Original Contribution

Mortality in a Population Exposed to Dioxin after the Seveso, Italy, Accident in 1976: 25 Years of Follow-Up

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The Seveso accident in 1976 caused a large, populated area north of Milan, Italy, to be contaminated by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). In this study, the authors followed up the exposed population for chronic effects; this paper reports the results of the mortality follow-up extension for 1997–2001. The study cohort includes 278,108 subjects resident at the time of the accident or immigrating/born in the 10 years thereafter in three contaminated zones with decreasing TCDD soil levels (zone A, very high; zone B, high; zone R, low) and in a reference territory comprising surrounding, noncontaminated municipalities. Vital status and cause-of-death ascertainment were 99% complete. Adjusted rate ratios and 95% confidence intervals were calculated by using Poisson regression. Results confirmed previous findings of excesses of lymphatic and hematopoietic tissue neoplasms in zones A (six deaths; rate ratio = 2.23, 95% confidence interval: 1.00, 4.97) and B (28 deaths; rate ratio = 1.59, 95% confidence interval: 1.09, 2.33). These zones also showed increased mortality from circulatory diseases in the first years after the accident, from chronic obstructive pulmonary disease, and from diabetes mellitus among females. A toxic and carcinogenic risk to humans after high TCDD exposure is supported by the results of this study.

accidents, occupational; carcinogens, environmental; chemical industry; cohort studies; mortality; tetrachlorodibenzodioxin

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

The most toxic member of the large family of polychlorodibenzodioxins is 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), a nonwanted by-product of numerous chemical reactions involving chlorine compounds, highly persistent in the environment and biologic organisms, that was recognized as a strong toxicant and carcinogen in experimental animals (1–4). In humans, the epidemiologic evidence for carcinogenicity was considered ''limited'' by an international expert group in 1997, yet mechanistic considerations led to its classification as a ''human carcinogen'' (3). This evaluation was supported by most subsequent studies involving military (5–8), occupational (9–12), and population cohorts (13–15); reanalyses with estimates of the dose-response relation (16–19); and meta-analyses and reviews (20, 21). Questions about the epidemiologic evidence and debate on the actual cancer risk posed by TCDD to the general population remain

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(22–25). Other health effects reported to be associated with TCDD exposure include diabetes mellitus, circulatory diseases, and pulmonary disease (3).

The Seveso, Italy, dioxin episode caused severe TCDD exposure to a population comprising people of both genders and all ages, with little or no interference by other contaminants. The accident took place on July 10, 1976, in the trichlorophenol production department of a chemical plant located near the town of Seveso, 25 km north of Milan. A chemical cloud containing several kilograms of TCDD was released into the environment and contaminated a vast and densely populated area (26, 27).

Several health outcomes were investigated in the early post-accident period, including spontaneous abortion (28), cytogenetic abnormalities (29, 30), congenital malformations (31, 32), liver function and lipid metabolism (33, 34), immunologic (35) and neurologic (36, 37) impairment, and chloracne (38). In 1984, the government-appointed International Steering Committee concluded that the only ascertained health effect was chloracne, occurring mainly in children (39).

In 1985, we implemented a cohort study to investigate the long-term impact of the accident on mortality and cancer incidence. We recorded elevated cardiovascular mortality in the first years after the event and suggestive increases in diabetes and chronic lung diseases. The most consistent finding was an elevated risk of lymphatic and hematopoietic neoplasm among both males and females (13, 14). We report here the results of the mortality follow-up extension for the period 1997–2001.

MATERIALS AND METHODS

Methods for cohort identification, exposure definition, follow-up, and cause-of-death ascertainment were previously described in detail (13, 40) and are summarized here.

Subjects

The contaminated area was divided into three zones, namely, A (very high contamination, from where people were displaced), B (high), and R (low) (figure 1). The study population (table 1) included two components: the first of more than 37,000 subjects residing in any of the three contamination zones on the day of the accident (''present'') who were directly exposed to the toxic cloud and may have consumed food from local crops and animals; and the second of about 8,000 persons who migrated into (or were newborn in) any of the contaminated zones in the 10-year period after the accident (''nonpresent''). The A, B, and R zones encompassed portions of the territory of six municipalities. As a reference population, we elected the residents of the unaffected areas of those six plus those residents of five surrounding non-contaminated towns (present: 181,574; nonpresent: 51,166). The overall study cohort (exposed and nonexposed) thus included 278,108 residents (79 percent residents at the time of the accident) of 11 municipalities.

Exposure

Subjects were assigned to one of the zones (A, B, R, or reference) based on their official residence on the day of the accident or at entry into the area. Residence has the advantage of being highly reliable and readily available for every member of this large cohort; in the Lombardy region of Italy, it is highly concordant with actual domicile (well over 95 percent). We also verified, in a small sample of cohort members, that residence was highly concordant with actual presence in the area on the day of the accident (41). Analytical constraints had precluded determination of biologic exposure markers at that time. When analytical advancements made it feasible to determine TCDD in small blood samples taken shortly after the accident, elevated levels indicating internal exposure to TCDD (and not to other dioxin-like compounds) were documented in individuals living in the contaminated zones (42, 43). High levels persisted in blood and milk samples collected years later (41, 44, 45). Importantly, the zone classification appeared in good agreement with the average blood levels measured in several samples of the study population (table 2).

Living in the area after the accident seemed not to entail additional exposure. None of zone B residents' serum dioxin levels increased over time, and no detectable serum TCDD levels were found in a small sample of people who entered the area after the accident (43), hence the stratification of the cohort into the two components present and nonpresent.

Follow-up

The overall population (exposed and referents) has been followed up as a single, unique cohort. The vital statistics offices of the 11 study municipalities have been transmitting whole population updates (births, deaths, migration within and outside the area) without knowledge of exposure categorization. For those who emigrated outside the study area and remained within the Lombardy region, we performed a record linkage with population databases and traced about 40,000 subjects resident or dead elsewhere within the region. Finally, for those not linked or who did emigrate outside the region (about 20,000), we performed an individual postal follow-up through the vital statistics offices of thousands of municipalities throughout Italy.

Cause of death has been ascertained by record linkage with databases of the National Central Statistics Institute and Lombardy region local health units or by postal contact with other vital statistics offices and local health units. In case of successful linkage, we obtained the *International Classification of Diseases* death codes. (The Eighth Revision was used for deaths before 1979 and the Ninth Revision for deaths thereafter. All codes were then translated to Ninth Revision codes.) When official codes were not available, the underlying cause of death was coded by trained personnel following standard rules blind to zone assignment. Epidemiology units of some large cities collaborated in both vital status and cause-of-death ascertainment.

Statistical analysis

We computed person-years of observation from beginning of follow-up (July 10, 1976, or date of first entry) until death or end of the study (December 31, 2001). We
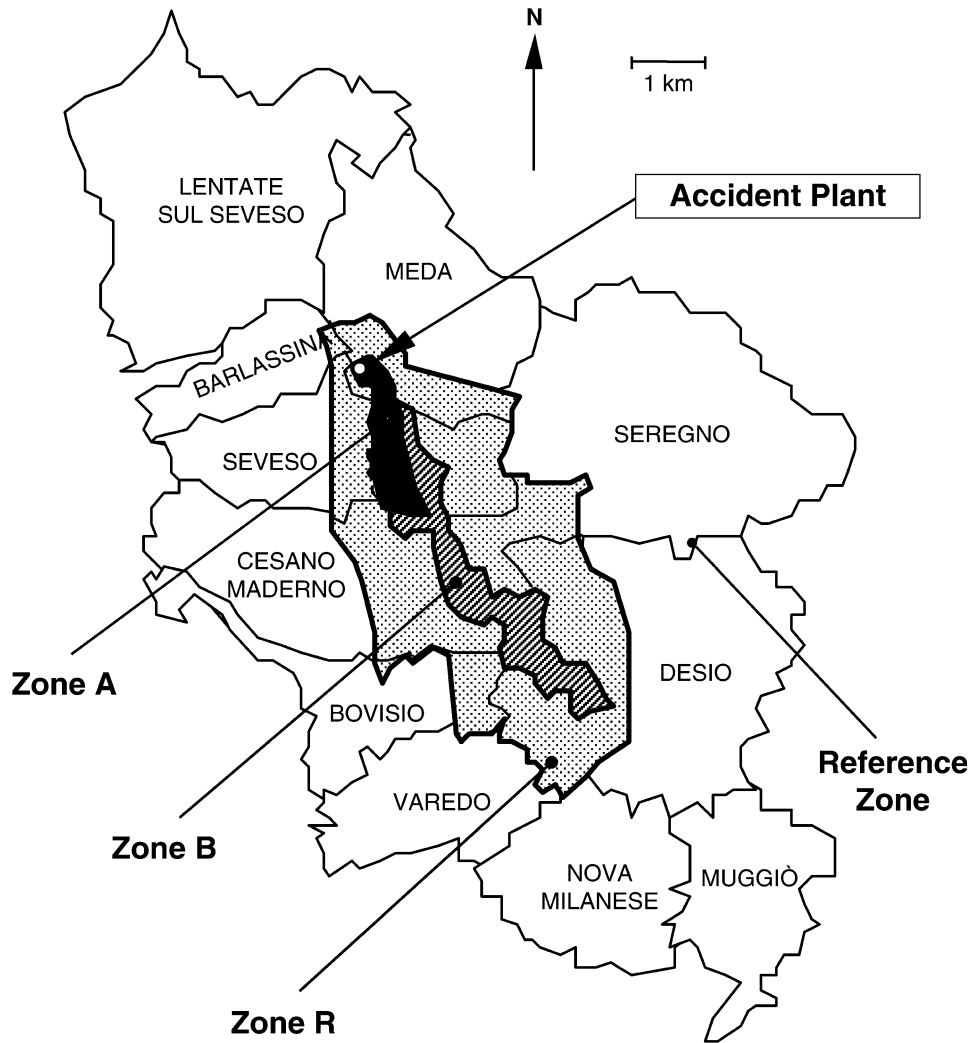
FIGURE 1. The Seveso, Italy, area, including the territory of 11 towns. The map indicates the three dioxin-contaminated zones with decreasing mean soil levels (A, B, and R) and the surrounding noncontaminated zone adopted as the reference.

calculated cause-specific mortality rate ratios and their 95 percent confidence intervals for every contaminated zone (A, B, and R) against the reference by using Poisson regression models (46). The regression models were adjusted for (or stratified by) the following covariates: presence at the accident, gender, period (1976–1981, 1982–1986, 1987–1991,

TABLE 1. Number of subjects in the Seveso, Italy, cohort, 1976–2001, by zone of residence* and presence in the area at the time of the dioxin accident

Zone	Present (resident of the area on July 10, 1976)			Nonpresent (entered the area after the accident)			Total
	Females	Males	Total	Females	Males	Total	
A	371	352	723	43	38	81	804
B	2,350	2,471	4,821	574	546	1,120	5,941
R	15,928	15,715	31,643	3,496	3,484	6,980	38,623
Reference	93,224	88,350	181,574	25,547	25,619	51,166	232,740
Total	111,873	106,888	218,761	29,660	29,687	59,347	278,108

* Refer to the Materials and Methods section of the text for a definition of these zones.

TABLE 2. TCDD* soil levels and serum concentrations measured in selected samples of residents in the study area† after the 1976 Seveso, Italy, accident

Zone	Mean soil level (μg/m²)‡	Median lipid-adjusted serum level in pg/g or parts per trillion	
	Minimum–maximum	Samples collected in 1976–1977§ (no.)	Samples collected in 1992–1996¶ (no.)
A	15.5–580.4	447.0 (296)	73.3 (7)
B	1.7–4.3	94.0 (80)	12.4 (51)
R	0.9–1.4	48.0 (48)	NA*
Reference	NA	NA	5.5 (52)

* TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; NA, not available.
† Refer to the Materials and Methods section of the text for a definition of the study zones.
‡ Refer to Bertazzi and di Domenico (26) for more information.
§ Refer to Needham et al. (43) for more information.
¶ Refer to Landi et al. (41) for more information.

1992–1996, and 1997–2001), age (<1, 1–4 years, then 5-year categories until age 84 years, and ≥ 85 years), and time since first exposure ("latency," 0–4, 5–9, 10–14, 15–19, and ≥ 20 years).

We performed further analyses on selected subgroups of the cohort including 182 persons with chloracne (47) and about 3,000 residents in a zone R quarter named "Polo"

TABLE 3. Person-years at risk and deaths in the Seveso, Italy, cohort, 1976–2001, by zone of residence,* among subjects resident (present) and not resident (nonpresent) in the area at the time of the dioxin accident

Zone	Person-years		Deaths	
	Present	Nonpresent	Present	Nonpresent
A				
No.	16,922	1,674	118	3
%	0.3	0.1	0.3	0.1
B				
No.	113,724	22,837	750	61
%	2.3	1.9	1.7	1.8
R				
No.	732,628	140,537	5,934	372
%	14.6	12.0	13.4	11.1
Reference				
No.	4,153,763	1,010,778	37,428	2,918
%	82.8	86.0	84.6	87.0
Total				
No.	5,017,038	1,175,826	44,230	3,354
%	100.0	100.0	100.0	100.0

* Refer to the Materials and Methods section of the text for a definition of these zones.

TABLE 4. Source of ICD-9* codes for underlying cause of death by zone of residence† in the Seveso, Italy, cohort, 1976–2001

Zone	Central Statistics Institute	Local health units	Internal coding	Missing	Total
A					
No.	61	14	46	0	121
%	50.4	11.6	38.0	0.0	100.0
B					
No.	340	70	394	7	811
%	41.9	8.6	48.6	0.9	100.0
R					
No.	2,806	700	2,728	72	6,306
%	44.5	11.1	43.3	1.1	100.0
Reference					
No.	18,174	4,180	17,580	412	40,346
%	45.1	10.4	43.6	1.0	100.0
Total					
No.	21,381	4,964	20,748	491	47,584
%	44.9	10.4	43.6	1.0	100.0

* ICD-9, *International Classification of Diseases*, Ninth Revision.
† Refer to the Materials and Methods section of the text for a definition of these zones.

with possible higher exposure than the surrounding zone R (14). Final data management, person-year calculation, and statistical analyses were performed by using Stata software, version 9 (48).

RESULTS

Follow-up was more than 99 percent complete in each zone. The total number of person-years at risk between 1976 and 2001 was more than 6 million (81 percent accrued by subjects present at the accident), we recorded 47,584 deaths (93 percent present) (table 3), and exposed individuals contributed 16.6 percent of the person-years and 15.2 percent of the deaths. There were some differences in the source distribution of *International Classification of Diseases*, Ninth Revision codes across zones: compared with R and the reference zones, there were 5 percent fewer official codes in zone B and 5 percent more in zone A, respectively (table 4).

Tables 5 and 6 show results for subjects present at the accident. During the whole study period, all-cause and all cancer mortality in the three polluted zones was not elevated in comparison with the reference population (table 5). The most notable finding was increased mortality from cancers of the lymphatic and hematopoietic tissues in the two most polluted zones, with a significant ($p = 0.04$) test for trend of rate ratios across zones (A > B > R). The increases were stronger for females (zone A: four deaths, rate ratio (RR) = 3.17, 95 percent confidence interval (CI): 1.18, 8.49; zone B: 15 deaths, RR = 1.94, 95 percent CI: 1.16, 3.25), with the

TABLE 5. Results of Poisson regression analyses of mortality in the Seveso, Italy, area, 1976–2001, for selected causes of death: number of deaths, rate ratios, and 95% confidence intervals for the polluted zones (A, B, and R) compared with the reference zone*,†

Cause of death (ICD-9‡ code)	Zone A			Zone B			Zone R		
	No.	RR‡	95% CI‡	No.	RR	95% CI	No.	RR	95% CI
All causes (001–999)	118	1.02	0.85, 1.22	750	0.96	0.89, 1.03	5,934	1.03	1.01, 1.06
All cancers (140–208)	42	1.03	0.76, 1.39	244	0.92	0.81, 1.05	1,848	0.97	0.92, 1.02
Digestive (150–159)	15	0.95	0.57, 1.57	81	0.78	0.63, 0.97	718	0.95	0.88, 1.03
Stomach (151)	3	0.65	0.21, 2.03	24	0.78	0.52, 1.17	212	0.95	0.82, 1.09
Colon (153)	3	0.98	0.31, 3.03	12	0.60	0.34, 1.06	137	0.94	0.78, 1.12
Rectum (154)	1	0.90	0.13, 6.42	11	1.51	0.83, 2.76	50	0.94	0.70, 1.27
Liver (155)	3	1.03	0.33, 3.20	16	0.86	0.52, 1.40	107	0.80	0.65, 0.98
Biliary tract (156)	0	0		2	0.56	0.14, 2.26	31	1.16	0.79, 1.70
Pancreas (157)	2	1.17	0.29, 4.68	5	0.45	0.19, 1.09	76	0.95	0.74, 1.21
Other digestive (159)	2	2.43	0.60, 9.76	8	1.49	0.74, 3.01	38	0.95	0.67, 1.33
Respiratory (160–165)	11	1.11	0.62, 2.01	70	1.10	0.87, 1.40	432	0.97	0.88, 1.07
Lung (162)	11	1.26	0.70, 2.29	62	1.11	0.87, 1.43	383	0.98	0.88, 1.09
Soft tissue sarcoma (171)	0	0		0	0		4	0.76	0.27, 2.14
Melanoma (172)	1	3.06	0.43, 22.01	2	0.97	0.24, 3.93	12	0.83	0.45, 1.51
Breast (174)	2	0.60	0.15, 2.41	13	0.65	0.37, 1.12	133	0.87	0.73, 1.05
Genitourinary tract (179–189)	3	0.62	0.20, 1.94	28	0.89	0.61, 1.29	240	1.04	0.91, 1.20
Uterus (179–182)	0	0		2	0.48	0.12, 1.92	41	1.26	0.90, 1.75
Ovary (183)	1	1.19	0.17, 8.46	2	0.39	0.10, 1.57	37	0.96	0.68, 1.36
Prostate (185)	1	0.87	0.12, 6.17	8	0.88	0.44, 1.77	65	1.06	0.81, 1.38
Bladder (188)	1	1.04	0.15, 7.39	6	0.90	0.40, 2.01	42	0.88	0.64, 1.22
Kidney (189)	0	0		3	0.63	0.20, 1.98	39	1.15	0.82, 1.62
Brain (191)	0	0		3	0.67	0.22, 2.11	34	1.10	0.76, 1.58
Lymphatic and hematopoietic tissue (200–208)	6	2.23	1.00, 4.97	28	1.59	1.09, 2.33	124	0.99	0.82, 1.20
Hodgkin's disease (201)	0	0		3	2.15	0.67, 6.86	9	0.94	0.46, 1.89
Non-Hodgkin's lymphoma (200, 202)	3	3.35	1.07, 10.46	7	1.23	0.58, 2.60	40	0.99	0.71, 1.38
Multiple myeloma (203)	2	4.34	1.07, 17.52	5	1.68	0.69, 4.10	24	1.10	0.71, 1.69
Leukemia (204–208)	1	0.89	0.12, 6.31	13	1.73	1.00, 3.02	51	0.96	0.72, 1.29
Lymphatic leukemia (204)	0	0		3	1.30	0.41, 4.10	23	1.41	0.90, 2.21
Myeloid leukemia (205)	1	2.12	0.30, 15.17	6	1.97	0.87, 4.46	16	0.74	0.44, 1.24
Leukemia, unspecified (208)	0	0		4	2.38	0.87, 6.52	10	0.84	0.43, 1.62
Diabetes mellitus (250)	3	1.01	0.33, 3.14	26	1.32	0.89, 1.94	192	1.26	1.08, 1.47
All circulatory diseases (390–459)	45	1.06	0.79, 1.42	289	0.99	0.88, 1.11	2,357	1.07	1.02, 1.12
Chronic rheumatic heart disease (393–398)	3	5.74	1.83, 17.99	1	0.30	0.04, 2.18	24	0.99	0.64, 1.52
Hypertension (400–405)	5	2.18	0.90, 5.25	11	0.72	0.40, 1.31	144	1.20	1.01, 1.43
Ischemic heart disease (410–414)	13	0.83	0.48, 1.43	102	0.95	0.78, 1.15	842	1.06	0.98, 1.14
Myocardial infarction (410)	6	0.63	0.28, 1.41	54	0.86	0.65, 1.12	447	0.98	0.89, 1.08
Chronic ischemic heart disease (412, 414)	7	1.11	0.53, 2.34	47	1.06	0.80, 1.42	390	1.16	1.04, 1.29
Cerebrovascular disease (430–438)	11	0.90	0.50, 1.63	101	1.21	0.99, 1.48	695	1.09	1.00, 1.18
Respiratory disease (460–519)	9	1.41	0.73, 2.71	48	1.03	0.77, 1.36	341	0.99	0.89, 1.11
Chronic obstructive pulmonary disease (490–493)	7	2.53	1.20, 5.32	26	1.26	0.85, 1.86	175	1.17	1.00, 1.38
Digestive disease (520–579)	5	0.72	0.30, 1.74	45	0.99	0.74, 1.33	366	1.11	1.00, 1.24
Cirrhosis of the liver (571)	2	0.46	0.11, 1.83	23	0.82	0.54, 1.24	217	1.09	0.94, 1.26
Unknown (799.9)	0	0		7	0.85	0.40, 1.79	60	1.06	0.80, 1.39
Accidents (800–999)	7	1.09	0.52, 2.30	46	1.03	0.77, 1.39	299	1.00	0.88, 1.13

* Refer to the Materials and Methods section of the text for a definition of these zones.
† Included were all ages of subjects, both genders, and resident in the Seveso area at the time of the accident.
‡ ICD-9, *International Classification of Diseases*, Ninth Revision; RR, rate ratio adjusted for gender, age, and period; CI, confidence interval.

TABLE 6. Results of Poisson regression analyses of mortality in the Seveso, Italy, area, 1976–2001, for selected causes of death, by time since the dioxin accident: number of deaths, rate ratios, and 95% confidence intervals for the polluted zones (A, B, and R) compared with the reference zone*,†

Cause of death and zone	No. of years since the accident				
	0–4	5–9	10–14	15–19	≥20
All cancers					
Zone A					
No.	4	8	4	8	18
RR‡	0.65	1.17	0.50	0.88	1.65
95% CI‡	0.24, 1.74	0.58, 2.34	0.19, 1.33	0.44, 1.77	1.04, 2.62
Zone B					
No.	30	52	59	64	39
RR	0.75	1.12	1.11	1.11	0.58
95% CI	0.53, 1.08	0.85, 1.47	0.86, 1.44	0.87, 1.42	0.42, 0.79
Zone R					
No.	271	315	358	402	502
RR	0.90	0.92	0.94	0.98	1.08
95% CI	0.80, 1.03	0.82, 1.03	0.84, 1.05	0.88, 1.08	0.98, 1.18
Lung cancer					
Zone A					
No.	1	2	1	3	4
RR	0.78	1.51	0.53	1.62	1.66
95% CI	0.11, 5.57	0.38, 6.06	0.07, 3.75	0.52, 5.04	0.62, 4.44
Zone B					
No.	8	13	13	14	14
RR	0.95	1.44	1.08	1.21	0.95
95% CI	0.47, 1.91	0.83, 2.50	0.62, 1.87	0.71, 2.06	0.56, 1.62
Zone R					
No.	47	55	90	88	103
RR	0.77	0.86	1.06	1.09	1.03
95% CI	0.57, 1.04	0.65, 1.14	0.85, 1.32	0.87, 1.37	0.84, 1.27
Lymphatic and hematopoietic tissue cancer					
Zone A					
No.	0	0	0	2	4
RR	0	0	0	3.30	5.38
95% CI				0.82, 13.31	2.00, 14.49
Zone B					
No.	4	5	8	7	4
RR	1.40	1.70	2.44	1.82	0.86
95% CI	0.52, 3.78	0.70, 4.15	1.20, 4.98	0.85, 3.86	0.32, 2.31
Zone R					
No.	12	17	27	33	35
RR	0.58	0.80	1.15	1.21	1.09
95% CI	0.32, 1.05	0.48, 1.32	0.76, 1.74	0.83, 1.75	0.76, 1.56

Table continues

TABLE 6. Continued

Cause of death and zone	No. of years since the accident				
	0–4	5–9	10–14	15–19	≥20
Diabetes mellitus					
Zone A					
No.	0	1	1	0	1
RR	0	1.84	1.63	0	1.61
95% CI		0.26, 13.09	0.23, 11.65		0.23, 11.51
Zone B					
No.	7	2	7	8	2
RR	2.42	0.51	1.66	1.67	0.51
95% CI	1.14, 5.17	0.13, 2.05	0.78, 3.51	0.83, 3.38	0.13, 2.06
Zone R					
No.	26	33	49	49	35
RR	1.10	1.06	1.49	1.33	1.24
95% CI	0.73, 1.67	0.74, 1.53	1.10, 2.04	0.98, 1.81	0.86, 1.78
All circulatory diseases					
Zone A					
No.	12	14	5	5	9
RR	1.36	1.84	0.67	0.59	0.88
95% CI	0.77, 2.40	1.09, 3.12	0.28, 1.60	0.24, 1.42	0.46, 1.69
Zone B					
No.	55	64	43	51	76
RR	0.96	1.10	0.79	0.87	1.18
95% CI	0.73, 1.25	0.86, 1.41	0.59, 1.07	0.66, 1.15	0.94, 1.48
Zone R					
No.	527	471	455	409	495
RR	1.14	1.06	1.14	0.95	1.07
95% CI	1.04, 1.25	0.96, 1.17	1.03, 1.26	0.85, 1.05	0.97, 1.18
Chronic obstructive pulmonary disease					
Zone A					
No.	4	0	0	3	0
RR	7.23	0	0	5.43	0
95% CI	2.69, 19.48			1.74, 17.01	
Zone B					
No.	3	8	5	5	5
RR	0.79	2.27	1.15	1.19	1.04
95% CI	0.25, 2.47	1.12, 4.62	0.47, 2.79	0.49, 2.90	0.43, 2.53
Zone R					
No.	27	36	38	33	41
RR	0.93	1.40	1.25	1.09	1.24
95% CI	0.62, 1.39	0.98, 2.00	0.88, 1.76	0.75, 1.57	0.89, 1.74

∗ Refer to the Materials and Methods section of the text for a definition of these zones.
† Included were all ages of subjects, both genders, and resident in the Seveso area at the time of the accident.
‡ RR, rate ratio adjusted for gender and age; CI, confidence interval.

highest risks for non-Hodgkin's lymphomas (zone A: two deaths, RR = 4.45, 95 percent CI: 1.10, 17.99), all lymphomas (zone B: seven deaths, RR = 2.14, 95 percent CI: 1.00, 4.57), and myelomas (zone B: four deaths, RR = 3.07, 95 percent CI: 1.12, 8.42). Among males, only leukemia deaths in zone B were significantly above expectation (nine deaths, RR = 2.07, 95 percent CI: 1.06, 4.05). No deaths from soft-tissue sarcomas were observed in zones A and B, and mortality from this cancer in zone R was below the reference.

In zone A, liver cancer was not elevated, whereas lung cancer showed a 26 percent increase; for both cancers, all deaths occurred among males, yielding increased rate ratios of 1.45 (95 percent CI: 0.47, 4.51) and 1.45 (95 percent CI: 0.80, 2.62), respectively. All circulatory diseases were not elevated. The chronic rheumatic heart diseases and hypertension increases were confined to females: among them, three deaths from chronic rheumatic heart diseases and four from hypertension yielded rate ratios of 9.19 (95 percent CI: 2.91, 29.01) and 2.60 (95 percent CI: 0.97, 6.95), respectively. Males showed elevated mortality from circulatory diseases (29 deaths, RR = 1.40, 95 percent CI: 0.97, 2.01) and chronic ischemic heart diseases (seven deaths, RR = 2.48, 95 percent CI: 1.18, 5.22). Chronic obstructive pulmonary disease was more than doubled; the risk was elevated for both genders, but there were very few deaths among females (males: five deaths, RR = 2.72, 95 percent CI: 1.13, 6.57; females: two deaths, RR = 2.07, 95 percent CI: 0.52, 8.33). There were only three noncancer deaths among subjects who entered zone A after the accident (RR = 1.01, 95 percent CI: 0.33, 3.14).

In zone B, there was a 50 percent nonsignificant increase in rectal and other digestive cancer mortality; the excesses were limited to males, with, respectively, eight deaths (RR = 1.81, 95 percent CI: 0.89, 3.67) and six deaths (RR = 2.52, 95 percent CI: 1.10, 5.74). Cerebrovascular diseases showed a moderate increase among both males (51 deaths, RR = 1.24, 95 percent CI: 0.94, 1.64) and females (50 deaths, RR = 1.19, 95 percent CI: 0.90, 1.58). Among females, we observed elevated rates of diabetes mellitus (20 deaths, RR = 1.78, 95 percent CI: 1.14, 2.77), chronic obstructive pulmonary disease (11 deaths, RR = 1.99, 95 percent CI: 1.09, 3.64), and digestive diseases (23 deaths, RR = 1.42, 95 percent CI: 0.94, 2.14). We recorded 17 cancer deaths among subjects nonpresent at the accident (RR = 1.60, 95 percent CI: 0.99, 2.59); six deaths were digestive cancers (RR = 1.88, 95 percent CI: 0.83, 4.22) and two were lymphatic and hematopoietic cancers (RR = 1.74, 95 percent CI: 0.43, 7.12); among noncancer causes, only accidents showed an increased rate (nine deaths, RR = 1.94, 95 percent CI: 1.00, 3.78).

In zone R, there was a 20 percent reduction in liver cancer mortality compared with the rates in the reference zone. We also observed modest increases in the rates of diabetes mellitus and several circulatory diseases, which, with the exception of cerebrovascular diseases, were limited to females (1,246 deaths from all circulatory diseases, RR = 1.09, 95 percent CI: 1.03, 1.16). Among people nonresident at the time of the accident, we did not observe meaningful increased (or decreased) rates of cancer and noncancer causes of death.

Table 6 shows results of the analyses by time since the accident ("latency") for causes selected because they were found in excess in this or in previous relevant epidemiologic studies. All cancer mortality showed a 65 percent increase after 20 years in zone A from lung (four deaths), digestive (six deaths, including three liver cancers that yielded an RR of 3.74, 95 percent CI: 1.20, 11.71), and lymphatic and hematopoietic tissue (four deaths) cancers. Among males, the rate ratio for all cancer mortality after 20 years (13 deaths) was 1.93 (95 percent CI: 1.12, 3.33); among females, the rate ratio was 1.17 (95 percent CI: 0.49, 2.83) based on five cases. The majority of lung cancer deaths in zone A (all males) occurred after 15 years since the accident, with 60–70 percent elevated rates (when only males were considered, the excesses were approximately 90 percent). No such increases were found in the other zones. In addition, the lymphatic and hematopoietic tissue cancer excesses in zone A occurred after 15 years; in zone B, the most affected categories were 10–14 and 15–19 years. Diabetes mellitus was elevated in zone B in the first 5 years and in zone R in the category 10–14 years after the accident; the excesses were observed among females only. Circulatory diseases in zone A were elevated mainly in the first 10 years. Chronic obstructive pulmonary disease mortality was elevated in zone A in the categories 0–4 and 15–19 years and in zone B in the 5–9–year category.

Among 182 subjects who had developed chloracne soon after the accident, we found two deaths, one (zone A) from myocarditis and one from suicide (zone R). No additional deaths occurred in the 1997–2001 extension. Among residents of the Polo quarter (located outside zones A and B but with possible high exposure), we observed no increased mortality from all causes or all cancers; there were 11 deaths from lymphatic and hematopoietic cancers (RR = 1.26, 95 percent CI: 0.69, 2.28); and mortality from all circulatory diseases was modestly elevated (159 deaths, RR = 1.18, 95 percent CI: 1.01, 1.39).

DISCUSSION

In this study, we found elevated mortality from lymphatic and hematopoietic cancers in the most polluted zones A and B; there were also suggestions of mortality increases for several other cancer (rectum, lung) and noncancer (circulatory diseases, chronic obstructive pulmonary disease, and diabetes mellitus) causes. The results for zone B confirmed previous findings (13, 14). Analysis for zone A alone was, for the first time, informative because of the increasing power of the study since follow-up is being continued.

We are confident that the study was not affected by major selection effects; vital status ascertainment was nearly complete. Limitations exist, the most important one being the definition of exposure, which could be only categorical, ecologic, and based on official residence. Some degree of misclassification was therefore unavoidable for two main reasons: first, there may have been heterogeneity of exposure to TCDD within each zone; second, residence may not have been concordant with domicile and/or the effective presence in the area at the time of the accident and

subsequent days or weeks. This nondifferential misclassification would tend (on average) to dilute any effect. This limitation is attenuated by the fact that zone categorization received support from results on blood dioxin measurements (41, 43, 44, 47), which clearly indicated that, in general, there was a definite dose gradient A > B > R and that, for referents, values were actually in the background range. Moreover, official residence is highly concordant with domicile and was found to be correlated with presence in the area at the time of the accident in cross-sectional studies within this same population (41).

The exposed and referent populations belonged to the same health districts and had similar access to the same health services; differential death registration patterns are therefore not expected. The follow-up procedures (tracing of vital status, collection and coding of causes of death) were performed blindly with regard to residence of the subjects. This method resulted (table 4) in a distribution of sources of causes of death fairly balanced across zone. Of course, the issue remains of some degree of (again, nondifferential) inaccuracy implicit in the use of death certificates.

Although confounding effects cannot be completely ruled out, their magnitude is expected to be small because of the use of a local reference population. As part of an earlier feasibility study, we compared preaccident (1969–1975) rates from selected causes in the four most versus the seven less contaminated towns (40): rate ratios were generally close to the null value or were modestly elevated (RR < 1.25). Exceptions were brain cancer (both genders) and leukemia and liver cirrhosis (females), all of which were not elevated after the accident.

All cancer mortality was not elevated in the whole period but showed a 60 percent increase after 20 years in the most polluted zone A because of elevated mortality among males only. In this zone, males also showed an elevation in lung cancer mortality after 15 years of follow-up. These results are in line with those from studies of highly exposed male workers (3, 9, 10, 49–55). The lung is also one of the target organs of the carcinogenic action of TCDD in animals (1, 2). We did not have individual data on smoking habits; however, information from independent surveys of random samples of the population suggests that geographic variation in smoking habits within the region is low (56, 57). Other indirect evidence is provided by the finding that other smoking-related cancers were not elevated.

The rectal cancer excess among males in zone B was lower than in previous follow-up periods (only one additional death was observed). For this type of cancer, there is little experimental evidence of an association with TCDD, although it has been occasionally found to be elevated in occupational cohort studies in Germany and New Zealand (12, 18).

The clearest and most consistent result remains the excess of lymphatic and hematopoietic neoplasms, which affected both genders and, in this update, was not limited to zone B but emerged in zone A as well. The increased pattern for specific neoplasms was not identical by gender, zone, and latency, partly because of the small number of deaths. This finding could hardly be explained by confounding from known risk factors, and excesses for these neoplasms were

reported in other occupational cohorts (3, 9–12, 18, 49, 53, 54, 58, 59), and the finding is concordant with experimental studies, which showed a dose-related, increased occurrence of lymphoma in mice (2, 60). The association with non-Hodgkin's lymphomas also gets support from the finding that, in a sample of residents of the Seveso area, the frequency of cells carrying the t(14;18) translocation (the most frequent chromosomal translocation in human lymphoid malignancies) was positively related to TCDD blood levels (61).

No deaths from soft-tissue sarcoma, a neoplasm that has been associated with TCDD exposure (3, 10, 11), were found in the most polluted zones in 25 years of follow-up. In addition, no excess was found in zone R.

We found no excess of breast and other gynecologic cancers, consistent with previous findings. Recent case-control studies in selected samples of the Seveso accident population suggested a positive association with breast cancer (62) and a negative one with uterine leiomyomas (63). Other gender-specific effects recently examined in relation to this well-established endocrine disruptor (3) were endometriosis and ovarian function, but no association was found (64, 65). A weak association with menstrual cycle length and age at menopause, but not with age at menarche, was found (66–68).

With regard to noncancer causes, we observed excess mortality from diabetes mellitus among females in all exposure zones, more marked in zone B, but with different patterns by latency within zones. Although the results might have been biased by (nondifferential) misclassification (the diagnostic accuracy of death certificates for this condition is low), the finding is interesting in light of recent evidence from a molecular epidemiologic study that identified a reliable marker for the diabetogenic action of TCDD (69). However, the fact that we observed risk excesses among only females is in contrast with the results of military cohort studies, which found increased frequency of diabetes and glucose levels among males (5, 7, 70, 71); controversial results emerged from occupational settings (17, 19, 72, 73).

Circulatory disease mortality was elevated in zone A in the early postaccident periods but was lower than expected in the most recent years. Possible explanations are the direct toxic role of TCDD itself on cardiac tissue or serum lipids and/or the tremendously stressful impact of the disaster, similar to that observed after natural disasters (27, 74, 75).

The increased chronic obstructive pulmonary disease mortality, especially apparent among zone A males but that also affected females in zones A and B, substantially reflects the rate excesses observed in the previous follow-up periods (no new cases were found in zone A in the latest years). A plurality of mechanistic considerations can be invoked to explain this finding, including direct toxicity of TCDD on bronchiolar/alveolar tissue (1, 2, 76) and interference with the immune system (77, 78), an effect that has also been found in a sample of Seveso residents (79), resulting in impaired protection against repeated lung infections and progression to chronic disease (80). In a mortality study, we cannot distinguish between an increase in incidence and a decrease in the survival of prevalent cases; therefore, we can also hypothesize, as for heart disease, that accident-related stressors might have precipitated death among

people with preexisting disease. The irregular pattern by latency somewhat stands against these hypotheses, and a residual confounding effect from smoking remains a possible explanation.

In conclusion, this study confirmed the excess of lymphatic and hematopoietic neoplasms in zone B and added new evidence of an excess also in the most highly polluted, although small, zone A. We confirmed rate excesses for other cancer and noncancer causes, whose interpretation is curbed for a number of reasons, including the possibility of some falsely positive associations due to the large number of comparisons made.

While mortality follow-up is continuing, further insight into those risks is being sought through molecular epidemiology studies, which demonstrated an interference of TCDD with gene expression (81–83). The forthcoming update of the concurrent cancer incidence study (14) is expected to further contribute to evaluation of the cancer risk to this population.

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