, 1.3	30	27.7	1.1	0.8, 1.6	20	23.9	0.8	0.5, 1.3	26	25.2	1.0	0.7, 1.5
Myocardial infarction (410)	11	15.4	0.7	0.4, 1.3	10	16.0	0.6	0.3, 1.2	11	15.3	0.7	0.4, 1.3	18	15.3	1.2	0.7, 1.9
Chronic ischemic heart disease (412, 414)	10	9.4	1.1	0.6, 2.0	19	11.5	1.6	1.0, 2.6	9	8.5	1.1	0.5, 2.0	8	9.9	0.8	0.4, 1.6
Cerebrovascular disease (430–438)	25	21.7	1.2	0.8, 1.7	25	19.7	1.3	0.9, 1.9	18	19.2	0.9	0.6, 1.5	20	20.4	1.0	0.6, 1.5

Respiratory disease (460-519)	11	11.2	1.0	0.5, 1.8	9	10.3	0.9	0.5, 1.7	8	9.8	0.8	0.4, 1.6	16	11.1	1.4	0.9, 2.4
Chronic obstructive pulmonary disease (490-493)	7	4.7	1.5	0.7, 3.1	8	4.1	2.0	1.0, 4.0	6	5.0	1.2	0.5, 2.7	8	5.2	1.5	0.8, 3.1
Digestive disease (520-579)	8	13.5	0.6	0.3, 1.2	13	11.7	1.1	0.6, 1.9	10	9.6	1.0	0.6, 1.9	12	10.3	1.2	0.7, 2.1
Cirrhosis of the liver (571)	5	8.9	0.6	0.2, 1.4	6	8.0	0.8	0.3, 1.7	5	6.3	0.8	0.3, 1.9	5	5.7	0.9	0.4, 2.1
Accidents (800-999)	13	12.3	1.1	0.6, 1.8	10	12.2	0.8	0.4, 1.5	14	10.8	1.3	0.8, 2.2	15	11.7	1.3	0.8, 2.1

\* Adjusted for age, calendar period, and gender.

† ICD-9, *International Classification of Diseases and Causes of Death*, Ninth Revision; Obs, observed no.; Exp, expected no.; RR, rate ratio; CI, confidence interval.

Given the large population size, 4 vs. 4.8 expected soft tissue sarcoma deaths were observed. Mortality from diabetes (observed no. = 168, expected no. = 132.2; rate ratio (RR) = 1.3, 95 percent CI: 1.1, 1.5), hypertension (observed no. = 130, expected no. = 99.2; RR = 1.3, 95 percent CI: 1.1, 1.6), and chronic ischemic heart disease (observed no. = 328, expected no. = 266.5; RR = 1.2, 95 percent CI: 1.1, 1.4) increased moderately.

Analyses by zone according to length of stay yielded results very similar to those according to number of years since first exposure; the great majority of study subjects (90 percent in zone A, 81 percent in zone B, 82 percent in zone R, and 78 percent of the reference population) resided in the area at the time of the accident, and the migration rate was limited. Consistently, analysis by residence on the date of the accident marginally influenced the risk ratio estimates.

A special group within the cohort, composed of 182 persons (57 in zone A, 11 in zone B, 69 in zone R, and 45 in the reference area), was diagnosed with chloracne after the accident. All were traced; two had died by the time of this follow-up extension, one zone A resident from myocarditis and one zone R resident from suicide.

## DISCUSSION

Extension of follow-up of the population exposed to dioxin after the Seveso, Italy, industrial accident failed to reveal an overall increase in all-cause and all-cancer mortality. However, it suggested that those residents living in the highly contaminated territory were at increased risk from some causes.

When we interpreted the results, major bias and confounding phenomena could be excluded. Follow-up was virtually complete. The reference population was local, closely similar to the index population, and large enough to ensure that the adopted reference rates were stable. Exceptions were pinpointed through comparison with the Region of Lombardy population rates and included other and not specified leukemia (high reference rates for males), digestive diseases (high reference rates for females), and brain cancer (low reference rates for males) (21). Tracing of vital status and coding of causes of death were uniform and were blinded for exposure status of the subjects. The exposed and referent populations belonged to the same health districts and had similar access to the same diagnostic and therapeutic services (from family physicians to hospitals). Therefore, no differential death registration pattern between exposed and referent populations should have occurred. Comparison of pre- and postaccident rates disclosed elevated risks in the exposed population, before the accident, for brain cancer (males and females) and leukemia (females) (35). The ecologic classification of exposure status based on soil levels was not refuted by classification based on available blood dioxin measurements. Blood measurements also strengthened confidence in the nonexposure status of the reference population; their estimated average blood concentration corresponded to background values measured in industrial areas (38).

Analyses by exposure zone, time since first exposure, and gender disclosed unusual mortality patterns for some

**TABLE 6. Observed and expected numbers of deaths, rate ratios,\* and 95% confidence intervals, by cause of death and years since first exposure (latency), for the female population in zones A and B exposed to dioxin after the Seveso, Italy, industrial accident, 1976–1996**

Cause of death (ICD-9† codes)	No. of years since first exposure																			
	0–4				5–9				10–14				15–20				Total			
	Obs†	Exp†	RR†	95% CI†	Obs	Exp	RR	95% CI	Obs	Exp	RR	95% CI	Obs	Exp	RR	95% CI	Obs	Exp	RR	95% CI
All causes (001–999)	67	72.2	0.9	0.7, 1.2	74	72.1	1.0	0.8, 1.3	76	71.8	1.1	0.8, 1.3	90	92.4	1.0	0.8, 1.2	307	308.5	1.0	0.9, 1.1
All cancers (140–208)	10	18.1	0.6	0.3, 1.0	20	21.1	0.9	0.6, 1.5	28	22.1	1.3	0.9, 1.8	25	29.8	0.8	0.6, 1.2	83	90.8	0.9	0.7, 1.1
Digestive (150–159)	3	7.7	0.4	0.1, 1.2	9	8.0	1.1	0.6, 2.2	13	8.7	1.5	0.9, 2.6	6	12.0	0.5	0.2, 1.1	31	36.0	0.9	0.6, 1.2
Stomach (151)	0	2.5			1	2.4	0.4	0.1, 3.0	7	2.7	2.6	1.2, 5.5	3	3.0	1.0	0.3, 3.1	11	10.6	1.0	0.6, 1.9
Colon (153)	0	1.7			3	2.0	1.5	0.5, 4.7	2	1.8	1.1	0.3, 4.6	0	2.9			5	8.3	0.6	0.2, 1.4
Rectum (154)	1	0.7	1.4	0.2, 10.5	0	0.4			1	0.7	1.4	0.2, 10.4	1	0.9	1.1	0.1, 7.7	3	2.7	1.1	0.4, 3.5
Hepatobiliary (155–156)	1	1.3	0.8	0.1, 5.7	2	1.5	1.3	0.3, 5.4	3	1.6	1.8	0.6, 5.8	1	2.3	0.4	0.1, 3.1	7	6.7	1.0	0.5, 2.2
Liver (155)	1	0.8	1.2	0.2, 8.7	1	1.2	0.9	0.1, 6.2	3	1.1	2.8	0.9, 8.9	1	1.6	0.6	0.1, 4.5	6	4.7	1.3	0.6, 2.9
Pancreas (157)	0	0.5			1	0.5	2.0	0.3, 15.0	0	0.9			0	1.6			1	3.5	0.3	0.03, 2.0
Other digestive (159)	1	0.4	2.2	0.3, 16.6	2	0.7	2.8	0.7, 11.7	0	0.6			1	0.9	1.1	0.1, 7.9	4	2.6	1.5	0.6, 4.1
Respiratory (160–165)	0	1.4			1	1.3	0.8	0.1, 5.6	1	1.9	0.5	0.1, 3.7	3	2.6	1.2	0.4, 3.7	5	7.2	0.7	0.3, 1.7
Lung (162)	0	1.1			1	1.1	0.9	0.1, 6.9	1	1.8	0.6	0.1, 4.1	2	2.2	0.9	0.2, 3.8	4	6.2	0.6	0.2, 1.7
Melanoma (172)	0	0.2			1	0.3	3.5	0.5, 27.1	0	0.3			1	0.4	2.6	0.3, 20.0	2	1.1	1.8	0.4, 7.3
Breast (174)	3	3.4	0.9	0.3, 2.8	3	5.0	0.6	0.2, 1.9	3	4.5	0.7	0.2, 2.1	5	6.1	0.8	0.3, 2.0	14	19.0	0.7	0.4, 1.3
Genitourinary (179–189)	0	2.6			2	3.1	0.6	0.2, 2.6	4	3.1	1.3	0.5, 3.5	3	3.5	0.9	0.3, 2.7	9	12.2	0.7	0.4, 1.4
Uterus (179–182)	0	1.1			1	1.1	0.9	0.1, 6.4	0	1.1			1	1.0	1.0	0.1, 7.4	2	4.4	0.5	0.1, 1.9
Ovary (183)	0	0.8			0	1.2			1	1.1	0.9	0.1, 6.9	2	1.5	1.3	0.3, 5.4	3	4.6	0.7	0.2, 2.0
Kidney (189)	0	0.3			0	0.4			3	0.5	6.1	1.8, 20.4	0	0.5			3	1.6	1.8	0.6, 5.8
Brain (191)	0	0.3			1	0.4	2.7	0.4, 20.1	2	0.4	4.9	1.1, 21.3	0	0.5			3	1.6	1.9	0.6, 6.0
Lymphatic and hemo- poietic (200–208)	1	1.4	0.7	0.1, 5.2	2	1.6	1.3	0.3, 5.3	4	1.8	2.3	0.8, 6.2	6	2.4	2.5	1.1, 5.7	13	7.1	1.8	1.1, 3.2
Hodgkin's disease (201)	0	0.1			1	0.1	8.5	0.9, 76.6	1	0.1	8.0	0.9, 69.2	0	0.2			2	0.5	3.7	0.9, 16.0
Non-Hodgkin's lymphoma (200, 202)	0	0.3			0	0.5			0	0.6			4	0.9	4.6	1.6, 12.9	4	2.2	1.8	0.7, 4.9
Multiple myeloma (203)	0	0.3			1	0.2	5.2	0.7, 40.8	3	0.2	14.0	4.0, 52.8	0	0.6			4	1.3	3.2	1.2, 8.8
Leukemia (204–208)	1	0.7	1.4	0.2, 10.5	0	0.8			0	0.8			2	0.8	2.6	0.6, 11.1	3	3.1	1.0	0.3, 3.0
Myeloid leukemia (205)	0	0.3			0	0.3			0	0.4			1	0.4	2.7	0.4, 20.9	1	1.4	0.7	0.1, 5.1
Diabetes mellitus (250)	4	2.0	2.0	0.8, 5.5	1	2.9	0.3	0.04, 2.5	7	3.2	2.2	1.0, 4.6	8	3.4	2.4	1.2, 4.8	20	11.6	1.7	0.1, 2.7
All circulatory diseases (390–459)	32	30.4	1.1	0.7, 1.5	37	31.4	1.2	0.9, 1.6	20	29.2	0.7	0.4, 1.1	26	35.8	0.7	0.5, 1.1	115	126.6	0.9	0.8, 1.1
Hypertension (400–405)	3	2.1	1.4	0.5, 4.6	1	2.0	0.5	0.1, 3.6	2	2.2	0.9	0.2, 3.6	1	2.1	0.5	0.1, 3.3	7	8.6	0.8	0.4, 1.7
Ischemic heart disease (410–414)	8	8.2	1.0	0.5, 2.0	10	10.1	1.0	0.5, 1.9	6	8.7	0.7	0.3, 1.6	8	10.4	0.8	0.4, 1.5	32	37.4	0.9	0.6, 1.2
Myocardial infarction (410)	5	3.7	1.4	0.6, 3.3	2	4.4	0.5	0.1, 1.8	2	4.9	0.4	0.1, 1.6	5	5.5	0.9	0.4, 2.2	14	18.5	0.8	0.4, 1.3
Chronic ischemic heart disease (412, 414)	3	4.6	0.7	0.2, 2.1	8	5.6	1.4	0.7, 2.9	4	3.8	1.1	0.4, 2.8	3	4.9	0.6	0.2, 1.9	18	18.8	1.0	0.6, 1.5
Cerebrovascular disease (430–438)	13	10.6	1.2	0.7, 2.1	11	9.8	1.1	0.6, 2.0	7	9.9	0.7	0.3, 1.5	9	11.5	0.8	0.4, 1.5	40	41.7	1.0	0.7, 1.3

Respiratory disease (460-519)	4	4.1	1.0	0.4, 2.6	2	3.5	0.6	0.1, 2.3	6	3.6	1.7	0.7, 3.8	5	4.6	1.1	0.4, 2.6	17	15.8	1.1	0.7, 1.7
Chronic obstructive pulmonary disease (490-493)	3	1.2	2.4	0.8, 7.7	2	1.0	1.9	0.5, 7.8	4	1.3	3.0	1.1, 8.1	3	1.7	1.8	0.6, 5.6	12	5.4	2.2	1.2, 4.0
Digestive disease (520-579)	4	4.1	1.0	0.4, 2.6	6	3.9	1.5	0.7, 3.5	4	3.4	1.2	0.4, 3.2	5	4.3	1.2	0.5, 2.8	19	15.9	1.2	0.8, 1.9
Cirrhosis of the liver (571)	2	2.3	0.9	0.2, 3.5	1	2.2	0.5	0.1, 3.2	0	2.0			2	2.0	1.0	0.2, 4.0	5	8.6	0.6	0.2, 1.4
Accidents (800-999)	3	3.1	1.0	0.3, 3.1	4	3.8	1.0	0.4, 2.8	5	3.7	1.4	0.6, 3.3	5	3.8	1.3	0.5, 3.2	17	14.4	1.2	0.7, 1.9

\* Adjusted for age and calendar period.

† ICD-9, *International Classification of Diseases and Causes of Death*, Ninth Revision; Obs, observed no.; Exp, expected no.; RR, rate ratio; CI, confidence interval.

diseases. In the zones A and B merged male population, all-cancer deaths were significantly in excess after 15 years. The magnitude of the excess was similar to that estimated in previous long-term studies of high-exposure, male occupational cohorts (30, 39-41). Lung cancer mortality also was elevated; the increase was significant in the highest-exposed zone A male population after 15 years of latency. Several independent studies examining occupational cohorts with biologically documented exposure to high levels of dioxin found elevated lung cancer risks (25-27, 29, 42, 43). The lung is also one of the organs targeted by the carcinogenic action of TCDD in rats (44) and mice (45). Individual tobacco smoking habits were not known, but the known homogeneity of educational and cultural features between the exposed and reference populations makes systematic differences quite improbable. Although rectal cancer was not considered a priori among the possible health outcomes associated with dioxin exposure, the hypothesis of a dioxin-related increase in rectal cancer is backed by at least one occupational cohort study (43) that found a statistically borderline significant increase, with a relative risk of 2.3 (95 percent CI: 1.0, 4.4). Among zone A plus zone B males, the magnitude of the risk ratio and the persistence of the excess over time converged to lend credibility to the finding. The dietary habits of the exposed and reference populations are known for their commonalities: meat consumption is frequent and includes beef, pork, and courtyard animals (chicken, rabbits); high consumption of vegetables, often grown in backyard gardens, is common. Possible involvement of other digestive sites (the stomach in both zones A and B and, less evidently, the liver in zone B) was suggested by results of latency analysis of females.

The clearest and most consistent excess in zones A and B was for lymphohemopoietic neoplasms, for which the numbers were elevated in both genders, with a latency-related pattern among females. The few observed deaths limited interpretation for specific causes. Non-Hodgkin's lymphoma was significantly elevated in the small, but highly exposed zone A population and increased nonsignificantly in zone B. In zone B, the increases in Hodgkin's disease were significant in the first postaccident decade, as were those for leukemia, in particular myeloid leukemia, in the longest latency category. Suggestive was the increase in multiple myeloma, and the excess risk became significant when females were analyzed separately. On the other hand, leukemia deaths showed the highest increase among males. In previous experimental studies, a dose-related increased occurrence of lymphoma was found in both sexes of mice (45, 46). In occupational cohorts with high levels of exposure to TCDD, non-Hodgkin's lymphoma and, less evidently, Hodgkin's disease were elevated (25, 29, 42, 47). An association with TCDD exposure was also seen for multiple myeloma (40, 42, 43) and possibly for leukemia (48). It is difficult to hypothesize about any systematic difference between the exposed and referent populations in terms of exposure to known biologic, chemical, or radiologic risk factors for hematologic neoplasms (49).

Mortality from noncancer deaths also showed some unusual features. An increase in diabetes mellitus was present

**TABLE 7. Observed and expected numbers of deaths, rate ratios,\* and 95% confidence intervals, by cause of death and years since first exposure (latency), for the male population in zones A and B exposed to dioxin after the Seveso, Italy, industrial accident, 1976–1996**

Cause of death (ICD-9† codes)	No. of years since first exposure																			
	0–4				5–9				10–14				15–20				Total			
	Obs†	Exp†	RR†	95% CI†	Obs	Exp	RR	95% CI	Obs	Exp	RR	95% CI	Obs	Exp	RR	95% CI	Obs	Exp	RR	95% CI
All causes (001–999)	103	109.4	0.9	0.8, 1.1	113	104.1	1.1	0.9, 1.3	95	105.7	0.9	0.7, 1.1	127	117.3	1.1	0.9, 1.3	438	436.2	1.0	0.9, 1.1
All cancers (140–208)	28	30.1	0.9	0.6, 1.4	43	34.7	1.2	0.9, 1.7	37	41.2	0.9	0.6, 1.2	58	44.2	1.3	1.0, 1.7	166	149.7	1.1	1.0, 1.3
Digestive (150–159)	7	11.5	0.6	0.3, 1.3	13	13.0	1.0	0.6, 1.7	13	16.0	0.8	0.5, 1.4	20	17.5	1.1	0.7, 1.8	57	57.6	0.9	0.7, 1.2
Stomach (151)	4	4.2	0.9	0.4, 2.6	3	4.7	0.6	0.2, 2.0	3	4.7	0.6	0.2, 2.0	6	4.3	1.4	0.6, 3.1	53	17.9	0.9	0.5, 1.5
Colon (153)	0	2.1			2	2.1	0.9	0.2, 3.8	3	2.5	1.2	0.4, 3.8	5	3.1	1.6	0.7, 3.9	16	9.8	1.0	0.5, 1.9
Rectum (154)	2	0.8	2.6	0.6, 10.8	1	1.0	1.0	0.1, 7.6	3	1.1	2.8	0.9, 9.0	3	1.0	2.9	0.9, 9.5	10	3.8	2.4	1.2, 4.6
Hepatobiliary (155–156)	0	1.8			3	2.2	1.4	0.4, 4.3	1	4.4	0.2	0.03, 1.6	2	4.8	0.4	0.1, 1.7	9	13.2	0.5	0.2, 1.0
Liver (155)	0	1.6			3	2.0	1.5	0.5, 4.8	1	4.1	0.2	0.03, 1.7	2	4.4	0.5	0.1, 1.8	6	12.1	0.5	0.2, 1.1
Pancreas (157)	1	1.2	0.8	0.1, 6.1	1	1.4	0.7	0.1, 5.2	1	1.4	0.7	0.1, 5.1	1	1.8	0.6	0.1, 4.1	6	5.8	0.7	0.3, 1.9
Other digestive (159)	0	0.2			2	0.5	4.2	1.0, 18.3	1	0.7	1.5	0.2, 10.9	2	1.0	2.0	0.5, 8.5	4	2.3	2.2	0.9, 5.4
Respiratory (160–165)	10	10.4	1.0	0.5, 1.8	18	11.8	1.5	1.0, 2.5	16	14.1	1.1	0.7, 1.9	20	14.1	1.4	0.9, 2.2	5	50.3	1.3	1.0, 1.6
Lung (162)	9	8.9	1.0	0.5, 2.0	15	9.7	1.5	0.9, 2.6	14	12.7	1.1	0.6, 1.9	19	12.8	1.5	0.9, 2.4	64	43.9	1.3	1.0, 1.7
Melanoma (172)	0	0.1			0	0.1			0	0.3			1	0.3	3.5	0.4, 27.2	57	0.7	1.5	0.2, 12.5
Genitourinary (179–189)	4	3.1	1.3	0.5, 3.5	5	3.9	1.3	0.5, 3.2	1	4.6	0.2	0.03, 1.5	7	4.9	1.4	0.7, 3.0	1	16.5	1.0	0.6, 1.7
Prostate (185)	3	1.5	2.0	0.6, 6.3	2	1.7	1.2	0.3, 4.9	1	2.0	0.5	0.1, 3.6	2	2.3	0.9	0.2, 3.5	17	7.5	1.1	0.5, 2.2
Bladder (188)	1	0.9	1.1	0.2, 8.2	3	1.2	2.6	0.8, 8.4	0	1.5			2	1.4	1.4	0.3, 5.9	8	5.0	1.2	0.5, 2.7
Kidney (189)	0	0.6			0	0.9			0	1.0			3	1.2	2.5	0.8, 8.0	6	3.7	0.8	0.3, 2.6
Brain (191)	0	0.2			1	0.8	1.2	0.2, 9.0	0	0.6			0	0.8			3	2.4	0.4	0.1, 3.0
Lymphatic and hemo- poietic (200–208)	4	2.1	1.9	0.7, 5.3	4	2.1	1.9	0.7, 5.3	4	2.2	1.8	0.7, 4.9	3	2.8	1.1	0.3, 3.4	1	9.1	1.7	1.0, 2.8
Hodgkin's disease (201)	1	0.2	5.3	0.7, 43.4	1	0.2	4.6	0.6, 37.2	0	0.3			0	0.1			15	0.8	2.6	0.6, 10.9
Non-Hodgkin's lymphoma (200, 202)	0	0.3			0	0.5			2	0.8	2.6	0.6, 11.0	1	0.9	1.1	0.1, 7.9	2	2.4	1.2	0.4, 3.9
Multiple myeloma (203)	0	0.3			1	0.4	2.5	0.3, 18.4	0	0.4			0	0.6			3	1.6	0.6	0.1, 4.3
Leukemia (204–208)	3	1.3	2.3	0.7, 7.5	2	1.0	1.9	0.5, 8.1	2	0.9	2.3	0.5, 9.6	2	1.1	1.7	0.4, 7.2	1	4.3	2.1	1.1, 4.1
Lymphatic leukemia (204)	1	0.3	4.0	0.5, 31.6	1	0.2	4.9	0.6, 39.2	0	0.3			0	0.5			9	2	1.2	1.6
Myeloid leukemia (205)	1	0.3	2.9	0.4, 22.3	0	0.4			2	0.3	6.0	1.3, 26.7	2	0.4	4.6	1.0, 20.0	5	1.5	3.4	1.3, 8.4
Leukemia, unspecified (208)	1	0.7	1.4	0.2, 10.6	1	0.4	2.4	0.3, 18.5	0	0.2			0	0.2			2	1.5	1.3	0.3, 5.3
Diabetes mellitus (250)	3	1.6	1.8	0.6, 5.8	2	1.8	1.1	0.3, 4.4	1	1.7	0.6	0.1, 4.1	0	2.5			6	7.7	0.8	0.3, 1.7
All circulatory diseases (390–459)	39	39.9	1.0	0.7, 1.3	44	37.5	1.2	0.9, 1.6	32	34.3	0.9	0.7, 1.3	35	36.2	1.0	0.7, 1.4	150	148.3	1.0	0.9, 1.2
Hypertension (400–405)	0	1.6			0	1.3			1	1.2	0.8	0.1, 5.9	1	1.5	0.7	0.1, 4.8	2	5.8	0.3	0.1, 1.4
Ischemic heart disease (410–414)	13	16.6	0.8	0.5, 1.4	20	17.3	1.2	0.7, 1.8	14	15.0	0.9	0.5, 1.6	18	14.8	1.2	0.8, 1.9	65	63.9	1.0	0.8, 1.3
Myocardial infarction (410)	6	11.7	0.5	0.2, 1.1	8	11.4	0.7	0.3, 1.4	9	10.3	0.9	0.5, 1.7	13	9.9	1.3	0.8, 2.3	36	43.5	0.8	0.6, 1.2
Chronic ischemic heart disease (412, 414)	7	4.8	1.5	0.7, 3.1	11	5.8	1.9	1.0, 3.5	5	4.7	1.1	0.4, 2.6	5	5.0	1.0	0.4, 2.4	28	20.3	1.4	0.9, 2.0
Cerebrovascular disease (430–438)	12	11.0	1.1	0.6, 1.9	14	9.7	1.4	0.8, 2.5	11	9.2	1.2	0.7, 2.2	11	8.9	1.2	0.7, 2.2	48	38.9	1.2	0.9, 1.6

Respiratory disease (460-519)	7	7.1	1.0	0.5, 2.1	7	6.8	1.0	0.5, 2.2	2	6.2	0.3	0.1, 1.3	11	6.5	1.7	0.9, 3.1	27	26.5	1.0	0.7, 1.5
Chronic obstructive pulmonary disease (490-493)	4	3.5	1.1	0.4, 3.1	6	3.0	2.0	0.9, 4.5	2	3.6	0.6	0.1, 2.3	5	3.5	1.4	0.6, 3.5	17	13.6	1.2	0.8, 2.0
Digestive disease (520-579)	4	9.4	0.4	0.2, 1.1	7	7.7	0.9	0.4, 1.9	6	6.2	1.0	0.4, 2.2	7	5.9	1.2	0.6, 2.5	24	29.2	0.8	0.5, 1.2
Cirrhosis of the liver (571)	3	6.6	0.5	0.1, 1.4	5	5.7	0.9	0.4, 2.1	5	4.3	1.2	0.5, 2.8	3	3.7	0.8	0.3, 2.6	16	20.2	0.8	0.5, 1.3
Accidents (800-999)	10	9.1	1.1	0.6, 2.1	6	8.3	0.7	0.3, 1.6	9	6.9	1.3	0.7, 2.5	10	7.9	1.3	0.7, 2.4	35	32.4	1.1	0.8, 1.5

\* Adjusted for age and calendar period.

† ICD-9, *International Classification of Diseases and Causes of Death*, Ninth Revision; Obs, observed no.; Exp, expected no.; RR, rate ratio; CI, confidence interval.

among females in all exposure zones, and the increase was suggestively time related. This finding should be interpreted with caution, however. The diagnostic accuracy of death certificates for this condition is poor, but inaccuracy should have affected exposed and nonexposed subjects nondifferentially. Systematic differences in dietary habits, as noted already, were improbable. A hypothetical role for dioxin is biologically plausible in light of the known, although not completely understood, interaction of dioxin with hormonal factors (50). An elevated prevalence of diabetes and a positive association between TCDD serum levels and fasting serum glucose levels were found in a survey of US chemical workers exposed to dioxin, but confounding by other variables could not be excluded. (51). Follow-up of a large cohort of US male chemical workers instead failed to detect any excess mortality from diabetes (40). In an accidentally exposed German industrial cohort, mean fasting glucose levels increased slightly with current, but not back-extrapolated, dioxin levels (52). In addition, highly exposed Vietnam veterans were found to have a high prevalence of diabetes and a decrease in time-to-diabetes onset with dioxin exposure (53); in addition, serum dioxin levels were associated with insulin and sex hormone-binding globulin (54). A merely suggestive increase also was found in an international cohort of chemical workers exposed to TCDD or higher chlorinated dioxins (55).

Among males, circulatory disease mortality (chronic ischemic heart disease in particular) was elevated in zone A in the early postaccident period. The previously mentioned similarities between the exposed and reference populations make differences in smoking and dietary habits a highly improbable explanation for this finding. A possibly differential cause-of-death certification in the early postaccident period can be hypothesized. However, health referral conditions were common in the exposed and reference areas; in addition, cardiovascular disease was not considered among the expected effects of dioxin exposure. That dioxin can adversely affect the cardiovascular system is well documented. TCDD has been shown experimentally to alter cardiac function and morphology (44, 56-60). It increases serum triglycerides and cholesterol, well-established risk factors for cardiovascular disease (61), in both experimental animals (62-64) and humans (65, 66). In an international cohort of pesticide manufacturers and applicators, exposure to TCDD and higher-chlorinated dioxins was associated with significantly increased ischemic heart disease mortality (55). One German (41) and one Dutch (29) study found a significant excess of ischemic heart disease associated with dioxin exposure, whereas another German study (27) did not.

Occurrence of the unusual circulatory disease mortality in the short postaccident period suggests another possibly relevant disease determinant, that is, the heavy psychosocial impact of the accident (67, 68). For months and possibly years after the accident, people experienced intense social rejection, deep anger and frustration, acute fear for their future and the health of their children, anxiety about relocation of their houses and work activities, and so forth. The burden of these disaster-linked psychosocial stressors might have precipitated early deaths from preexisting ill-health

conditions. Disruption of the social environment following a disastrous event is a well-known cause of distress and can also influence coronary heart disease risk factors (69–72).

The increased chronic obstructive pulmonary disease mortality was especially apparent among males in zone A, but without a distinct time-related pattern, and it also affected women in zones A and B. Previous studies of TCDD-exposed populations do not support this association. It is difficult to hypothesize such an extreme and systematic difference in smoking habits between the otherwise-similar index and reference populations that would explain a threefold increased relative risk. In addition, such a difference would have affected the results for smoking-associated cancer. The most plausible way in which TCDD might have contributed to this finding is through its recognized immunotoxic activity (73, 74). Impaired protection and defense against episodes of respiratory infection play a major role in the natural history of chronic obstructive pulmonary disease (75). As for chronic ischemic heart disease, even among people with preexisting chronic obstructive pulmonary disease, the accident-related stressors might have been relevant in precipitating early deaths.

The limited number of available blood dioxin measurements did not allow individual categorization by TCDD dose. Therefore, no appropriate dose-response estimates were possible, and population exposure characterization remained ecologic. The noted increased risks became apparent in the high-exposure zones. Results for the least-contaminated zone R failed to suggest increased cancer risks, whereas a possible modest excess mortality from diabetes and chronic ischemic heart disease could not be excluded.

Extrapolation of these high-exposure risk estimates to current environmental dioxin levels is problematic. Instead, results of this study are informative with regard to hazard identification. They add further evidence in support of the recent evaluation (76) of dioxin as a human carcinogen, and they corroborate the hypotheses of its association with cardiovascular and endocrine-related health effects. To further elucidate the TCDD action mechanism, epidemiologic studies that use biochemical and molecular markers are being conducted in subsamples of the study population (77). Additional insight into cancer risk is also expected from the concurrent incidence study (24). The increased relative risk estimates for several causes of cancer in the >15-year latency period make continuation of the follow-up mandatory.

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