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Original research

Mortality and cancer incidence in a population exposed to TCDD after the Seveso, Italy, accident (1976–2013)

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ABSTRACT

Objectives The Seveso accident (1976) caused the contamination with 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) in an area north of Milan, Italy. We report the results of the update of mortality and cancer incidence in the exposed population through 2013.

Methods The study cohort includes subjects living in three contaminated zones with decreasing TCDD soil concentrations (zone A, B and R) and in a surrounding uncontaminated territory (reference). Poisson models stratified/adjusted for gender, age and period were fitted to calculate rate ratios (RRs) and 95% CIs.

Results In zone A in males, we found elevated mortality from circulatory diseases in the first decade after the accident (17 deaths, RR 2.00, 95% CI 1.24 to 3.23). In females, mortality from diabetes mellitus was increased, with a positive trend across zones. Incidence of soft tissue sarcoma was increased in males in zone R in the first decade (6 cases, RR 2.62, 95% CI 1.01 to 6.83). In females in zone B, there was an excess of non-Hodgkin's lymphoma after 30 years (6 cases, RR 2.87, 95% CI 1.14 to 7.23). Multiple myeloma was increased in the second decade in females in zone B (4 cases, RR 5.09, 95% CI 1.82 to 14.2) and in males in zone R (11 cases, RR 2.15, 95% CI 1.08 to 4.26). In males in zone R, there was a leukaemia excess after 30 years (23 cases, RR 2.02, 95% CI 1.04 to 3.93).

Conclusions Although with different patterns across gender, zone and time, we confirmed previous results of increased cardiovascular diseases, diabetes, soft tissue sarcoma, and lymphatic and haematopoietic cancers.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies of the Seveso population living in the area contaminated with tetrachlorodibenzo-para-dioxin (TCDD) after an industrial accident (1976) showed elevated risks for cardiovascular diseases, diabetes, chronic obstructive pulmonary disease, lymphatic and haematopoietic neoplasms and breast cancer.

WHAT THIS STUDY ADDS

⇒ We confirmed lack of elevated all cause mortality and all cancer incidence.

⇒ We confirmed elevated mortality from circulatory diseases and diabetes mellitus and elevated incidence of soft tissue sarcomas and lymphatic and haematopoietic cancers. These results are consistent with old and recent literature findings (except for diabetes, for which epidemiological evidence is weak).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Although patterns of mortality and cancer incidence showed differences across gender and zones and over time, our findings are in line with literature findings and IARC evaluation of TCDD carcinogenicity.

⇒ Communication of findings has been and is important for the affected population and for the institutions (the local municipalities and the Regional Government of Lombardy).

INTRODUCTION

2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) is the most toxic among dioxin-like compounds. It is a persistent organic pollutant,[1] with a half-life of 9–15 years on the soil surface and 25–100 years in subsurface soil.[2] TCDD is highly lipophilic and accumulates in fat tissues of bio-organisms: the half-life in humans ranges from 5.1 to 11.3 years.[3] The International Agency for Research on Cancer (IARC) classified TCDD as a group 1 carcinogen.[4] Although epidemiological studies showed positive associations with soft-tissue sarcoma (STS), non-Hodgkin's lymphoma (NHL) and lung cancer, IARC rated the human epidemiological evidence as sufficient based on results for all cancers combined, sufficient evidence in experimental animals and mechanistic information.[4] TCDD binds to the aryl hydrocarbon receptor (AhR) and most of its toxic effects are initiated through this mechanism. There is strong evidence of an AhR-mediated mechanism in humans for TCDD carcinogenesis: the primary mechanism is the promotion of tumour development through modification of cell replication and apoptosis while a secondary mechanism is related to increases of oxidative stress causing DNA damage.[4]

Human exposures can occur in occupational and environmental settings. Release of TCDD in the environment occurred after industrial accidents in 1953 in Ludwigshafen, Germany,[5 6] in 1963 in the Netherlands,[7–10] and 1976 in Seveso, Italy. The Seveso accident took place on 10 July 1976, when a chemical cloud was released from a plant producing 2,4,5-trichlorophenol and caused the

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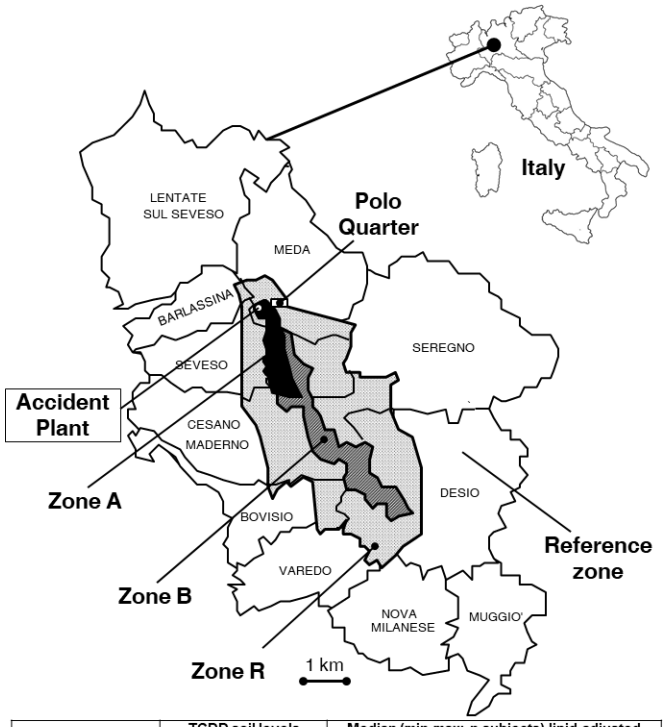

Zone	TCDD soil levels (μg/m²)*	Median (min-max; n subjects) lipid-adjusted TCDD serum levels (pg/g or parts per trillion, ppt)	
	Minimum-Maximum	Samples collected in 1976-77†	Samples collected in 1992-96‡
A	15.5-580.4	447 (1.5-56,000; 296)	73.3 (9.8-89.9; 7)
B	1.7-4.3	94 (1-725; 80)	12.4 (1.2-62.6; 51)
R	0.9-1.4	48 (1-545; 48)	Not measured
Reference	<0.75 (undetectable)	Not measured	5.5 (1.0-18.1; 52)

Figure 1 The Seveso, Italy, area, including the territory of 11 towns. The map indicates the three contaminated zones A (black), B (dark grey) and R (light grey), and the surrounding non-contaminated reference zone (white). The table reports soil and lipid-adjusted 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) levels. *Schecter[1]; †Needham *et al*[27]; ‡Landi *et al*[28].

contamination with more than 34 Kg of TCDD of a densely populated area. The population had been directly exposed to the cloud in the first days: visible effects were not immediate, they appeared a few days later on trees and vegetation, on birds and courtyard animals, and on humans (eye irritation and skin lesions, mainly in children). Consumption of locally produced food was prohibited. The fact that the cloud contained TCDD was communicated by the company owning the chemical plant only on 23 July.[1]

Preliminary TCDD measurements in soil were made soon after the accident, and in the following months and years systematic campaigns were performed in which TCDD in soil samples was quantified with low-resolution gas-liquid chromatography in combination with MID-mass spectrometry (analytical detection threshold: 0.75 μg/m2).[11] Based on thousands of TCDD measurements, the area was divided into three zones with decreasing TCDD levels, named A, B and R ('respect') zones (figure 1).[1 11] In zone A, residents were evacuated, their houses were destroyed and the top 50 cm of soil removed. The accident had worldwide resonance and a profound impact: three European Directives aimed at controlling major chemical accident hazards were issued in 1982, 1996 and 2012.

In the early postaccident period, the only ascertained health effect was chloracne, occurring mainly in children.[12] Subsequent studies reported the association of TCDD with lymphocyte alterations,[13] thyroid-stimulating hormone (TSH) levels in children of exposed mothers,[14] dental abnormalities[15] and reduction of the male/female ratio at birth,[16] IgG levels[17] and sperm quality.[18] The Seveso Women's Health Study (SWHS), a cohort study launched in 1996 including 981 women with blood samples collected near the time of the accident, reported positive associations between TCDD blood levels and incidence of all cancer, breast cancer and cardiovascular diseases.[19] Workers of the chemical plant (about 325 subjects) were included in an IARC multicentre mortality study of workers exposed to phenoxy herbicides, chlorophenols and dioxins (36 cohorts in 12 countries, almost 22 000 workers), which found elevated mortality from STS, NHL, all cancers, lung cancer and ischaemic heart disease (IHD).[20 21]

The whole population living in TCDD polluted zones and a reference population from the surrounding non-contaminated territory were included in a large cohort study. In the most polluted zones, we recorded elevated cardiovascular mortality in the first years after the accident and increases in diabetes and chronic obstructive pulmonary disease (COPD).[22–24] In the same zones, the most consistent finding was the elevated mortality from and incidence of lymphatic and haematopoietic (LH) neoplasms in both genders.[25 26] Elevated breast cancer incidence in the most polluted zone was observed 15–19 years after the accident.[26] We report here the mortality and cancer incidence regarding the period 1976–2013 among people living in the area at the time of the accident.

METHODS

Methods for cohort identification, exposure definition, follow-up and cause of death or cancer diagnosis ascertainment (which varied over time) were previously described and are briefly summarised here.[23 26]

The Seveso cohort

Subjects living in zones A, B and R at the time of the accident represent the exposed group of the cohort. They had been directly exposed to the toxic cloud and may have consumed locally produced food in the days and weeks after the accident, before preventive measures had been undertaken. The three zones included parts of the territory of six municipalities (Barlassina, Bovisio Masciago, Cesano Maderno, Desio, Meda and Seveso) (figure 1). Residents in the unaffected territory of these six municipalities and those living in five surrounding non-contaminated towns (Lentate sul Seveso, Muggiò, Nova Milanese, Seregno and Varedo) were taken as reference. The overall study cohort thus included residents in 11 municipalities.

Exposure definition

Assignment of individuals to zones was based on the official residence on the day of accident, provided by the Vital Statics Offices (VSO) of the 11 municipalities. The main advantage of the official residence is its availability for every cohort member. The zone-based classification was in good agreement with blood TCDD measurements (figure 1).[27 28] Living in the area after the accident appeared 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.[27] For this reason, we restricted the analysis to people who were residents there at the time of the accident.

Follow-up

For the period 1976–2006, the VSO of the 11 municipalities regularly provided population updates (residents and deaths,

migration outside the area). For those who emigrated outside the study area (either within the Lombardy Region or to other Italian regions), we performed a postal follow-up through the VSOs of thousands of municipalities throughout Italy. For the period 2007–2013, for all members of the cohort (including residents in the 11 municipalities) vital status was ascertained through record linkage with two databases of the Lombardy Region (one containing all residents and one containing deaths). For those not linked or emigrated outside region, we performed a postal follow-up as above. These latter activities were started in mid-2014.

Causes of deaths

In the first years of follow-up, death certificates were provided by VSO and coding of the underlying cause of death was performed by trained personnel following international rules of the International Classification of Diseases (ICD). Since 1996 death codes were retrieved by record linkage with databases of the National Central Statistics Institute (ISTAT), of Lombardy region, or of local Lombardy Region Local Health Units, or (for those who emigrated outside the region) by postal contact with VSOs and Local Health Units in other Italian regions.

Cancer cases

Due to lack of cancer registries, identification of cancer cases was restricted to people living in Lombardy using different procedures. For the period 1977–1996, the cohort dataset had been linked with anonymous hospital admission databases of the region using gender, date of birth and residence. On verification of demographics, clinical information was collected from paper medical records and data stored in a dedicated database. Then, date of first primary cancer diagnosis, site and histology were defined and coded for each individual according to the ICD in use at the time of cancer occurrence and to the ICD for Oncology (ICD-O-3).[26]

For the period 1997–2006, the same procedures were followed, but (because of the increasing number of cancer cases over time and the resulting work burden) data collection was restricted to all subject in the contaminated zones and to a random sample of 40 000 residents in the non-ABR reference zone.

For the period 2007–2013, for all subjects, we obtained data by record linkage with the ATS Brianza Cancer Registry, which covers a population of approximately 1.25 million people, including all those living in the 11 municipalities of the Seveso area.

Statistical analysis

We included in analyses only people who were residents in the area at the time of the accident. For mortality analyses (non-neoplastic diseases), we computed person-years of observation from 10 July 1976 to the earliest of death, loss to follow-up or end of study (31 December 2013). For cancer incidence analysis, we started counting person-years from 1 January 1977 to the earliest of first cancer occurrence (excluding non-melanoma skin cancers), death, loss to follow-up or 31 December 2013. Only the first cancer occurrence was analysed. We included in analyses death certificate only (DCO) cancer cases. The reason for this choice was that we had no information on cancer occurrence for people who emigrated outside Lombardy in the period 1977–2006 and for those who emigrated outside the area covered by the local cancer registry in the period 2007–2013. In cancer incidence analyses, non-sampled subjects in the reference zone in 1997–2006 were censored on 31 December 1996.

We calculated cause-specific mortality and cancer incidence rate ratios (RR) and 95% CI using Poisson regression models adjusted for period (5-year categories except 2007–2013) and age (<1, 1–4 years, then 5 year categories until 84 and 85+ years). For selected diseases, we performed age-adjusted analyses of time since first exposure ('latency', 0–9, 10–19, 20–29, 30+ years). All analyses were adjusted/stratified by gender. We performed secondary analyses on selected subgroups of the cohort including 180 persons with chloracne and 2418 residents in a quarter named 'Polo' in the town of Meda, possibly with higher exposure than the surrounding zone R, as witnessed by the frequency of chloracne in children (19 cases, 2.5%), which was higher compared with that in zone B (8 cases, 0.5%) and R (63 cases, 0.7%).[12 29] Data management, person-year calculation and statistical analyses were performed with Stata V.18 (StataCorp. 2023).

RESULTS

The cohort included 218 682 subjects (111 832 females and 106 850 males) living in the area on 10 July 1976 (table 1). Age was slightly lower in zone B. Most of the residents in zone A lived in Seveso. The follow-up was over 98% complete in each zone. The proportion of missing or non-informative causes of death was 1.1% (2397), with small differences across zones. Cancers with histological or cytological confirmation were the majority; DCO cancer diagnoses were about 10%.

Mortality

In the whole study period, all-cause and all non-cancer mortality in zones A-B were not elevated while in zone R a minimal elevation was found, especially in females (table 2). In females, mortality from diabetes was higher than the reference in all the three polluted zones, with a positive trend from the less to the most polluted zone; slightly elevated mortality from circulatory disease, chronic IHD and cerebrovascular disease was observed in zone R while increased risk from hypertension was observed in zone A. In males, chronic IHD and other heart disease mortality were higher in zone A; other heart diseases mortality was slightly higher also in zone R. Mortality from COPD was elevated in zone B (females) and R (males). Finally, slightly elevated mortality from digestive diseases was observed in zone R (both genders).

Cancer incidence

Overall cancer incidence did not increase in both genders in the three zones (except for a slight elevation in females in zone A) (table 3). Rectal cancer incidence was increased in zone B (both genders). The excess of other digestive cancers in zone A was based on only two cases in females. Ovarian cancer incidence was increased in zone R. Incidence of LH cancers was increased in females in zone A (based on very few cases across various LH cancer types), and in zone B, to which contributed Hodgkin's disease (HD, few cases), NHL, multiple myeloma and myeloid leukaemia.

Analyses of time since the accident

In both genders, we observed 41% elevated mortality in zone A in the first 10 years since the accident (table 4). Mortality from diabetes mellitus showed a different pattern across zones and latency. There was a 59% excess mortality from circulatory diseases in zone A within the first decade. COPD mortality was elevated in zone A in the first 20 years. STS was increased in zone R in the first decade. The incidence of LH tissue cancers

Table 1 Characteristics of subjects of the Seveso, Italy, cohort, by zone of residence at the time of the accident, 1976–2013

	Zone A		Zone B		Zone R		Reference zone	
	n or mean (SD)	% or range	n or mean (SD)	% or range	n or mean (SD)	% or range	n or mean (SD)	% or range
Subjects	723	100	4818	100	31 630	100	181 511	100
Females	371	51.3	2349	48.8	15 918	50.3	93 194	51.3
Males	352	48.7	2469	51.2	15 712	49.7	88 317	48.7
Age at the accident (1976)	30.3 (19.8)	0.2–86.8	29.1 (19.6)	0–92.8	31.2 (20.4)	0–92.1	32.7 (20.9)	0–98.7
Age at the end of follow-up (2013)	62.9 (15.9)	1.5–104.2	61.9 (15.8)	4.3–102.6	63.1 (16.0)	1.4–107.9	64.2 (16.1)	0.2–113.7
Municipality								
Barlassina	0	0	0	0	60	0.2	5585	3.1
Bovisio Masciago	0	0	0	0	164	0.5	10 995	6.1
Cesano Maderno	0	0	2838	58.9	14 536	46.0	16 257	9.0
Desio	0	0	1357	28.2	4982	15.8	26 469	14.6
Lentate sul Seveso	0	0	0	0	0	0	13 132	7.2
Meda	61	8.4	0	0	4009	12.7	15 432	8.5
Muggiò	0	0	0	0	0	0	18 586	10.2
Nova Milanese	0	0	0	0	0	0	18 422	10.1
Seregno	0	0	0	0	0	0	37 049	20.4
Seveso	662	91.6	623	12.9	7879	24.9	7760	4.3
Varedo	0	0	0	0	0	0	11 824	6.5
Vital status								
Alive	526	72.8	3529	73.2	21 964	69.4	121 184	66.8
Dead with cause	184	25.4	1178	24.5	8914	28.2	55 566	30.6
Dead without cause*	4	0.6	35	0.7	294	0.9	2064	1.1
Lost	9	1.2	76	1.6	458	1.5	2697	1.5
Person-years in analysis (x1000)								
Mortality†	23.6		158.0		1010.2		5707.5	
Cancer incidence‡	22.7		153.6		978.3		3766.7	
Cancer diagnosis§	117	100	677	100	4888	100	17 544	100
With HC	84	71.8	524	77.4	3654	74.8	12 304	70.1
Without HC	18	15.4	94	13.9	758	15.5	3355	19.1
DCO	15	12.8	59	8.7	476	9.7	1885	10.7

*Missing or non-informative causes of death.
†From date of the accident (10 July 1976) to the earliest of death, loss to follow-up or 31 December 2013.
‡From 1 January 1977 to the earliest of first cancer occurrence (excluding non-melanoma skin cancers), death, loss to follow-up, or 31 December 2013. Not including person-years 1997–2013 in non-sampled subjects in the reference zone.
§Not including cases 1997–2013 in non-sampled subjects in the reference zone.
DCO, death certificate only; HC, histology or cytology.

increased by 60% in zone B in the first two decades, driven by multiple myeloma.

Analyses of time since the accident in females (online supplemental table 1) showed a more than doubled mortality from diabetes mellitus in zone B in the second decade and (based on few deaths) after 30 years, while in zone R, we found about a 50% excess 10–37 years after the accident. Breast cancer incidence was moderately in excess in zone A 10–19 years after the accident, but the estimate was imprecise. LH tissue cancers were in excess in zone B in the first two decades and more than doubled in zone A in the second and third decades (based on very few cases). We observed an excess of NHL after 30 years in zone B and R and of multiple myeloma (based on a few cases) in the second decade in zones A–B.

In males (online supplemental table 2), in zone A we observed elevated mortality in the first 10 years after the accident, especially from circulatory diseases and few deaths from COPD. STS was increased in zone R in the first decade. In zone R, multiple myeloma was increased in the second decade and leukaemia after 30 years. In zone B, leukaemia incidence was increased in the second and third decade.

Secondary analyses

Among 180 chloracne cases, on average quite young at the time of the accident, we recorded four deaths and four cancer cases (online supplemental table 3). We observed RRs below unity for all-cause mortality and for all cancer incidence (online supplemental table 4).

Among 2724 residents in the 'Polo' quarter (1334 females, 1390 males), we observed no increased non-cancer mortality (online supplemental table 5). Mortality from circulatory diseases (chronic IHD in particular) was elevated in females while other heart diseases were elevated in males. COPD mortality was elevated in both genders.

Among Polo residents, overall cancer incidence was not elevated (online supplemental table 6). In males, we found an increased incidence of cancer of the oesophagus and of sarcomas (any site, based on few cases). Increased incidence of multiple myeloma was observed, and the excess concerned both genders. This excess was concentrated in the period 20–29 years since the accident (6 cases, RR 4.60, 95% CI 1.90 to 11.1) and was observed for both females (3 cases, RR 4.46, 95% CI 1.29 to 15.4) and males (3 cases, RR 4.74, 95% CI 1.33 to 16.9).

Table 2 Results of Poisson regression analyses of mortality in the Seveso cohort, Italy, 1976–2013: number of deaths (n), rate ratio (RR) adjusted/stratified for gender, age and period, and 95% CIs for the polluted zones (A, B, R) compared with the reference zone

	Zone A			Zone B			Zone R		
Cause of death (ICD-9 code)	n	RR	95% CI	n	RR	95% CI	n	RR	95% CI
All causes (001–999)	188	0.95	0.82 to 1.09	1213	0.96	0.91 to 1.02	9208	1.02	1.00 to 1.04
Females	83	0.90	0.73 to 1.12	523	0.97	0.89 to 1.06	4338	1.03	0.99 to 1.06
Males	105	0.98	0.81 to 1.19	690	0.96	0.89 to 1.03	4870	1.01	0.98 to 1.04
Non-cancer causes (001–139, 240–999)	118	0.92	0.77 to 1.10	796	0.97	0.91 to 1.04	6171	1.04	1.01 to 1.07
Females	57	0.90	0.69 to 1.16	367	1.00	0.90 to 1.11	3125	1.06	1.02 to 1.10
Males	61	0.94	0.73 to 1.21	429	0.96	0.87 to 1.06	3046	1.02	0.98 to 1.06
Diabetes mellitus (250)	6	1.51	0.68 to 3.36	38	1.49	1.08 to 2.06	246	1.28	1.11 to 1.46
Females	5	2.06	0.86 to 4.97	25	1.73	1.16 to 2.57	164	1.39	1.18 to 1.65
Males	1	0.63	0.09 to 4.48	13	1.17	0.68 to 2.04	82	1.09	0.86 to 1.37
Neurological disease (320–359)	2	0.45	0.11 to 1.81	22	0.81	0.53 to 1.24	218	1.14	0.98 to 1.31
Females	1	0.41	0.06 to 2.92	10	0.70	0.37 to 1.30	126	1.18	0.98 to 1.43
Males	1	0.51	0.07 to 3.60	12	0.93	0.53 to 1.66	92	1.08	0.86 to 1.35
All circulatory diseases (390–459)	67	1.00	0.79 to 1.27	416	0.97	0.88 to 1.07	3364	1.06	1.02 to 1.10
Females	30	0.85	0.59 to 1.22	200	0.99	0.86 to 1.14	1820	1.09	1.04 to 1.14
Males	37	1.15	0.84 to 1.59	216	0.96	0.84 to 1.10	1544	1.02	0.96 to 1.07
Hypertension (400–405)	10	2.21	1.19 to 4.12	19	0.68	0.44 to 1.08	232	1.10	0.96 to 1.27
Females	9	3.07	1.59 to 5.91	9	0.54	0.28 to 1.04	156	1.14	0.96 to 1.35
Males	1	0.63	0.09 to 4.49	10	0.91	0.49 to 1.70	76	1.03	0.81 to 1.32
Ischaemic heart disease (410–414)	16	0.68	0.42 to 1.11	137	0.90	0.76 to 1.06	1145	1.03	0.97 to 1.10
Females	2	0.19	0.05 to 0.78	51	0.86	0.65 to 1.13	527	1.08	0.98 to 1.18
Males	14	1.03	0.61 to 1.75	86	0.93	0.75 to 1.15	618	0.99	0.91 to 1.07
Myocardial infarction (410)	6	0.46	0.21 to 1.03	74	0.88	0.70 to 1.11	576	0.96	0.88 to 1.05
Females	1	0.22	0.03 to 1.53	24	0.88	0.59 to 1.31	213	0.98	0.85 to 1.13
Males	5	0.59	0.25 to 1.42	50	0.89	0.67 to 1.17	363	0.95	0.85 to 1.06
Chronic IHD (412, 414)	10	0.96	0.51 to 1.78	62	0.92	0.71 to 1.18	563	1.12	1.02 to 1.22
Females	1	0.18	0.03 to 1.27	27	0.86	0.59 to 1.26	312	1.17	1.04 to 1.32
Males	9	1.80	0.93 to 3.46	35	0.98	0.70 to 1.37	251	1.05	0.92 to 1.20
Other heart disease (420-429)	16	1.44	0.88 to 2.35	64	0.90	0.70 to 1.15	587	1.09	1.00 to 1.19
Females	7	1.08	0.51 to 2.26	37	1.02	0.74 to 1.41	325	1.06	0.94 to 1.19
Males	9	1.91	0.99 to 3.69	27	0.78	0.53 to 1.14	262	1.14	1.00 to 1.30
Cerebrovascular disease (430–438)	16	0.84	0.51 to 1.37	146	1.20	1.02 to 1.42	992	1.09	1.01 to 1.16
Females	7	0.64	0.30 to 1.34	77	1.22	0.98 to 1.53	595	1.14	1.04 to 1.24
Males	9	1.10	0.57 to 2.13	69	1.18	0.93 to 1.50	397	1.01	0.91 to 1.12
Respiratory disease (460–519)	12	0.99	0.56 to 1.75	89	1.14	0.92 to 1.40	535	0.94	0.86 to 1.03
Females	3	0.57	0.18 to 1.76	38	1.26	0.91 to 1.74	212	0.86	0.74 to 0.99
Males	9	1.34	0.69 to 2.57	51	1.06	0.81 to 1.41	323	1.01	0.90 to 1.13
COPD (490–493)	7	1.40	0.67 to 2.94	42	1.27	0.93 to 1.72	264	1.11	0.98 to 1.27
Females	2	1.17	0.29 to 4.68	17	1.74	1.07 to 2.82	78	0.97	0.77 to 1.23
Males	5	1.52	0.63 to 3.67	25	1.07	0.72 to 1.59	186	1.18	1.01 to 1.38
Digestive disease (520–579)	10	1.00	0.54 to 1.86	64	1.00	0.78 to 1.28	501	1.09	1.00 to 1.20
Females	6	1.43	0.64 to 3.19	30	1.21	0.84 to 1.74	209	1.08	0.94 to 1.25
Males	4	0.68	0.25 to 1.81	34	0.87	0.62 to 1.22	292	1.10	0.97 to 1.25
Liver disease (570–579)	3	0.51	0.16 to 1.58	32	0.85	0.60 to 1.21	277	1.05	0.92 to 1.19
Females	0			11	0.91	0.50 to 1.65	87	0.96	0.76 to 1.20
Males	3	0.76	0.25 to 2.37	21	0.82	0.53 to 1.27	190	1.09	0.94 to 1.27
Urogenital disease (580–629)	3	1.03	0.33 to 3.20	16	0.86	0.53 to 1.42	140	1.04	0.87 to 1.24
Females	2	1.34	0.33 to 5.36	9	1.04	0.54 to 2.02	61	0.89	0.68 to 1.17
Males	1	0.72	0.10 to 5.15	7	0.70	0.33 to 1.49	79	1.19	0.94 to 1.51
Accidents (800–999)	10	1.11	0.60 to 2.06	64	1.06	0.83 to 1.36	393	0.97	0.87 to 1.08
Females	4	1.20	0.45 to 3.21	18	0.91	0.57 to 1.45	139	0.92	0.77 to 1.10
Males	6	1.05	0.47 to 2.35	46	1.15	0.86 to 1.54	254	0.99	0.87 to 1.13

COPD, chronic obstructive pulmonary diseases; ICD-9, International Classification of Diseases, Ninth Revision; IHD, ischaemic heart disease.

Table 3 Results of Poisson regression analyses of cancer incidence in the Seveso cohort, Italy, 1976–2013: number of cancer cases (n), rate ratio (RR) adjusted/stratified for gender, age and period, and 95% CIs for the polluted zones (A, B, R) compared with the reference zone

	Zone A			Zone B			Zone R		
Cancer site (ICD-9 code)	n	RR	95% CI	n	RR	95% CI	n	RR	95% CI
All cancers (140–208)	117	1.01	0.84 to 1.21	677	0.92	0.85 to 1.00	4888	0.98	0.94 to 1.01
Females	57	1.12	0.86 to 1.46	288	0.90	0.80 to 1.02	2179	0.97	0.92 to 1.02
Males	60	0.91	0.71 to 1.18	389	0.93	0.84 to 1.03	2709	0.98	0.94 to 1.03
Digestive (150–159)	35	0.99	0.71 to 1.38	201	0.91	0.79 to 1.05	1465	0.95	0.90 to 1.01
Females	16	1.10	0.67 to 1.80	74	0.83	0.66 to 1.05	620	0.95	0.85 to 1.04
Males	19	0.91	0.58 to 1.43	127	0.96	0.80 to 1.15	845	0.96	0.89 to 1.04
Oesophagus (150)	3	2.41	0.77 to 7.56	4	0.50	0.19 to 1.35	64	1.17	0.88 to 1.56
Females	1	3.65	0.50 to 26.7	0			10	0.79	0.39 to 1.59
Males	2	2.04	0.50 to 8.26	4	0.64	0.23 to 1.72	54	1.28	0.93 to 1.76
Stomach (151)	11	1.31	0.72 to 2.37	45	0.84	0.63 to 1.14	334	0.89	0.79 to 1.01
Females	6	1.87	0.84 to 4.19	18	0.92	0.58 to 1.48	142	0.95	0.76 to 1.15
Males	5	0.95	0.40 to 2.30	27	0.80	0.54 to 1.17	192	0.84	0.72 to 0.99
Colon (153)	7	0.71	0.34 to 1.49	53	0.86	0.65 to 1.13	410	0.96	0.86 to 1.08
Females	4	0.86	0.32 to 2.29	20	0.69	0.44 to 1.08	192	0.92	0.78 to 1.30
Males	3	0.58	0.19 to 1.80	33	1.01	0.71 to 1.43	218	1.00	0.86 to 1.18
Rectum (154)	6	1.31	0.59 to 2.94	40	1.40	1.01 to 1.93	206	1.05	0.89 to 1.24
Females	2	1.10	0.27 to 4.42	15	1.33	0.78 to 2.25	82	1.01	0.78 to 1.30
Males	4	1.45	0.54 to 3.89	25	1.45	0.96 to 2.18	124	1.08	0.87 to 1.33
Liver (155)	3	0.58	0.19 to 1.80	27	0.84	0.57 to 1.24	201	0.92	0.78 to 1.08
Females	0			6	0.71	0.31 to 1.62	58	0.93	0.69 to 1.26
Males	3	0.79	0.25 to 2.46	21	0.89	0.57 to 1.38	143	0.91	0.75 to 1.11
Biliary tract (156)	0			12	1.19	0.66 to 2.15	69	0.98	0.74 to 1.30
Females	0			5	0.83	0.34 to 2.05	50	1.15	0.82 to 1.61
Males	0			7	1.70	0.77 to 3.75	19	0.70	0.42 to 1.19
Pancreas (157)	2	0.57	0.14 to 2.29	12	0.55	0.31 to 0.98	143	0.95	0.78 to 1.16
Females	1	0.58	0.08 to 4.17	6	0.58	0.26 to 1.31	67	0.89	0.67 to 1.19
Males	1	0.56	0.08 to 4.00	6	0.53	0.24 to 1.20	76	1.02	0.77 to 1.33
Other digestive (159)	2	4.19	1.02 to 17.1	5	1.66	0.67 to 4.10	22	0.97	0.60 to 1.56
Females	2	7.01	1.70 to 28.9	2	1.21	0.29 to 4.96	14	1.02	0.57 to 1.84
Males	0			3	2.17	0.65 to 7.21	8	0.87	0.39 to 1.93
Respiratory (160–165)	17	0.90	0.56 to 1.46	106	0.89	0.73 to 1.09	790	0.99	0.91 to 1.07
Females	1	0.32	0.04 to 2.26	10	0.51	0.27 to 0.96	135	0.97	0.79 to 1.20
Males	16	1.02	0.62 to 1.67	96	0.97	0.79 to 1.19	655	0.99	0.90 to 1.08
Lung (162)	16	1.03	0.63 to 1.69	85	0.87	0.70 to 1.09	662	1.01	0.92 to 1.10
Females	1	0.38	0.05 to 2.69	8	0.48	0.24 to 0.98	114	0.98	0.78 to 1.22
Males	15	1.17	0.70 to 1.95	77	0.95	0.76 to 1.20	548	1.02	0.92 to 1.12
Soft tissue sarcoma (171)	0			4	1.19	0.43 to 3.31	23	1.03	0.62 to 1.70
Females	0			1	0.66	0.09 to 4.88	11	1.06	0.51 to 2.20
Males	0			3	1.63	0.49 to 5.41	12	1.00	0.50 to 1.99
Sarcoma, any site	0			7	1.05	0.49 to 2.26	47	1.06	0.75 to 1.49
Females	0			3	0.88	0.27 to 2.80	23	0.99	0.61 to 1.60
Males	0			4	1.23	0.44 to 3.40	24	1.14	0.70 to 1.85
Melanoma (172)	2	1.00	0.25 to 4.03	10	0.76	0.40 to 1.45	76	0.89	0.68 to 1.16
Females	2	1.90	0.47 to 7.72	6	0.88	0.38 to 2.01	42	0.93	0.64 to 1.33
Males	0			4	0.63	0.23 to 1.72	34	0.84	0.56 to 1.26
Breast (174) Females	16	1.01	0.62 to 1.65	87	0.85	0.69 to 1.06	659	0.95	0.87 to 1.04
Breast (175) Males	1	7.43	0.97 to 56.9	1	1.16	0.15 to 8.83	6	1.05	0.40 to 2.76
Genito-urinary (179–189)	27	1.08	0.74 to 1.58	134	0.85	0.71 to 1.01	1079	1.01	0.94 to 1.09
Females	10	1.21	0.65 to 2.25	49	0.93	0.70 to 1.24	372	1.01	0.90 to 1.14
Males	17	1.00	0.62 to 1.61	85	0.80	0.64 to 1.00	707	1.01	0.93 to 1.11
Uterus (179-182)	6	1.57	0.70 to 3.51	25	1.02	0.68 to 1.53	162	0.96	0.80 to 1.15
Cervix (179-182)	3	2.68	0.85 to 8.39	10	1.38	0.73 to 2.62	50	1.02	0.74 to 1.39
Endometrium (179–182)	2	0.95	0.24 to 3.84	12	0.89	0.50 to 1.60	90	0.97	0.76 to 1.24
Ovary (183)	2	1.10	0.27 to 4.41	6	0.52	0.23 to 1.16	101	1.25	0.99 to 1.58

continued

Table 3 continued

Cancer site (ICD-9 code)	Zone A			Zone B			Zone R		
	n	RR	95% CI	n	RR	95% CI	n	RR	95% CI
Prostate (185)	7	0.78	0.37 to 1.63	39	0.72	0.52 to 0.99	365	1.02	0.90 to 1.16
Testis (186)	1	1.56	0.22 to 11.2	5	1.04	0.42 to 2.57	35	1.20	0.80 to 1.80
Bladder (188)	8	1.35	0.67 to 2.71	36	0.96	0.69 to 1.35	245	0.97	0.84 to 1.12
Females	1	1.03	0.14 to 7.41	5	0.85	0.35 to 2.09	38	0.87	0.60 to 1.26
Males	7	1.41	0.67 to 2.97	31	0.98	0.68 to 1.42	207	0.99	0.84 to 1.16
Kidney (189)	3	0.87	0.28 to 2.73	18	0.83	0.52 to 1.34	138	0.95	0.78 to 1.16
Females	1	0.81	0.11 to 5.77	9	1.15	0.58 to 2.27	50	0.92	0.66 to 1.28
Males	2	0.91	0.23 to 3.69	9	0.65	0.33 to 1.27	88	0.97	0.75 to 1.25
Brain (191)	2	1.10	0.27 to 4.42	9	0.77	0.39 to 1.50	66	0.84	0.64 to 1.12
Females	1	1.23	0.17 to 8.81	5	0.96	0.39 to 2.38	30	0.84	0.55 to 1.28
Males	1	1.00	0.14 to 7.19	4	0.61	0.23 to 1.67	36	0.85	0.58 to 1.24
Thyroid (193)	2	1.41	0.35 to 5.70	12	1.27	0.70 to 2.30	61	1.01	0.74 to 1.38
Females	2	2.11	0.52 to 8.60	9	1.46	0.73 to 2.91	52	1.30	0.92 to 1.84
Males	0			3	0.87	0.27 to 2.84	9	0.42	0.20 to 0.88
LH tissue (200–208)	10	1.18	0.63 to 2.21	67	1.24	0.97 to 1.59	394	1.09	0.96 to 1.23
Females	6	1.65	0.73 to 3.69	32	1.40	0.97 to 2.00	168	1.05	0.88 to 1.26
Males	4	0.83	0.31 to 2.23	35	1.12	0.79 to 1.58	226	1.12	0.95 to 1.31
Hodgkin's disease (201)	1	1.23	0.17 to 8.84	5	0.91	0.37 to 2.24	36	1.03	0.70 to 1.52
Females	1	2.56	0.35 to 18.6	4	1.58	0.57 to 4.41	19	1.16	0.68 to 1.98
Males	0			1	0.33	0.05 to 2.39	17	0.90	0.51 to 1.59
NHL (200, 202)	3	0.82	0.26 to 2.54	32	1.36	0.95 to 1.96	174	1.11	0.92 to 1.33
Females	2	1.27	0.31 to 5.12	15	1.51	0.89 to 2.56	72	1.04	0.79 to 1.37
Males	1	0.48	0.07 to 3.41	17	1.25	0.76 to 2.06	102	1.16	0.91 to 1.48
Multiple myeloma (203)	2	1.68	0.42 to 6.81	10	1.35	0.71 to 2.58	61	1.19	0.88 to 1.62
Females	1	1.86	0.26 to 13.4	7	2.10	0.96 to 4.61	27	1.12	0.71 to 1.76
Males	1	1.55	0.21 to 11.2	3	0.73	0.23 to 2.34	34	1.26	0.83 to 1.92
Leukaemia (204–208)	4	1.45	0.54 to 3.90	20	1.14	0.72 to 1.80	122	1.03	0.83 to 1.28
Females	2	1.75	0.43 to 7.07	6	0.84	0.37 to 1.92	50	0.99	0.71 to 1.38
Males	2	1.24	0.31 to 5.02	14	1.34	0.78 to 2.33	72	1.06	0.80 to 1.41
Lymphatic leukaemia (204)	1	0.96	0.13 to 6.90	5	0.76	0.31 to 1.86	54	1.21	0.87 to 1.68
Females	1	2.42	0.33 to 17.6	0			21	1.15	0.68 to 1.93
Males	0			5	1.23	0.49 to 3.07	33	1.25	0.82 to 1.92
Myeloid leukaemia (205)	3	2.38	0.76 to 7.47	13	1.61	0.91 to 2.85	51	0.94	0.68 to 1.30
Females	1	1.80	0.25 to 13.0	5	1.43	0.57 to 3.56	23	0.94	0.58 to 1.52
Males	2	2.81	0.69 to 11.5	8	1.73	0.83 to 3.60	28	0.93	0.60 to 1.45
Leukaemia, unspecified (208)	0			2	1.06	0.25 to 4.47	10	0.77	0.37 to 1.60
Females	0			1	1.21	0.15 to 9.47	4	0.68	0.22 to 2.16
Males	0			1	0.93	0.12 to 7.10	6	0.84	0.33 to 2.18

ICD-9, International Classification of Diseases, Ninth Revision; LH, lymphatic and haematopoietic; NHL, non-Hodgkin's lymphoma.

DISCUSSION

Over the whole follow-up period, in the polluted zones, we found no increased all-cause mortality and all cancer incidence. In males we observed elevated non-cancer mortality in the most polluted zone A in the first decade after the accident, mainly due to circulatory diseases and a few cases of COPD. In females, mortality from diabetes mellitus was increased in the polluted area, with a positive trend from the less to the most polluted zone. There was a breast cancer excess in zone A in the second decade after the accident. Incidence of soft tissue sarcoma was increased in males in zone R in the first decade. In females, LH tissue cancers were in excess in zone B in the first two decades and in zone A in the second and third decades. In females in zone B, there was an excess of NHL 30+ years after the accident. Multiple myeloma was increased in the second decade in females in zone B and in males in zone R. There was an isolated leukaemia excess in males in zone R 30 years after the accident.

We did not find elevated mortality and cancer incidence risks among chloracne cases. Conversely, multiple myeloma was elevated in both genders in the Polo quarter, an area with possibly higher TCDD exposure within zone R.

These results are in general in agreement with previous mortality (1976–2001)[22 23 30] and cancer incidence (1977–1996)[25 26] studies in this cohort because most associations were observed in the first decades after the accident. In this updated follow-up, the overall LH cancer increase was less evident while NHL in females (zone B and R) and leukaemia (zone R) emerged 20–37 years after the accident. Moreover, we observed high multiple myeloma incidence in the Polo quarter 20–29 years after the accident.

Table 4 Results of Poisson regression analyses of mortality and cancer incidence in the Seveso cohort, Italy, 1976–2013, for selected causes, by time since the accident (latency): number of deaths or cancer cases (n), rate ratio (RR) adjusted for gender and age and 95% CIs for the polluted zones (A, B, R) compared with the reference zone

Cause of death or cancer site (ICD-9 codes) and latency	Zone A			Zone B			Zone R		
	n	RR	95% CI	n	RR	95% CI	n	RR	95% CI
Non-cancer causes (001–139, 240–999)									
<10 years	40	1.41	1.04 to 1.93	185	0.93	0.81 to 1.08	1638	1.07	1.02 to 1.13
10–19 years	21	0.73	0.47 to 1.12	193	0.96	0.84 to 1.11	1525	1.05	0.99 to 1.10
20–29 years	26	0.69	0.47 to 1.02	229	0.99	0.87 to 1.13	1688	1.04	0.98 to 1.09
30–37 years	31	0.93	0.65 to 1.32	189	0.99	0.86 to 1.15	1320	1.00	0.94 to 1.06
Diabetes mellitus (250)									
<10 years	1	0.99	0.14 to 7.07	9	1.33	0.68 to 2.57	59	1.08	0.82 to 1.42
10–19 years	1	0.74	0.10 to 5.22	15	1.66	0.99 to 2.78	98	1.41	1.14 to 1.76
20–29 years	2	1.71	0.42 to 6.86	8	1.13	0.56 to 2.28	66	1.31	1.02 to 1.71
30–37 years	2	4.33	1.07 to 17.5	6	2.25	0.99 to 5.12	23	1.24	0.79 to 1.94
Circulatory diseases (390–459)									
<10 years	26	1.59	1.08 to 2.34	117	1.02	0.85 to 1.22	998	1.10	1.03 to 1.17
10–19 years	10	0.62	0.33 to 1.15	94	0.84	0.68 to 1.03	865	1.04	0.97 to 1.12
20–29 years	15	0.77	0.46 to 1.28	129	1.09	0.92 to 1.30	875	1.04	0.97 to 1.11
30–37 years	16	1.05	0.65 to 1.72	76	0.89	0.71 to 1.11	626	1.04	0.96 to 1.14
COPD (490-493)									
<10 years	4	4.13	1.54 to 11.1	11	1.52	0.83 to 2.76	63	1.15	0.88 to 1.50
10–19 years	3	2.71	0.87 to 8.44	10	1.18	0.63 to 2.22	71	1.17	0.91 to 1.51
20–29 years	0			14	1.54	0.91 to 2.63	74	1.19	0.93 to 1.52
30–37 years	0			7	0.81	0.39 to 1.72	56	0.93	0.70 to 1.23
All cancers (140–208)									
<10 years	21	1.08	0.70 to 1.65	122	0.96	0.80 to 1.15	917	0.98	0.91 to 1.05
10–19 years	26	0.93	0.63 to 1.36	190	1.07	0.92 to 1.23	1203	0.96	0.91 to 1.02
20–29 years	39	1.03	0.75 to 1.41	207	0.88	0.76 to 1.01	1586	1.01	0.95 to 1.08
30–37 years	31	1.01	0.71 to 1.44	158	0.82	0.70 to 0.97	1182	0.95	0.88 to 1.03
Lung cancer (162)									
<10 years	4	1.39	0.52 to 3.71	18	0.94	0.59 to 1.50	125	0.92	0.76 to 1.11
10–19 years	3	0.75	0.24 to 2.33	25	1.00	0.67 to 1.49	187	1.09	0.93 to 1.27
20–29 years	5	1.02	0.42 to 2.47	29	0.98	0.67 to 1.43	192	0.98	0.82 to 1.18
30–37 years	4	0.97	0.36 to 2.60	13	0.53	0.30 to 0.93	158	0.98	0.80 to 1.21
Soft tissue sarcoma (171)									
<10 years	0			0			8	2.06	0.93 to 4.60
10–19 years	0			0			1	0.23	0.03 to 1.66
20–29 years	0			2	2.91	0.60 to 14.0	5	1.08	0.34 to 3.41
30–37 years	0			2	1.48	0.33 to 6.68	9	1.04	0.43 to 2.50
LH cancers (200–208)									
<10 years	0			14	1.60	0.94 to 2.73	57	0.92	0.69 to 1.21
10–19 years	4	2.05	0.77 to 5.48	20	1.58	1.01 to 2.47	93	1.06	0.85 to 1.33
20–29 years	5	1.78	0.73 to 4.33	21	1.18	0.74 to 1.84	135	1.15	0.92 to 1.44
30–37 years	1	0.45	0.06 to 3.26	12	0.88	0.48 to 1.59	109	1.23	0.95 to 1.60
Hodgkin's disease (201)									
<10 years	0			2	1.55	0.38 to 6.39	10	1.20	0.60 to 2.36
10–19 years	0			2	1.43	0.35 to 5.86	13	1.45	0.79 to 2.66
20–29 years	1	3.73	0.50 to 28.1	1	0.53	0.07 to 4.04	7	0.61	0.25 to 1.47
30–37 years	0			0			6	0.79	0.28 to 2.23
NHL (200, 202)									
<10 years	0			4	1.43	0.53 to 3.88	25	1.23	0.80 to 1.89
10–19 years	1	1.07	0.15 to 7.65	9	1.50	0.77 to 2.92	35	0.84	0.59 to 1.20
20–29 years	1	0.77	0.11 to 5.55	9	1.09	0.55 to 2.17	62	1.15	0.82 to 1.60
30–37 years	1	1.05	0.14 to 7.60	10	1.70	0.86 to 3.36	52	1.37	0.92 to 2.02
Multiple myeloma									
<10 years	0			4	3.36	1.22 to 9.26	6	0.66	0.28 to 1.52
10–19 years	1	4.09	0.57 to 29.5	4	2.56	0.94 to 7.02	19	1.68	1.02 to 2.80

continued

Table 4 continued

Cause of death or cancer site (ICD-9 codes) and latency	Zone A			Zone B			Zone R		
	n	RR	95% CI	n	RR	95% CI	n	RR	95% CI
20–29 years	1	2.24	0.31 to 16.5	2	0.72	0.17 to 3.02	20	1.08	0.61 to 1.91
30–37 years	0			0			16	1.12	0.57 to 2.20
Leukaemia (204–208)									
<10 years	0			4	1.16	0.43 to 3.12	16	0.65	0.39 to 1.10
10–19 years	2	3.49	0.86 to 14.1	5	1.34	0.55 to 3.38	26	1.01	0.67 to 1.53
20–29 years	2	2.51	0.61 to 10.3	9	1.79	0.88 to 3.64	46	1.40	0.93 to 2.09
30–37 years	0			2	0.47	0.11 to 1.95	34	1.21	0.75 to 1.94

COPD, chronic obstructive pulmonary diseases; ICD-9, International Classification of Diseases, Ninth Revision; LH, lymphatic and haematopoietic; NHL, non-Hodgkin's lymphoma.

Strengths and limitations

This study has several strengths. First, it allowed to have a comprehensive picture of mortality and cancer incidence for 37 years after the accident in the absence (until recently) of a cancer registry. Second, a reference area very close to the polluted zones has been used with similar public, free-access and good quality healthcare services, lowering the possibility of important confounding effects from environmental determinants and lifestyle habits and of misclassification of effects from differential ascertainment of causes of death or diagnostic performance. Third, the whole population (exposed and unexposed components) has been followed up as a unique cohort using the same procedures (although varying over time) to determine vital status, causes of death and cancer diagnoses. Fourth, vital status and cause of death ascertainment were nearly complete, so important selection biases are unlikely.

The main limitation is the exposure definition, which was ecological, being based on residence in areas defined according to soil TCDD concentrations. Although studies showed clear gradients of serum TCDD across zones,[27 28 31] some degree of misclassification is unavoidable because of heterogeneity of exposure to TCDD within zones. Additionally, it is possible that a fraction of the population was not in the area in the days after the accident (although it was probably small, given that the typical holiday month is August). Second, differently from mortality, cancer diagnoses could only be ascertained for people living in Lombardy (1977–2006) and for those living in the area covered by the cancer registry (2007–2013); for these reasons, we included DCO cancer cases in analysis to minimise potential selection biases. In this way, we introduced some misclassification bias, which, at least on average, was towards the null and probably small, given the relatively small DCO proportion (about 10%).

Biological plausibility

Different mechanisms for the action of TCDD on glucose metabolism have been hypothesised in in vitro and epidemiological studies. Animal and human studies showed that TCDD can adversely affect the cardiovascular system through various mechanisms. Moreover, a potential contributor to the circulatory disease excess in the early postaccident period is the heavy psychosocial impact of the accident on people living in zone A. Regarding respiratory effects, possible mechanisms include direct toxicity of TCDD on bronchiolar and alveolar tissue, interference with the immune system and oxidative stress. Regarding the increased LH cancer incidence, positive associations were found between TCDD and lymphocytes t(14;18) translocations in lymphocytes and impaired B lymphopoiesis. More details and references on biological plausibility can be found in the online supplemental material.

Comparison with published research

Old studies found weak evidence regarding TCCD and diabetes while results regarding cardiovascular diseases have been more consistent (increased IHD mortality with positive exposure-response associations). In a non-systematic search, we found several studies and reviews on the effects of TCCD published after (or not included in) the last IARC evaluation. Studies of occupational cohorts in the USA, the Netherlands, Germany and New Zealand found positive associations between exposure to TCDD and various diseases, including circulatory diseases, all cancers, NHL, STS, leukaemia, multiple myeloma and breast cancer. Studies among Korean Veterans found elevated risks (mortality, incidence or prevalence) of all cancers, lung cancer, NHL, circulatory and respiratory diseases and diabetes. The SWHS reported positive associations between TCDD blood levels and incidence of all cancer, breast cancer and cardiovascular diseases. A meta-analysis found a dose–response relationship between serum TCDD and diabetes only at low TCDD levels and no association at high levels. The association of TCCD exposure with haematological cancer risk has been evaluated in two reviews that reached opposite conclusions. A meta-analysis found that TCDD was associated with all cancer incidence and mortality and with NHL mortality. A detailed discussion of these studies (with references) and how our study compares with them can be found in the online supplemental material.

CONCLUSIONS

The Seveso cohort study represented a landmark in Italy because cancer incidence could be assessed in a large population in an area not covered by a cancer registry until 2006, by means of record linkage and manual search of clinical records in hospital archives. Several papers on results in the whole and in the young population have been published over the years in various journals. Communication of findings has been important for the affected population and for the institutions (the local municipalities and the Regional Government of Lombardy). Although with different patterns across gender, zone and time, some results (increased cardiovascular diseases, soft tissue sarcomas and LH cancers) are consistent with previous researches (in this and other populations) and with IARC evaluation of TCDD carcinogenicity.

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Supplementary Table 1 Results of Poisson regression analyses of **mortality and cancer incidence** among **females** in the Seveso cohort, Italy, 1976-2013, for selected causes, **by time since the accident:** number of deaths or cancer cases (n), rate ratios (RR) adjusted for age and 95% confidence intervals (CI) for the polluted zones (A, B, R) compared with the reference zone

Cause of death or cancer site (ICD-9 codes) and latency	**Zone A**			**Zone B**			**Zone R**		
	n	**RR**	**95% CI**	**n**	**RR**	**95% CI**	**n**	**RR**	**95% CI**
Non-cancer causes (001-139, 240-999)									
<10 years	15	1.15	0.69-1.91	81	1.03	0.83-1.28	761	1.06	0.99-1.15
10-19 years	10	0.67	0.36-1.25	87	0.97	0.78-1.19	768	1.04	0.97-1.13
20-29 years	15	0.75	0.45-1.25	107	1.03	0.85-1.25	877	1.06	0.98-1.14
30-37 years	17	1.10	0.68-1.76	92	0.97	0.79-1.19	719	1.06	0.98-1.15
Diabetes mellitus (250)									
<10 years	1	1.59	0.22-11.3	4	1.04	0.39-2.79	38	1.10	0.78-1.55
10-19 years	1	1.09	0.15-7.76	14	2.51	1.47-4.29	68	1.49	1.15-1.94
20-29 years	2	3.25	0.81-13.1	3	0.87	0.28-2.73	41	1.55	1.10-2.18
30-37 years	1	3.84	0.53-27.6	4	2.52	0.92-6.90	17	1.52	0.90-2.58
Circulatory diseases (390-459)									
<10 years	9	1.11	0.58-2.13	55	1.12	0.86-1.46	512	1.12	1.02-1.23
10-19 years	4	0.46	0.17-1.22	39	0.73	0.53-1.01	451	1.02	0.93-1.13
20-29 years	7	0.63	0.30-1.33	66	1.17	0.92-1.50	498	1.09	0.99-1.20
30-37 years	10	1.39	0.75-2.59	40	0.90	0.66-1.23	359	1.13	1.01-1.27
COPD (490-493)									
<10 years	1	3.36	0.47-24.0	4	2.23	0.82-6.05	18	1.10	0.67-1.80
10-19 years	1	2.40	0.34-17.1	5	2.00	0.82-4.87	25	1.19	0.78-1.82
20-29 years	0			5	1.91	0.78-4.67	23	1.07	0.69-1.66
30-37 years	0			3	1.02	0.32-3.19	12	0.56	0.31-1.02
All cancers (140-208)									
<10 years	13	1.50	0.87-2.59	41	0.77	0.57-1.05	427	1.02	0.92-1.13
10-19 years	16	1.31	0.80-2.15	82	1.08	0.87-1.35	504	0.91	0.83-1.00
20-29 years	13	0.82	0.48-1.42	88	0.88	0.71-1.10	688	1.01	0.92-1.11
30-37 years	15	1.08	0.65-1.79	77	0.85	0.67-1.08	560	0.96	0.86-1.07
Breast cancer (174)									
<10 years	1	0.40	0.06-2.86	10	0.66	0.35-1.23	128	1.11	0.92-1.94
10-19 years	6	1.63	0.73-3.63	20	0.85	0.55-1.33	148	0.90	0.75-1.07
20-29 years	4	0.73	0.27-1.94	28	0.78	0.53-1.14	220	0.92	0.78-1.09
30-37 years	5	1.23	0.51-2.99	29	1.07	0.72-1.57	163	0.94	0.77-1.15
Soft tissue sarcoma (171)									
<10 years	0			0			2	1.25	0.27-5.72
10-19 years	0			0			0		
20-29 years	0			1	3.59	0.37-34.5	3	1.56	0.32-7.75
30-37 years	0			0			6	2.58	0.64-10.3
LH cancers (200-208)									
<10 years	0			6	1.61	0.72-3.65	28	1.00	0.67-1.49
10-19 years	2	2.11	0.52-8.47	11	1.85	1.01-3.39	40	0.92	0.66-1.29
20-29 years	3	2.85	0.90-9.05	8	1.25	0.60-2.59	52	1.18	0.82-1.69
30-37 years	1	1.06	0.15-7.70	7	1.15	0.52-2.53	48	1.21	0.82-1.79
Hodgkin's disease (201)									
<10 years	0			1	1.75	0.24-13.0	6	1.59	0.64-3.92
10-19 years	0			2	2.55	0.61-10.7	7	1.35	0.59-3.08
20-29 years	1	9.89	1.19-82.2	1	1.77	0.21-14.7	2	0.52	0.10-2.58
30-37 years	0			0			4	0.97	0.26-3.61
NHL (200, 202)									
<10 years	0			1	0.78	0.11-5.65	12	1.21	0.65-2.25
10-19 years	0			4	1.43	0.50-4.07	11	1.31	0.77-2.24
20-29 years	1	2.20	0.30-16.1	4	1.43	0.50-4.07	25	1.31	0.77-2.24
30-37 years	1	3.04	0.41-22.8	6	2.87	1.14-7.23	24	1.75	0.95-3.23
Multiple myeloma (203)									
<10 years	0			2	4.13	0.98-17.4	4	0.99	0.35-2.83
10-19 years	1	7.82	1.07-57.0	4	5.09	1.82-14.2	8	1.33	0.62-2.84
20-29 years	0			1	0.69	0.09-5.25	6	0.59	0.23-1.51
30-37 years	0			0			9	1.67	0.62-4.48
Leukaemia (204-208)									
<10 years	0			2	1.45	0.36-5.94	6	0.58	0.25-1.34
10-19 years	1	4.25	0.59-30.6	1	0.69	0.10-4.95	14	1.29	0.73-2.29
20-29 years	1	3.83	0.51-28.8	2	1.25	0.29-5.42	19	1.72	0.90-3.32
30-37 years	0			1	0.40	0.05-2.97	11	0.67	0.32-1.38

ICD-9, International Classification of Diseases, Ninth Revision; COPD, chronic obstructive pulmonary diseases; LH, lymphatic and haematopoietic; NHL, non-Hodgkin's lymphoma.

Supplementary Table 2 Results of Poisson regression analyses of **mortality and cancer incidence** among **males** in the Seveso cohort, Italy, 1976-2013, for selected causes, **by time since the accident**: number of deaths or cancer cases (n), rate ratios (RR) adjusted for age and 95% confidence intervals (CI) for the polluted zones (A, B, R) compared with the reference zone

Cause of death or cancer site (ICD-9 codes) and latency	**Zone A**			**Zone B**			**Zone R**		
	n	**RR**	**95% CI**	**n**	**RR**	**95% CI**	**n**	**RR**	**95% CI**
Non-cancer causes (001-139, 240-999)									
<10 years	25	1.60	1.08-2.36	104	0.88	0.72-1.07	877	1.07	1.00-1.15
10-19 years	11	0.76	0.42-1.38	106	0.97	0.80-1.17	757	1.03	0.96-1.12
20-29 years	11	0.61	0.34-1.10	122	0.97	0.81-1.16	811	1.01	0.94-1.09
30-37 years	14	0.81	0.48-1.37	97	1.03	0.84-1.25	601	0.94	0.86-1.02
Diabetes mellitus (250)									
<10 years	0			5	1.73	0.71-4.22	21	1.03	0.65-1.64
10-19 years	0			1	0.29	0.04-2.05	30	1.24	0.84-1.84
20-29 years	0			5	1.37	0.56-3.35	25	1.05	0.68-1.60
30-37 years	1	4.90	0.67-35.6	2	1.84	0.45-7.60	6	0.82	0.35-1.92
Circulatory diseases (390-459)									
<10 years	17	2.00	1.24-3.23	62	0.95	0.74-1.22	486	1.07	0.97-1.18
10-19 years	6	0.78	0.35-1.73	55	0.94	0.72-1.23	414	1.04	0.94-1.16
20-29 years	8	0.91	0.46-1.83	63	1.04	0.81-1.33	377	0.97	0.87-1.08
30-37 years	6	0.78	0.35-1.74	36	0.87	0.63-1.21	267	0.95	0.83-1.08
COPD (490-493)									
<10 years	3	4.45	1.42-13.9	7	1.28	0.60-2.72	45	1.18	0.86-1.61
10-19 years	2	2.81	0.70-11.3	5	0.84	0.35-2.04	46	1.15	0.84-1.57
20-29 years	0			9	1.40	0.72-2.73	51	1.24	0.92-1.68
30-37 years	0			4	0.71	0.27-1.92	44	1.14	0.82-1.57
All cancers (140-208)									
<10 years	8	0.73	0.37-1.47	81	1.08	0.87-1.35	490	0.94	0.86-1.04
10-19 years	10	0.63	0.34-1.17	108	1.05	0.87-1.27	699	1.01	0.93-1.09
20-29 years	26	1.16	0.79-1.71	119	0.86	0.72-1.04	898	1.01	0.93-1.10
30-37 years	16	0.93	0.57-1.53	81	0.80	0.63-1.00	622	0.95	0.85-1.05
Lung cancer (162)									
<10 years	4	1.53	0.57-4.09	17	0.98	0.60-1.58	103	0.84	0.69-1.03
10-19 years	3	0.87	0.28-2.69	24	1.11	0.74-1.66	166	1.13	0.96-1.33
20-29 years	5	1.17	0.48-2.82	24	0.93	0.61-1.41	155	0.92	0.75-1.13
30-37 years	3	1.05	0.33-3.30	12	0.73	0.41-1.32	124	1.16	0.91-1.49
Soft tissue sarcoma (171)									
<10 years	0			0			6	2.62	1.01-6.83
10-19 years	0			0			1	0.56	0.07-4.40
20-29 years	0			1	2.35	0.26-21.0	2	0.73	0.13-3.97
30-37 years	0			2	2.02	0.43-9.51	3	0.47	0.12-1.76
LH cancers (200-208)									
<10 years	0			8	1.58	0.78-3.20	29	0.85	0.57-1.25
10-19 years	2	2.01	0.50-8.08	9	1.34	0.69-2.61	53	1.21	0.90-1.62
20-29 years	2	1.13	0.28-4.57	13	1.13	0.63-2.00	83	1.14	0.85-1.52
30-37 years	0			5	0.66	0.26-1.63	61	1.25	0.87-1.78
Hodgkin's disease (201)									
<10 years	0			1	1.37	0.19-10.1	4	0.87	0.30-2.49
10-19 years	0			0			6	1.58	0.64-3.92
20-29 years	0			0			5	0.64	0.22-1.86
30-37 years	0			0			2	0.58	0.11-3.18
NHL (200, 202)									
<10 years	0			3	1.97	0.62-6.27	13	1.25	0.69-2.27
10-19 years	1	2.17	0.30-15.5	5	1.64	0.67-4.02	24	1.19	0.77-1.85
20-29 years	0			5	0.90	0.36-2.27	37	1.06	0.69-1.62
30-37 years	0			4	1.04	0.36-2.94	28	1.14	0.68-1.91
Multiple myeloma (203)									
<10 years	0			2	2.81	0.67-11.7	2	0.39	0.09-1.63
10-19 years	0			0			11	2.15	1.08-4.26
20-29 years	1	4.88	0.63-37.5	1	0.78	0.10-6.00	14	1.70	0.79-3.67
30-37 years	0			0			7	0.78	0.30-2.02
Leukaemia (204-208)									
<10 years	0			2	0.95	0.23-3.86	10	0.71	0.37-1.37
10-19 years	1	2.94	0.41-21.1	4	1.76	0.65-4.80	12	0.80	0.44-1.46
20-29 years	1	1.84	0.25-13.5	7	2.01	0.89-4.57	27	1.22	0.73-2.04
30-37 years	0			1	0.57	0.08-4.37	23	2.02	1.04-3.93

ICD-9, International Classification of Diseases, Ninth Revision; COPD, chronic obstructive pulmonary diseases; LH, lymphatic and haematopoietic; NHL, non-Hodgkin's lymphoma.

Supplementary Table 3 Deaths and cancer cases among **chloracne cases** in the Seveso cohort, Italy, 1976-2013

	All	**Females**	**Cause of death/cancer site**	**Males**	**Cause of death/cancer site**
	n or mean (SD) range	**n or mean (SD) range**		**n or mean (SD) range**	
All subjects	180	82		98	
Age at the accident (1976)	10.1 (7.2) 0.6-49.8	11.5 (9.7) 0.6-49.8		8.8 (3.6) 1.7-28.4	
Age at the end of follow-up (2013)	46.9 (7.7) 22.7-84.7	48.5 (9.6) 22.7-84.7		45.5 (5.2) 26.3-65.9	
Deaths	4	2		2	
Zone A	2	2	Acute cerebrovascular disease. Diabetes with circulatory disease	0	-
Zone B	0	0	-	0	-
Zone R	2	0	-	2	Liver cirrhosis. Suicide
Cancers	4	3		1	
Zone A	3	2	Thyroid. Cervix	1	Testis
Zone B	0	0	-	0	-
Zone R	1	1	Acute lymphoblastic leukaemia	0	-

Supplementary Table 4 Results of Poisson regression analyses of **mortality and cancer incidence** among **chloracne cases** in the Seveso cohort, Italy, 1976-2013: number of cancer cases (n), rate ratios (RR) adjusted/stratified for gender, age, and period, and 95% confidence intervals (CI) compared with the reference zone

Cause of death or cancer site (ICD-9 code)	n	RR	95% CI
Mortality			
All causes (001-999)	4	0.59	0.22-1.57
Females	2	0.57	0.14-2.29
Males	2	0.62	0.16-2.50
Non-cancer causes (001-139, 240-999)	4	0.88	0.33-2.35
Females	2	0.96	0.24-3.84
Males	2	0.82	0.21-3.30
Cancer incidence			
All cancers (140-208)	4	0.70	0.26-1.87
Females	3	0.79	0.25-2.46
Males	1	0.55	0.08-3.93

ICD-9, International Classification of Diseases, Ninth Revision.

Supplementary Table 5 Results of Poisson regression analyses of **mortality** among **residents in the "Polo" quarter"** in the Seveso cohort, Italy, 1976-2013: number of deaths (n), rate ratios (RR) adjusted/stratified for gender, age, and period, and 95% confidence intervals (CI) compared with the reference zone

Cause of death (ICD-9 code)	n	RR	95% CI
All causes (001-999)	545	0.97	0.89-1.06
Females	246	1.04	0.92-1.18
Males	299	0.92	0.82-1.03
Non-cancer causes (001-139, 240-999)	346	0.97	0.88-1.08
Females	167	1.06	0.91-1.23
Males	179	0.91	0.78-1.05
Diabetes mellitus (250)	13	1.22	0.71-2.11
Females	10	1.66	0.89-3.09
Males	3	0.64	0.21-2.00
Neurological disease (320-359)	12	0.96	0.54-1.69
Females	8	1.24	0.62-2.48
Males	4	0.66	0.25-1.77
All circulatory diseases (390-459)	199	1.10	0.95-1.26
Females	105	1.23	1.01-1.49
Males	94	0.98	0.80-1.20
Hypertension (400-405)	13	1.11	0.64-1.91
Females	10	1.43	0.75-2.62
Males	3	0.65	0.21-2.02
Ischemic heart disease (410-414)	60	0.91	0.71-1.18
Females	32	1.27	0.90-1.80
Males	28	0.69	0.47-1.00
Myocardial infarction (410)	29	0.78	0.54-1.13
Females	10	0.85	0.45-1.59
Males	19	0.75	0.48-1.17
Chronic IHD (412, 414)	31	1.11	0.78-1.58
Females	22	1.67	1.10-2.54
Males	9	0.60	0.31-1.16
Other heart disease (420-429)	45	1.51	1.12-2.03
Females	19	1.24	0.80-1.95
Males	26	1.79	1.21-2.63
Cerebrovascular disease (430-438)	58	1.14	0.88-1.48
Females	30	1.13	0.78-1.61
Males	28	1.16	0.80-1.69
Respiratory disease (460-519)	28	0.86	0.59-1.25
Females	8	0.63	0.31-1.25
Males	20	1.01	0.65-1.57
COPD (490-493)	20	1.45	0.93-2.26
Females	6	1.43	0.64-3.20
Males	14	1.47	0.89-2.49
Digestive disease (520-579)	26	0.90	0.61-1.33
Females	9	0.82	0.43-1.58
Males	17	0.95	0.59-1.54
Liver disease (570-579)	16	0.92	0.56-1.50
Females	4	0.73	0.27-1.96
Males	12	1.01	0.57-1.78
Urogenital disease (580-629)	7	0.89	0.42-1.87
Females	3	0.81	0.26-2.51
Males	4	0.97	0.36-2.61
Accidents (800-999)	27	0.94	0.64-1.38
Females	5	0.56	0.23-1.34
Males	22	1.12	0.73-1.70

ICD-9, International Classification of Diseases, Ninth Revision; IHD, ischemic heart diseases; COPD, chronic obstructive pulmonary diseases.

Supplementary Table 6 Results of Poisson regression analyses of **cancer incidence** among **residents in the "Polo" quarter"** in the Seveso cohort, Italy, 1976-2013: number of cancer cases (n), rate ratios (RR) adjusted/stratified for gender, age, and period, and 95% confidence intervals (CI) compared with the reference zone

Cancer site (ICD-9 code)	n	RR	95% CI
All cancers (140-208)	325	0.93	0.83-1.03
Females	129	0.86	0.72-1.02
Males	196	0.98	0.85-1.13
Digestive (150-159)	100	0.98	0.80-1.20
Females	35	0.87	0.62-1.22
Males	65	1.05	0.82-1.35
Oesophagus (150)	6	1.60	0.70-3.63
Females	0		
Males	6	1.94	0.85-4.44
Stomach (151)	23	0.96	0.64-1.46
Females	11	1.28	0.70-2.33
Males	12	0.78	0.44-1.38
Colon (153)	25	0.86	0.58-1.28
Females	10	0.75	0.40-1.41
Males	15	0.95	0.57-1.59
Rectum (154)	18	1.34	0.83-2.15
Females	4	0.79	0.29-2.14
Males	14	1.65	0.96-2.85
Liver (155)	13	0.87	0.50-1.51
Females	3	0.76	0.24-2.40
Males	10	0.91	0.48-1.71
Biliary tract (156)	6	1.30	0.57-2.94
Females	4	1.43	0.52-3.92
Males	2	1.10	0.27-4.56
Pancreas (157)	8	0.83	0.41-1.68
Females	3	0.68	0.22-2.13
Males	5	0.98	0.40-2.39
Other digestive (159)	0		
Females	0		
Males	0		
Respiratory (160-165)	59	1.02	0.79-1.33
Females	9	0.95	0.49-1.84
Males	50	1.04	0.79-1.39
Lung (162)	50	1.06	0.80-1.41
Females	9	1.13	0.58-2.20
Males	41	1.06	0.77-1.44
Soft tissue sarcoma (171)	2	1.21	0.29-5.04
Females	0		
Males	2	1.93	0.45-8.27
Sarcoma, any site	4	1.25	0.46-3.40
Females	0		
Males	4	2.38	0.85-6.27
Melanoma (172)	9	1.41	0.72-2.76
Females	3	0.93	0.29-2.94
Males	6	1.90	0.82-4.39
Breast (174) Females	32	0.64	0.45-0.92
Breast (175) Males	0		
Genito-urinary (179-189)	67	0.88	0.69-1.13
Females	23	0.94	0.62-1.42
Males	44	0.85	0.63-1.15
Uterus (179-182)	7	0.60	0.28-1.27
Cervix (179-182)	3	0.87	0.28-2.73
Endometrium (179-182)	3	0.49	0.15-1.52
Ovary (183)	9	1.73	0.88-3.38
Prostate (185)	20	0.77	0.49-1.21

Cancer site (ICD-9 code)	n	RR	95% CI
Testis (186)	3	1.17	0.37-3.74
Bladder (188)	19	1.05	0.66-1.66
Females	2	0.76	0.19-3.09
Males	17	1.09	0.67-1.78
Kidney (189)	8	0.75	0.37-1.53
Females	5	1.31	0.53-3.21
Males	3	0.45	0.14-1.41
Brain (191)	5	0.82	0.34-2.00
Females	4	1.54	0.56-4.24
Males	1	0.29	0.04-2.08
Thyroid (193)	3	0.63	0.20-1.97
Females	3	0.96	0.30-3.04
Males	0		
LH tissue (200-208)	32	1.23	0.86-1.75
Females	12	1.12	0.63-2.00
Males	20	1.30	0.83-2.05
Hodgkin's disease (201)	2	0.67	0.17-2.75
Females	2	1.52	0.37-6.30
Males	0		
NHL (200, 202)	14	1.24	0.72-2.12
Females	3	0.70	0.22-2.19
Males	11	1.57	0.85-2.90
Multiple myeloma (203)	8	2.16	1.05-4.54
Females	4	2.31	0.83-6.42
Males	4	2.07	0.74-5.76
Leukaemia (204-208)	8	1.00	0.49-2.02
Females	3	0.90	0.29-2.85
Males	5	1.07	0.43-2.61
Lymphatic leukaemia (204)	2	0.69	0.17-2.79
Females	0		
Males	2	1.11	0.27-4.57
Myeloid leukaemia (205)	5	1.34	0.55-3.30
Females	2	1.26	0.31-5.21
Males	3	1.39	0.44-4.47
Leukaemia, unspecified (208)	0		
Females	0		
Males	0		

ICD-9, International Classification of Diseases, Ninth Revision; LH, lymphatic and haematopoietic; NHL, non-Hodgkin's lymphoma.

SUPPLEMENTARY DISCUSSION

Biological plausibility

Different mechanisms for the diabetogenic action of TCDD have been hypothesized. An *in vitro* study found that the addition of TCDD to adipocyte cultures increased the secretion of tumor necrosis factor (TNF) and affected glucose transport.[1] A study was performed among US Air Force Vietnam (exposed to TCDD while spraying the herbicide Agent Orange) and other (unexposed) veterans. In adipose tissue samples it was found that the ratio of mRNA of glucose transporter 4 (GLUT4) and nuclear transcription factor kappa B (NFκB, a marker of inflammation), was associated with fasting glucose, even at low serum dioxin levels.[2] An *in vitro* study was performed by treating rat insulin-secreting beta cells with TCDD. Based on the results, the authors hypothesized that TCDD might exert adverse effects on beta cells by continuous insulin release followed by beta cell exhaustion.[3]

Animal and human studies showed that TCDD can adversely affect the cardiovascular system (including altered cardiac function and morphology and increases in serum lipids (see references in Bertazzi et al. 1991[4]). Other potential mechanisms mediated by the AhR have been suggested, including oxidative stress, growth factor modulation, and ionic current alteration.[5] Moreover, a potential contributor to the circulatory disease excess in the early post-accident period is the heavy psychosocial impact of the accident on people living in zone A, who were evacuated in the weeks after the accident and for months and years suffered from social rejection, fear of health effects, and anxiety about work.

Regarding respiratory effects, possible mechanisms include direct toxicity of TCDD on bronchiolar and alveolar tissue and interference with the immune system (see references in Consonni et al.[6]). Moreover, an *in vitro* study using human bronchial epithelial cells showed that TCDD induces MUC5AC (a gene coding mucin-5AC, a gel-forming glycoprotein with protective function) and that the protein is elevated in TCDD-treated cells; these effects were independent of the AhR pathway.[7] Among foundry workers exposed to TCDD and other dioxins it was found that dioxin serum levels were associated with decreased lung function and that part of the effect was mediated by urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG), a marker of oxidative stress.[8]

Regarding the increased LH cancer incidence, in a sample of healthy subjects from the Seveso cohort a positive association was found between TCDD serum levels and number of circulating lymphocytes carrying the t(14;18) translocations, an alteration found in some types of NHL.[9] Other putative mechanisms were studied *in vitro* study and involve impaired B lymphopoiesis induced by TCDD and mediated by activation of the AhR receptor.[10]

Comparison with published research

Results on the risk of diabetes in occupationally exposed subjects had been reviewed long time ago and found to be inconsistent.[11] In old studies increased prevalence of diabetes or glucose levels have been observed in military cohorts, while controversial results were found in occupational settings (see references in Consonni et al.[6]). A large US mortality study of more than 5000 chemical workers at 12 US plants that produced TCDD-contaminated products did not show a positive exposure-response trend for diabetes.[12] The IARC multicentre mortality study of workers exposed to phenoxy herbicides, chlorophenols, and dioxins found only suggestive diabetes mortality increase.[13] Past results regarding cardiovascular diseases have been more consistent. An increased IHD risk was showed in industrial cohorts (including the large US and IARC cohorts quoted above) and with positive exposure-response relationships.[4 12 13]

In a non-systematic search we found several studies and reviews on the effects of TCCD published after (or not included in) the last IARC evaluation.

In the USA, in a cohort study (1940-1980) of 773 pentachlorophenol (PCP) workers exposed to TCDD and other dioxins in a chemical plant in Michigan, elevated standardised mortality ratios (SMR) for NHL were found (SMR 2.4, 8 deaths), particularly in the highest category of cumulative exposure (SMR 4.5, 4 deaths).[14] A study in the same plant (1942-2003) performed among 1615 workers exposed to TCDD during trichlorophenol (TCP) or 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), both referred as TCP workers, showed elevated mortality soft tissue sarcomas (STS) (SMR 4.1, 4 deaths and positive exposure-response trends), leukaemia (SMR 1.9, 13 deaths) and slightly elevated mortality from NHL, diabetes, and IHD.[15] In an extension of follow-up (1940-2011) elevated mortality from STS (SMR 3.08, 4 deaths, with positive

exposure-response trend) and acute non-lymphatic leukaemia (SMR 2.88, 9 deaths) was found in TCP workers; in PCP workers elevated mortality was observed for NHL (SMR 1.92, 8 deaths) and IHD (SMR 1.20, 150 deaths).[16]

In the Netherlands, the "Dutch herbicide cohort study" included workers of two production facilities (factories A and B). In factory A workers had been exposed to TCDD during 2,4,5-T and TCP production and after an industrial accident in 1963.[17-20] Using data of the third and last follow-up (1955-2006) of 2056 male workers in this cohort (1020 in factory A, 1036 in factory B) modelled plasma TCDD levels were associated with mortality from NHL (hazard ratio (HR) 1.36 per ln-TCDD unit, 7 deaths) and IHD (HR 1.19, 93 deaths), with positive exposure-responses for both causes.[18]

In Germany, mortality in a cohort of workers of a chemical plant in Hamburg producing herbicides and insecticides including 2,4,5-T had been previously examined.[21 22] In the third and last follow-up update (1952-2007), 23 years after closure of the plant, among 1589 men increased mortality was found for all cancers (SMR 1.37, 226 deaths), oesophageal cancer (SMR 2.56, 11 deaths), rectum cancer (SMR 1.96, 11 deaths), and lung cancer (SMR 1.52, 68 deaths) and for circulatory diseases (SMR 1.16, 251 deaths), while among 398 women increased breast cancer mortality (SMR 1.86, 19 deaths) was observed.[23]

In New Zealand a cohort study (1969-1987) of 1025 phenoxy herbicide producers (in a plant in New Plymouth) and 703 sprayers reported elevated mortality from all-causes and multiple myeloma.[24] Mortality of herbicide producers was updated through 2004 and included workers of a nearby filed station where 2,4,5-T was occasionally used and tested: among 1599 workers no increasing trend of mortality with increasing TCDD exposure estimated using serum TCDD collected in a 22% sample of workers was observed, with the possible exception of all cancer mortality.[25] In a further follow-up update through 2011 slightly to moderately elevated mortality was found among ever exposed worker for all cancers (SMR 1.08, 84 deaths), NHL (SMR 1.57, 3 deaths), STS (SMR 2.38, 1 death), diabetes (SMR 1.27, 8 deaths), and IHD (SMR 1.21, 81 deaths); no clear exposure-response associations were observed.[26]

The Korean Veterans Health Study examined mortality and cancer incidence in a cohort of about 180 000 Vietnam veterans exposed to Agent Orange. In those with high exposure moderately elevated mortality (1992-2005) was found for all cancers (HR 1.13, 3479 deaths), lung cancer (HR 1.15, 673 deaths), circulatory (HR 1.04, 1716 deaths), and respiratory diseases (HR 1.24, 266 deaths).[27] Cancer incidence (1992-2003) was found to be elevated in the more exposed veterans for all cancers (HR 1.08, 4583 cases), lung cancer (HR 1.12, 649 cases), and NHL (HR 1.09, 96 deaths, with wide CI).[28] In the prevalence study (about 112 000 veterans, 2000-2005) higher prevalence (+4%) of diabetes was found in those with estimated higher TCDD exposure.[29]

In a sample (981 women) of the Seveso population the SWHS reported positive associations between TCDD blood levels and incidence of all cancer, breast cancer, and, although imprecise, cardiovascular diseases, but did not find a positive association between serum TCDD and diabetes (see references in Eskenazi[30]).

In a systematic review no consistent or convincing evidence of a causal relationship between exposure to Agent Orange or TCDD and prostate cancer was found.[31] A meta-analysis of studies of workers, military personnel, and general population samples found a dose-response relationship between serum TCDD and diabetes only at low TCDD levels and no association at high levels.[32] The association of TCCD exposure with haematological cancer risk has been evaluated in two reviews that reached opposite conclusions. The first examined lymphoid cancers, including NHL, HD, and multiple myeloma and concluded that a causal effect of TCDD has not been established.[33] The second, which examined also experimental studies, concluded for a positive association.[34] A meta-analysis of many neoplastic diseases found that TCDD was associated with all cancer incidence and mortality and with NHL mortality.[35]

Taken together, the results of new studies and reviews are in line with the last IARC evaluation. Positive associations of TCDD with all cancer, NHL, and STS emerged, although sometimes based on small number of cases. The new findings are also suggestive of increased mortality from cardiovascular diseases, mainly IHD. In comparing our results with those of the above cohort studies we must consider several differences. The occupational studies concerned cohort of workers chronically exposed to various chemicals contaminated with TCDD and other dioxins, while the Seveso study is on a residential cohort with short (days or weeks) and exclusive exposure to TCDD.[36] Although occupational studies are affected by the healthy worker effect (unless an internal reference was used), their strength is that serum TCDD levels could

be exploited to construct quantitative indices of exposure. Finally, the occupational cohorts covered longer follow-up periods (form 42 up to 72 years, compared with 37 years of our study).

Notwithstanding the dissimilarities between our study and the occupational studies, and although in the Seveso cohort patterns of mortality and cancer incidence showed differences across gender and zones and over time, our results (increased mortality from circulatory diseases, increased incidence of some LH cancers and STS) are consistent with old and new literature findings, the major difference being that we did not find increased all cancer incidence. Although diabetes emerged in our study in females and in some other studies, the overall evidence of an association with TCDD appears weak, while that on TCDD and circulatory diseases seems more consistent.

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