Mortality and cancer incidence in the Seveso population.

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The Seveso accident took place in 1976 in a plant where trichlorophenol (TCP) had been in production since 1970, and was due to an uncontrolled reaction causing the rupture of a safety valve and the release of a cloud of toxic chemicals, including 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), which deposited its content over several square miles of populated countryside. Soil contamination measurements lead to the delimitation of three main areas with decreasing TCDD levels. Zone A (735 subjects) had mean TCDD soil levels ranging from 15.5 $\mu g\ m^{-2}$ to 580.4 $\mu g\ m^{-2}$. Zone B (nearly 5,000 subjects) had mean levels between 1.7 $\mu g\ m^{-2}$ and 4.3 $\mu g\ m^{-2}$. Zone R (over 31,000 subjects) had a patchy contamination with levels ranging from 0.9 $\mu g\ m^{-2}$ to 1.4 $\mu g\ m^{-2}$.[1] This paper summarizes the results of the long-term epidemiologic studies designed to examine the possible late occurrence of health effects, particularly cancer, in the Seveso population, in which the highest levels of TCDD exposure ever reported in humans were documented [2].

The mortality and cancer incidence study included all resident in eleven towns surrounding the accident scene[3]. Subjects were categorized according to their residence within the contaminated area (zone A, or B, or R); people living in the territory surrounding these three zones were the reference population. All residents in the study area were followed-up from the accident until the end of 1986. The tracing of subjects who moved away was virtually complete (99.5%). Mortality was examined thanks to the cooperation of thousands of local vital statistics offices which provided information on vital status and death certificates[3]. Cancer incidence was investigated using the hospital admission/discharge individual records of the Lombardy region (nearly 9 millions inhabitants) where the accident area is located. Original medical records were checked by expert physicians at the relevant hospital(s) for each putative cancer case. Histologic confirmation rate was close to 80%. The proportion of non-detected cases was evaluated in a pilot study and for malignancies ranged from 3% to 7%[4]. The analyses were performed using Poisson regression techniques.

Among non-cancer causes of death one result was outstanding, i.e. a 56% statistically significant increase in mortality from chronic ischaemic heart disease. The increase was highest in zone A, where the impact of the chemical contamination and of the psycho-social stress caused by the accident was strongest. The stressful post-disaster experience suffered by the population in the contaminated area seemed a more plausible explanation than TCDD toxicity[5].

A possible increased risk from certain types of cancer was suggested by the same mortality study[3]. The increases mainly concerned gallbladder and extrahepatic bile ducts among fe-

males, brain cancer, and lymphatic and hematopoietic neoplasms, particularly leukemia in males. Suggestions of an increased risk were also obtained for soft tissue sarcoma and melanoma. The incidence study shed further light on the cancer experience of this population. Table 1 shows main cancer findings in the population aged 20-74 years living in each contamination zone. For each cancer site, the number of observed cases (Obs), the point estimate (RR) and the 95% confidence interval (CI_{95}) of the relative risk are shown. It is obvious that in zone A the limited number of deaths prevents any meaningful interpretation of the numerically increased relative risks. In zone B an increased incidence of hepatobiliary cancer was obvious and statistically significant. The elevated risk was particularly evident for gallbladder and bile ducts cancer, especially for females, thus confirming the results of the mortality study. Hematopoietic neoplasms as a whole had a statistically significant increased relative risk, consistent with the mortality findings. The increase was also visible in nearly each specific tumor type (see, in particular, lymphoreticulosarcoma - elevated especially among men, and multiple myeloma - which had the highest risk among females). In zone R the only significantly increased relative risk concerned soft tissue sarcoma. Primary liver cancer showed a significant deficit.

Stratification by gender revealed another interesting finding, namely a decreased incidence of breast cancer in zone A (RR=0.45) and in zone B (RR=O.71). Another cancer type related to estrogen metabolism (uterine cancer) showed an obvious decrease, with a relative risk of 0.59 in the contaminated zones vs. the non-contaminated referent population.

Overall, the incidence findings were consistent with the mortality results with the only major exception of brain cancer.

In interpreting these results, major limitations are the short period of time elapsed since the accident, the merely ecological definition of exposure status, and the limited number of cases, particularly in subgroups of small size and high exposure (such as, for instance, zone A, and 193 chloracne cases among whom no cancer cases were observed and 0.5 were expected). Yet it is of interest that we observed an excess risk for those cancer types for which an association with TCDD exposure had been hypothesized a priori on the basis of previous experimental and epidemiological research. Soft tissue sarcoma is the cancer type most consistently associated with human exposure to TCDD. Malignant lymphoma, in particular N-H linfoma, has been repeatedly, but not always, associated with exposure to herbicides contaminated with TCDD. An increased risk for hepatobiliary cancer is suggested by long term experimental studies. Finally, 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.

Mortality and cancer occurrence were analysed separately for subjects aged 0-19 years[6]. The number of events observed was quite limited. Five leukemia deaths were observed with a relative risk of 2.1 among males and of 2.5 among females. Two lymphatic leukemia deaths among males represented a noteworthy increase above expectations (RR=9.6). None of the increases was statistically significant. Mortality due to congenital anomalies showed a nearly twofold increase, however 5 out of 7 observed cases were born before the accident.

Overall cancer incidence was slightly (26%) and non-significantly increased (Table 2). The most prominent result at specific sites concerned the increased risk for thyroid cancer (both cases of follicular cell origin), not only for the magnitude of the increase but mainly for its consistency with experimental data and previous observations in humans[4,7]. Also the results of these analyses should be viewed vith caution because of short time since initial exposure, ecological definition of exposure and limited number

Table 1. Cancer morbidity, 1977-1986, in the Seveso population aged 20-74 years.

CANCER SITE (ICD Code)[§]	ZONE A Obs	ZONE A RR	ZONE A CI_{95}	ZONE B Obs	ZONE B RR	ZONE B CI_{95}	ZONE R Obs	ZONE R RR	ZONE R CI_{95}
All malignancies (140-208)	14	0.82	0.5-1.4	115	1.01	0.8-1.2	745	0.95	0.9-1.0
Buccal cavity (140-149)	0	(0.59)*		6	1.53	0.7-3.5	29	1.06	0.7-1.6
Digestive system (150-159)	5	1.09	0.5-2.6	30	0.96	0.7-1.4	211	0.90	0.8-1.0
Stomach (151)	1	0.66	0.1-4.7	9	0.87	0.5-1.7	70	0.90	0.7-1.2
Colon (153)	2	1.67	0.4-6.7	4	0.50	0.2-1.3	58	0.96	0.7-1.3
Rectum (154)	0	(0.54)		5	1.37	0.6-3.3	26	0.96	0.6-1.4
Hepatobiliary (155,156)	1	1.58	0.2-11.2	10	2.31	1.2-4.4	23	0.70	0.5-1.1
Liver, primary (155.0,155.1)	0	(0.34)		4	1.68	0.6-4.6	5	0.28	0.1-0.7
Gallbladder, bile ducts (156)	1	5.13	0.7-37.0	5	4.01	1.6-10.0	10	1.03	0.5-2.0
Respiratory system (160-165)	2	0.57	0.1-2.3	24	1.02	0.7-1.5	163	0.97	0.8-1.1
Nose and nasal cavity (160)	0	(0.05)		0	(0.32)		2	2.39	0.2-3.7
Lung (162)	2	0.76	0.2-3.0	18	1.01	0.6-1.6	115	0.90	0.7-1.1
Soft tissues (171)	0	(0.07)		0	(0.49)		8	2.27	1.0-5.1
Melanoma (172)	0	(0.18)		1	0.83	0.1-6.0	8	0.93	0.4-2.0
Other skin (173)	2	2.97	0.7-12.0	4	0.90	0.3-2.4	33	1.00	0.7-1.4
Breast (174)	1	0.45	0.1-3.2	10	0.71	0.4-1.3	113	1.08	0.9-1.3
Genitourin. organs (179-189)	4	1.31	0.5-3.5	18	0.88	0.6-1.4	133	0.89	0.7-1.1
Bladder (188)	2	2.18	0.5-8.8	9	1.44	0.7-2.8	43	0.95	0.7-1.3
Kidney, urinary organs (189)	0	(0.37)		1	0.41	0.1-2.9	18	1.00	0.6-1.6
Brain (191)	0	(0.30)		1	0.50	0.1-3.6	11	0.78	0.4-1.5
Thyroid gland (193)	0	(0.12)		0	(0.86)		8	1.35	0.6-2.9
Hematopoietic system (200-208)	0	(1.04)		15	2.09	1.2-3.5	45	0.88	0.6-1.2
N-H. lymphoma (200,202)	0	(0.37)		4	1.60	0.6-4.3	23	1.26	0.8-2.0
Lymphoreticulosarcoma (200)	0	(0.15)		4	3.91	1.4-10.9	10	1.33	0.7-2.6
Hodgkin's disease (201)	0	(0.16)		3	2.56	0.8-8.2	7	0.92	0.4-2.0
Multiple myeloma (203)	0	(0.15)		4	3.87	1.4-10.7	4	0.50	0.2-1.4
Leukemia (204-208)	0	(0.36)		4	1.64	0.6-4.4	11	0.63	0.3-1.2
Lymphatic leukemia (204)	0	(0.13)		0	(0.87)		3	0.47	0.1-1.5
Myeloid leukemia (205)	0	(0.16)		3	2.81	0.9-9.0	7	0.93	0.4-2.1

[§] International Classification of Diseases, IX Rev. * No. of expexcted cases

of events.

Table 2. Cancer morbidity, 1977-1986, in the Seveso population aged 0-19 years. Results for selected cancers.

Cancer sites (ICD IX)	Observed	Expected	RR	$CI_{95\%}$
All (140-208)	23	18.2	1.26	0.8-2.0
Ovary and uterine adnexa (183)	2	0.0	-	-
Nervous system (191-192)	5	3.4	1.45	0.5-3.9
Brain (191)	4	3.0	1.32	0.4-4.0
Thyroid (193)*	2	0.4	4.66	0.7-33.1
Non-Hodgkin Lymphoma (200,202)	2	1.3	1.54	0.3-7.6
Hodgkin Lymphoma (201)	3	1.9	1.54	0.4-5.7
Lymphatic leukemia (204)	3	2.8	1.07	0.3-3.7
Myeloid leukemia (205)	2	0.9	2.30	0.6-9.2

* Cases are restricted to females

The carcinogenic potential of TCDD remains an open issue. The follow-up of the Seveso population is continuing. Individual susceptibility, either genetically determined or acquired, might represent a highly relevant explanatory factor for the mixed findings obtained. Our research endeavour is accordingly addressing this specific hypothesis in the context of the long-term surveillance for cancer occurrence.

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