Cancer Incidence in a Population Accidentally Exposed to 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin

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In 1976, an accident in a plant near Seveso, Italv, exposed the local population to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Persons residing in three zones of decreasing **TCDD** contamination (A, B, and R) and a reference population were followed up for cancer Occurrence in 1977-1986. The most exposed subgroup (A) was small, and only 14 cancer cases were observed. **In** zone B, hepatobiliary cancer was elevated, especially for those living in the area for >5 years [relative risk (RR) = 2.8; 95% confidence interval (CI) = 1.2-6.3]. Men exhibited an increase in hematologic neoplasms, **most** notablv lymphoreticulosarcoma (RR = **5.7**;95% CI = 1.7-19.0). Women experienced an increased incidence of multiple myeloma (RR = 5.3; 95% **CI** = 1.2-22.6) and myeloid leukemia RR = 3.7; 95% CI = 0.3-13.7). In zone R, the incidence of **soft** tissue **tumors** and non-Hodgkin's lymphomas was elevated, particularly among persons living in the area for >5 years (RR = 3.5; 95% **CI** = 1.2-10.4 for sarcomas, and RR = **2.0**;95% **CI** = 1.2-3.6 **for** non-Hodgkin's lymphomas). Breast cancer **among** females was **below expectations** in the most contaminated zones, **and** a clear deficit **for** endometrial cancer was **observed** in zones B **and** R. (Epidemiology1993;4:398-406)

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Dioxins **are** widespread contaminants of our environment. They have no commercial value but originate as undesirable byproducts from several sources.[1] The most toxic congener of the family, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD or simply 'dioxin') is a potent carcinogen in experimental animals,- whereas its human carcinogenicity is **still** a matter of controversy.[3]

Epidemiologic studies have focused on persons exposed to products possibly contaminated with TCDD during **manufacture**,[4-6] on TCDD **use** in agriculture and related *fields*[9-19] or in war,[11,20] and on TCDD **use** after industrial accidents.[24-26] Here, we report on the population living near Seveso, Italy, where in 1976, an accidental explosion in a chemical plant caused the highest documented human exposure to TCDD.[27,28] **A** monalirv study during 1976-1986 brought to light an increase of cardiovascular deaths in the early post-accident period and suggested an unusually high occurrence of cancers at several sites.[29] We report here on cancer incidence in the **same** post-accident decade.

Methods

EXPOSURE

Environmental analyses within the territory covered by the toxic cloud provided the basis for delineating zones with different mean levels of contamination.[30] Zone **A**, the **most** heavily contaminated, had mean soil levels of TCDD ranging from 15.5 **μg per m²** to 580 μg per m². **A** total of 181 families were evacuated from this area. In zone B, the levels of TCDD **soil** contamination did not exceed, on the average, 50 μg per **m²**. Its 1,721 families were asked to follow strict regulations regarding personal and home hygiene and consumption of local water and food. **A** third area, with low-level and patchy contamination, referred to **as** the "zone of respect" (zone R), in which TCDD levels were

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generally found below 5 μg per m², surrounded zones A and B.

Information on TCDD blood levels was available for few subjects. Ten children from zone A affected by chloracne (an established marker of TCDD toxicity) showed lipid-adjusted blood levels as high as 56,000 pans per trillion (ppt). Nine adults without chloracne, from the same area, showed values ranging from 1,770 ppt to 10,400 ppt. In nine of ten persons living in the area, but outside the contaminated zones. TCDD was not detected, and in one. the observed concentration of 137 ppt was probably explained by laboratorv contamination.[28] More recentlv, results for a group of 13 subjects from zone B have become available; their blood concentrations ranged from 74 to 526 ppt (P Mocarelli and LL Needham, personal communication, 1992). All blood samples had been taken shortly after the accident.

STUDY POPULATION

The contaminated :ones included parts of the territories of six municipalities (Seveso being the most severely and extensivelv affected). These were located within the boundaries of two health districts encompassing a total of 11 municipalities.[27] The study was based on all persons ever resident in anv of these 11 municipalities at anv time from the dare of the accident onward (including newborns and immigrants,. irrespective of their current residence The information provided by the municipal vital statistics offices about addresses was the basis for assigning subjects to one of the three exposure :ones (zone A, N = 724; zone B, N = 4,824; :one R, N = 31,647) or to the surrounding noncontaminated area (N = 181,579).The population living in this latter area served as a reference population for our comparisons. The results that we report here refer to the experience of all subjects ace 20-74 vears and living in the studv area at the time of the accident, during the period Januarv 1, 1977, through December 31, 1986

FOLLOW-UP AND CASE ASCERTAINMENT

All tracing procedures were implemented at the same time and uith the same methods for the population from the contaminated zones and the noncontaminated area, without knowledge of cohort members' exposure status Tracing of persons who moved outside the studv are3(over 30,000 subjects) and ascertainment of their vital status had a hicher than 99% success rate.

Contrarv to causes of death, cancer diagnoses in Italy are not recorded on a routine basis. Consequently, cancer Occurrence ascertainment had to be limited to the region of Lombardy (nearly 9,000,000 inhabitants), where an efficient hospital admission/discharge registration system exists. All Lombardy hospitals routinely provide the regional health department uith information on any hospitalization. The automatic linkage of this information with records of smdv population members led to the identification of studv subjects admitted for any possible neoplasm to anv Lombardv hospital. For each putative case, all original medical records were reexamined in the relevant hospital(s) to ascertain the true diagnosis and date of first occurrence. The number of individual medical files identified was 41,801, and 41,778 of them were successfullv reviewed.

The anticipated loss to follow-up caused by restricting the follow-up to Lombardy residents was limited in the light of the regional emigration rate of *0.62%* per vear among the inhabitants in the contaminated :ones, and 0.64% per vear among those in the reference area.

The concurrent mortalitv studv[27] provided information on cause of death of deceased study subjects.

DATA QUALITY

The svstem of incidence data collection precluded detection of cancer cases admitted to hospitals outside Lombardv, of cases diagnosed without hospitalization (outpatients), and ot those not identified due to errors in recording or coding data. Each of these sources of loss was evaluated.

The proportion of cancer cases admitted to hospitals outside Lombardy could confidentlv be considered negligible. The main hospitals and, particularlv, the cancer hospitals are located inside the region, and they ordinarilv serve as referral hospitals for cancer patients from other Italian regions.

To estimate the proportion of cases lost because thev were diagnosed as outpatients, we checked. for rhe period 1979-1982, all cytohistologic records positive for anv neoplasm at the San Gerardo Hospital in Monza, the largest hospital near the smdv area. The proportion of undetected cases among outpatients was close to 20%, 50% of which were non-melanoma skin cancers. Among the inpatient cancer cases, 93% had been correctlv identified bv our data collection svstern

The proportion of true cases that ue did not detect because of erroneous records was estimated with an ad hoc investigation in the two main hospitals within the study area (Desio and Seregno). All original medical files for a 1½-year period (N = 27,500) were checked against the central regional records of hospital dis-

charge diagnoses. For malignancies, the proponion of nondetected cases ranged from 3.6% to 6.8%.

The completeness of case ascertainment can also he appreciated from the proportion of cases diagnosed through death certificate only. This proportion steadily decreased from 13% in 1977 to <5% in the latest study years. In zones B and R and the reference area, the death certificate-only cases ranged between 6% and 8%, whereas in :one A, two cancer deaths of a total of 14 cancer cases brought this proportion to 144.

The overall histology confirmation rate over the 10-vear studv period was 72%. This value is similar to the proportion reported for persons age 35-74 years in the period relevant to our studv bv three major Italian cancer registries: Varese = 78.7%; Florence = 73.5%; Latina = 73.6%. Some variation was observed across study areas, 83% in zone A, 18% in :one B, 75% in :one R, and 72% in the reference area. The histology confirmation rate for cancers of *a priori* interest was: soft tissue sarcomas, 100%; Hodgkin's disease and non-Hodgkin's lymphomas. >90%; various leukemias, 70-80%; breast, 85%; liver, 40%;biliary tract, 63%.

ANALYSIS

The study covered malignant tumors at any site, plus benign tumors of liver, bladder, and central nervous system first diagnosed afrer the date of the accident.

We computed person-years at risk, stratified bv age. calendar rime. duration of residence. and gender. using standard techniques:" Each person contributed time to the denominator of the rate from the date of the accident or time of first residence in the area through the end of follow-up, or date of cancer diagnosu. or date of death. For each subject. we attributed all person-vears to the initial :one of residence.

We calculated incidence rates separatelv for males and females. in 5-year time periods. and within 5-vear age classes.

We used Poisson regression techniques"." for comparing rates between each contaminated :one and rhe reference area. We estimated relative risks (RR) with their 95% confidence intervals (CI), and expected number of cases, using the GLIM package,[14] separatelv for each cancer cause and by gender (controlling for age and calendar period).

Results

The total number of cancer cases detected in the contaminated zones was 891, compared with 501 cancer deaths identified by the monalirv investigation.

In :one A. few cancer cases occurred. results are shown in Table 1. Results for zone B are shown in Table 2. Among females. the increased incidence of cancer of the gallbladder and biliary tract was noteworthv Breast cancer incidence showed a 30% deficit; for women younger than 45 years, the relative risk was 0.9 (95% CI = 0.3-2.91, and for those older than 45 years, 0.7 (95% CI = 0.3-1.5). There also was a clear deficit for cancer of the uterus. A pattern of increased risk was apparent for neoplasms of the hematopoietic system, in particular for multiple myeloma and myeloid leukemia.

Among males. primarv liver cancer and neoplasms of the hematopoietic tissue exhibited a twofold increase. Three incident cases of lvmphoreticulosarcoma, a non-Hodgkin's Ivmphoma. yielded a relative risk of 5.7, with a lower 95% confidence limit of 1.7. The relative risk estimate for multiple myeloma. although based on only 2 cases, was also elevated, at 3.2.

There was no case of soft tissue sarcoma [*International Classification of Diseases* (ICD) code 171: "malignant neoplasms of connective and other soft tissues"]. There were, however, 2 soft tissue sarcomas of parenchvmal organs. 1 among females. and 1 among males. For comparison. the expected numbers for all soft tissue sarcomas (ICD 171 plus parenchvmal organs) were 0.6 and 0.8, rerpectivelv.

In zone R (Table 3), among females. there were 2 incident cases of nasal cancer, with 0.8 expected. We noted a slightlv increased nsk of soft tissue sarcomas. based on 2 cases: ue observed 3 additional cases of sarcoma of parenchvmal organs, yielding a total number of 5 cases, vs 4.2 expected. Breast cancer incidence did not differ much from the reference rate, whereas uterine cancer exhibited a remarkable deficit.

Among males in :one R, there was a notable deficit of liver cancer. Soft tissue sarcomas showed a nearly threefold elevated relative risk; 2 additional cases were observed in parenchvmal organs, for a total of 7 cases, vs 4.9 expected.

We compared the findings bv contamination zone. period of follow-up. and length of residence for selecced rumors (Table 4). The increased incidence of hepatobiliarv cancer was restricted to :one B, and it showed a remarkable increase in the late quinquennium of observation (RR = 3.0; 95% CI = 1.5-6.1) and among persons living in the area for longer than 5 years (RR = 2.8; 959 CI = 1.2-6.3). The elevated soft tissue Sarcoma nsk uncovered only in zone R was especiallv evident in the late studv period (RR = 3.0; 95% CI = 1.0-8.8) and in the categorv of longest residence (RR = 3.5; 959 CI = 1.2-10.4). Hematologic neoplasms tended to occur earlier in time, as was

TABLE 1. Cancer Morbidity, 1977–1986, among the Zone A Population Age 20–74 Years

Cancer Site (ICD Code)*	Females (2,313 Person-Years) Cases Observed	Relative Risk	95% Confidence Interval	Males (2,255 Person-Years) Cases Observed	Relative Risk	95% Confidence Interval
All malignancies (140–208)	7	1.0	0.5–2.1	7	0.7	0.3–1.5
Digestive system (150–159)	3	1.7	0.6–5.4	2	0.7	0.2–2.8
Trachea, bronchus, lung (162)	0 (0.2)†			2	0.8	0.2–3.4
Connective and other soft tissue (171)	0 (0.0)†			0 (0.0)†		
Skin (173)	1	3.9	0.5–28.1	1	2.4	0.3–17.2
Breast (174)	1	0.5	0.1–3.3	0 (0.0)†		
Uterus (179–182)	2	2.6	0.6–10.4			
Bladder (188)	0 (0.1)†			2	2.7	0.7–10.8
Non-Hodgkin's lymphoma (200, 202)	0 (0.2)†			0 (0.2)†		

* From the *International Classification of Diseases*, 9th revision
† Number of cases expected

clearly visible in zone B, whereas a moderate excess in zone R was appreciable after 5 or more years since the accident.

Table 5 reports results for estrogen-dependent cancers, which exhibited a decreased risk. Breast cancer incidence was moderately and consistently decreased in zones A and B; in zone R, a deficit was seen only for persons living longest in the area. Corpus uteri

TABLE 2. Cancer Morbidity, 1977–1986, among the Zone B Population Age 20–74 Years

Cancer Site (ICD Code)*	Females (15,608 Person-Years) Cases Observed	Relative Risk	95% Confidence Interval	Males (15,781 Person-Years) Cases Observed	Relative Risk	95% Confidence Interval
All malignancies (140–208)	36	0.8	0.6–1.1	76	1.1	0.9–1.4
Buccal cavity (140–149)	0 (0.4)†			6	1.7	0.8–3.9
Digestive system (150–159)	13	1.1	0.6–1.9	18	0.9	0.6–1.5
Stomach (151)	2	0.6	0.2–2.5		1.0	0.5–2.1
Colon (153)	7	0.6	0.1–2.3		0.5	0.1–2.0
Rectum (154)	7	1.3	0.3–5.4	3	1.4	0.4–4.4
Hepatobiliary (155, 156)	5	3.3	1.3–8.1	5	1.8	0.7–4.4
Liver, primary (155.0, 155.1)	0 (0.5)†			4	2.1	0.8–5.8
Gallbladder, bile ducts, extrahepatic (156)	4	4.9	1.8–13.6	1	2.3	0.3–17.6
Respiratory system (160–165)	0 (1.8)†			24	1.1	0.8–1.7
Trachea, bronchus, and lung (162)	0 (1.4)†			18	1.1	0.7–1.8
Connective and other soft tissue (171)	0 (0.2)†			0 (0.5)†		
Skin, nonmelanoma (173)	2	1.3	0.3–5.1	2	0.7	0.2–2.9
Breast (174)	10	0.7	0.4–1.4	0 (0.1)†		
Genitourinary organs (179–189)	5	0.5	0.2–1.3	13	1.3	0.7–2.2
Uterus (179–182)	2	0.4	0.1–1.6			
Testis (186)				1	1.0	0.1–7.5
Bladder (188)	1	1.2	0.2–8.4	8	1.6	0.8–3.2
Brain (191)	0 (0.5)†			0 (1.4)†		
Hematopoietic system (200–208)	6	1.9	0.8–4.4	8	2.1	1.0–4.3
Non-Hodgkin's lymphoma (200, 202)	1	0.9	0.1–6.4	3	2.3	0.7–7.4
Lymphoreticulosarcoma (200)	1	2.3	0.3–16.9	3	5.7	1.7–19.0
Hodgkin's disease (201)	1	2.1	0.3–15.7	1	1.7	0.2–12.8
Multiple myeloma (203)	2	5.3	1.2–22.6	2	3.2	0.8–13.3
Leukemia (204–208)	2	1.5	0.4–7.3	2	1.6	0.4–6.5
Myeloid leukemia (205)	2	3.7	0.9–15.7	1	2.0	0.3–14.6

* From the *International Classification of Diseases*, 9th revision

TABLE 3. Cancer Morbidity, 1977–1986, among the Zone R Population Age 20–74 Years

Cancer Site (ICD Coder)	Females (105,951 Person-Years)			Males (103,930 Person-Years)		
	Cases Observed	Relative Risk	95% Confidence Interval	Cases Observed	Relative Risk	95% Confidence Interval
All malignancies (140–208)	318	0.9	0.8–1.1	447	0.9	0.9–1.0
Buccal cavity (140–149)	0 (3.2)†			28	1.2	0.8–1.7
Digestive system (150–159)	75	0.9	0.7–1.1	131	0.9	0.8–1.1
Stomach (151)	25	1.0	0.6–1.5	45	0.9	0.7–1.2
Colon (153)	23	0.8	0.5–1.3	32	1.1	0.8–1.6
Rectum (154)	7	0.6	0.3–1.3	17	1.1	0.7–1.9
Hepatobiliary (155, 156)	12	0.9	0.5–1.7	11	0.5	0.3–1.0
Liver, primary (155.0, 155.1)		0.5	0.1–2.1	3	0.2	0.1–0.7
Gallbladder, bile ducts, extrahepatic (156)	7	1.0	0.5–2.3	3	1.0	3.3–3.4
Respiratory system (160–165)	29	1.1	0.8–2.3	138	0.9	0.8–1.1
Sinus and nasal cavity (160)	2	2.6	0.5–13.3	0 (1.5)†		
Trachea, bronchus, and lung (162)	16	1.5	0.8–2.5	96	0.8	0.7–1.0
Connective and other soft tissue (171)	2	1.6	0.3–7.4	6	2.8	1.0–7.3
Melanoma (172)	5	0.9	0.3–2.2	2	0.7	0.2–3.0
Other skin (173)	13	1.0	0.6–1.9	20	1.0	0.6–1.6
Breast (174)	106	1.1	0.9–1.3	1	1.2	0.1–10.2
Genitourinary organs (179–189)	53	0.8	0.6–1.0	75	1.0	0.8–1.3
Uterus (179–182)	21	0.6	0.4–0.9			
Cervix (180)	9	0.6	0.3–1.2			
Corpus uteri (182)	9	0.5	0.2–1.0			
Ovary (183)	20	1.1	0.7–1.7			
Prostate (185)				16	0.9	0.5–1.5
Testis (186)				9	1.4	0.7–3.0
Bladder (188)				39	1.1	0.8–1.5
Kidney and other urinary organs (189)			0.5–2.7	10	3.9	0.4–1.7
Brain (191)	6	1.4	0.6–3.4	6	0.6	0.3–1.4
Thyroid gland (193)	7	1.7	0.7–4.0	1	0.7	0.1–5.2
Metastatic sites (196–198)	10	1.8	0.9–3.6	11	1.1	0.6–2.1
Hematopoietic system (200–208)	18	0.8	0.5–1.3	25	1.0	0.6–1.5
Non-Hodgkin's lymphoma (200–202)	10	1.2	0.6–2.3	17	1.3	0.7–2.5
Lymphoreticulosarcoma (200)	6	1.7	0.7–4.2	4	1.1	0.4–3.2
Hodgkin's disease (201)	3	1.0	0.3–3.2	4	1.1	0.4–3.1
Multiple myeloma (203)	2	0.6	0.2–2.8	1	0.2	0.0–1.6
Leukemia (204–208)	3	0.4	0.1–1.2	8	0.9	0.4–1.9
Lymphatic leukemia (204)	1	0.3	0.0–2.6	2	0.6	0.1–2.5
Myeloid leukemia (205)	2	0.5	0.1–2.1	5	1.4	0.5–3.8

* From the *International Classification of Diseases*, 9th revision
† Number of cases expected.

TABLE 4. Ratio of Observed/Expected Cases for Selected Neoplasms, in Each Contamrnanon Zone (A, B, R), Stratified by Period of Follow-up, and Years Lived in the Zones

	Hepatobiliary Gncer			Non-Hodgkin's Lymphoma			Sok Tissue Sarcoma		
	A	B	R	A	B	R	A	B	R
Follow-up period									
1977–1981	1/0.3	2/1.7	10/12.8	0/0.2	2/1.1	5/7.9	0/0.0	0/0.2	3/1.8
1982–1986	0/0.4	8/2.7	13/20.0	0/0.2	2/1.4	17/9.7	0/0.0	0/0.2	5/1.7
Length of residence (years)									
All	1/0.0	1/0.2	1/1.3	0/0.0	0/0.2	1/1.2	0/0.0	0/0.1	0/0.3
1–5	0/0.3	3/1.9	12/14.7	0/0.2	2/1.2	5/8.6	0/0.0	0/0.2	3/1.7
>5	0/0.2	6/2.1	10/16.7	0/0.1	2/1.0	16/7.8	0/0.0	0/0.2	5/1.4

TABLE 5. Ratio of Observed/Expected Cases for Estrogen-Dependent Neoplasms, in Each Contamination Zone (A, B, R), Stratified by Period of Follow-up, and Years Lived in the Zones

	Breast			Corpus Uteri		
	A	B	R	A	B	R
Follow-up period						
1977–1981	0/1.0	5/6.1	55/46.5	0/0.1	0/0.9	7/7.1
1982–1986	1/1.2	5/7.5	51/54.0	0/0.2	0/1.5	2/11.5
Length of residence (years)						
<1	9/02	0/0.8	7/5.7	0/0.0	0/0.1	1/0.6
1–5	1/1.3	6/6.8	57/50 *i*	0/0.2	0/1.0	8/8.0
>5	3/0.6	4/5.9	42/44.1	0/0.2	5/1.5	5, 13.4

Cancer showed a decrease in each zone; this decrease was especially evident in the late follow-up quinquennium (RR = 0.2; 95% CI = 0.0–0.7) and among those living longest in the area (0 cases observed *vs* 13.4 expected; 95% CI = 0.0–0.2).

We conducted an additional analysis that included those who moved to one of 11 towns after the accident. The results were affected only marginally.

No case of cancer was detected among the 193 subjects who had chloracne diagnosed after the accident;" the expected number was 0.5.

Discussion

The main long-term health effect anticipated in a population exposed to TCDD was a possible increase in cancer Occurrence. Existing experimental and epidemiologic work suggested specific cancer types of concern.'' The mortality study suggested an increased risk in this population for some cancers of a *priori* interest and, in addition. gave rise to some new hypotheses as, for example. an increased brain cancer risk.[29]

Case ascertainment was enhanced hv the very low annual Lombardy emigration rate and by the fact that the region hosts some of the main cancer hospitals. Ad hoc evaluations of the regional case identification system based on hospital discharge records consistently Yielded malignancy identification rates well above 90%.

The index and referent populations were similar regarding broad personal. social. cultural, and environmental characteristics. It is quite possible that. after the accident, persons involved in the accident received better medical attention. Tho possible source of bias was mitigated by the use of the population from the immediately surrounding area as a reference population; these persons. in fact. were using the same health [illegible] and were probably confronted with the same care as the exposed, because the exact boundaries of the contaminated territory remained uncertain tor a rather long time. Because all tracing and follow-up procedures were uniformly implemented for the four cohorts studied, without identifying the residence of the subject. anv misclassification should be nondifferential. with risk estimates biased toward the null.

The study was limited by the short period of time since the accident and the ecolonic exposure definition. The few blood TCDD measurements available were consistent with the exposure classification provided by zone delimitation. As for the short time span since the accident, two major considerations applv: first. at least for some of the outcomes of *a priori* interest (for example. hematologic neoplasms). a 10-vear period aher exposure mav be sufficient';; second, dioxin has been suggested, in experimental studies,[39,39] to act in late stages of the carcinogenesis process. One might then expect to see an increased risk early after exposure among those subjects who had "completed" previous stages. Despite these limitations, we observed an excess risk for those cancer types for which an association with TCDD exposure had been hvpothesized a priori on the basis of previous experimental and epidemiologic research

Soft tissue sarcoma is rhe cancer tvpe most consistentlv associated with hurndn exposure to dioxin,[4,5,8,13,15,18,23,42–45] despite the fact that some investigations do not support this hvpothesis.[13,20–22,44,45] The increase noted in the Seveso mortalitv studv was confirmed here. The relative risk for soh tissue sarcoma (males and females combined) was 2.3, based on 8 incident cases in zone R. the least contaminated. but with the largest population size: the increase was highest among persons living longest in the area. When soft tissue tumors occurring in parenchvmal organs were added, the relative risk was lower

Malignant lymphoma, in particular non-Hodgkin's lymphoma, has been repeatedlv associated with exposure to herbicides contaminated uith TCDD,[4,5,10,44,46,47] but with noncontaminated herbi-

cides as well.[48,52] Our mortality findings were only suggestive of a possible involvement of the hematopoietic system. Incidence data showed an increase of hematologic neoplasms in zone E sustained mainly by non-Hodgkin's lymphoma and multiple myeloma. The nonanticipated finding regarding multiple myeloma is consistent with the results of a recent investigation in Sweden.[53] Previous studies had suggested a link between farming occupations involving exposure to herbicides and risk of multiple myeloma.[54] Vineis *et al*[55] have hypothesized a mechanism for the possible association of TCDD and malignant lymphoma.

Only one epidemiologic investigation in western countries indicated an increased liver cancer risk,[4] whereas in long-term experimental studies, TCDD emerged as a potent liver carcinogen.[35-38] A clear excess of primary liver cancer affected males living in zone B, whereas women exhibited an elevation of gallbladder and extrahepatic biliary tract cancers, particularly among those with longest residence in the contaminated area, a finding fully consistent with mortality results.

Few data exist on exposure and long-term health effects in female populations, and these indicate a possibly increased cancer risk.[3,4] The results of our study indicate an elevated risk for biliary cancer, and possibly for certain hematologic neoplasms. At the same time, however, breast cancer incidence was decreased in zones A and B (particularly in the age class 45-74), and among women living longest in zone R. Endometrial cancer showed a remarkable decrease, particularly in zones B and R. A lowered occurrence for these tumors was also suggested by mortality data.

A reduced incidence of hormone-dependent tumors of the mammary gland and uterus has been observed in female rats after long-term exposure to TCDD.[56] Endometrial cancer is an estrogen-dependent tumor,[57] and estrogens are thought to play a major, although not completely elucidated, role in breast cancer etiology.[58] TCDD does possess antiestrogenic activity; it can decrease levels of estrogen receptors[59] and interfere with estradiol metabolic pathways.[60] This hypothetical explanation for the decreased risk would, however, conflict with the increase of extrahepatic bile duct cancer, which includes estrogens among the most plausible, albeit putative, risk factors.[4] Interestingly, however, it has been suggested that the reduction of effective estrogen receptors caused by TCDD would be compensated by a feedback mechanism producing an increase of estrogen levels.[61] Thus, the effects of TCDD may be linked to the reduction of estrogen receptors in certain tissues (for example, breast, endometrium) and to the increased amount of estrogen levels acting on tissues (for example, the biliary tract), where estrogen receptors do not play a major regulative role. Furthermore, estrogens and TCDD have been shown to interact in several experimental carcinogenesis systems.[60-68]

Other cancers have been found to be elevated in previous investigations on TCDD-exposed people: respiratory,[5-7,26] stomach,[10,69] testis,[8,17] thyroid,[7] and nasal.[8,70] Our findings lent little support to these hypotheses. Modest and inconsistent increases were seen for thyroid, nasal, and testis cancer.

The most striking discrepancy between the mortality and incidence findings was for brain tumors. The increase in the mortality study was deemed credible notwithstanding the questionable validity of the reference rates for this cause of death.[4] No indication of an increased cancer risk emerged, however, in the present study.

The absence of cancer cases among chloracne subjects and the very few cases in zone A can be explained in terms of small population size, youth of the subjects, and short follow-up period and cannot be taken as sound indication of a lack of carcinogenicity. The most consistently suggestive pattern of increased cancer risk was seen among people living in zone B, which had a fairly large population and a fairly high exposure level.

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