CANCER MORTALITY IN WORKERS EXPOSED TO 2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN

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Abstract Background In both animal and epidemiologic studies, exposure to dioxin (2,3,7,8-tetrachlorodibenzo-*p*-dioxin, or TCDD) has been associated with an increased risk of cancer

Methods We conducted a retrospective cohort study of mortality among the 5172 workers at 12 plants in the United States that produced chemicals contaminated with TCDD. Occupational exposure was documented by reviewing job descriptions and by measuring TCDD in serum from a sample of 253 workers. Causes of death were taken from death certificates.

Results Mortality from several cancers previously associated with TCDD (stomach, liver, and nasal cancers, hodgkin's disease, and non-Hodgkin's lymphoma) was not significantly elevated in this cohort. Mortality from soft-tissue sarcoma was increased, but not significantly (4 deaths; standardized mortality ratio [SMR], 338; 95 percent confidence interval, 92 to 865). In the subcohort of 1520 workers with ≥1 year of exposure and ≥20 years of latency, however, mortality was significantly increased for soft-tissue sarcoma (3 deaths; SMR, 922; 95 percent confidence interval, 190 to 2695) and for cancers of the respiratory system (SMR, 142; 95 percent confidence interval, 103 to 192). Mortality from all cancers combined was slightly but significantly elevated in the overall cohort (SMR, 115; 95 percent confidence interval, 102 to 130) and was higher in the subcohort with ≥1 year of exposure and ≥20 years of latency (SMR, 146; 95 percent confidence interval, 121 to 176).

Conclusions. This study of mortality among workers with occupational exposure to TCDD does not confirm the high relative risks reported for many cancers in previous studies. Conclusions about an increase in the risk of soft-tissue sarcoma are limited by small numbers and misclassification on death certificates. Excess mortality from all cancers combined, cancers of the respiratory tract, and soft-tissue sarcoma may result from exposure to TCDD, although we cannot exclude the possible contribution of factors such as smoking and occupational exposure to other chemicals. (N Engl J Med 1991; 324:212-8.)

SEVERAL epidemiologic and toxicologic studies have suggested an association between 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), or the chemicals it contaminates, and soft-tissue sarcoma,[1-4] Hodgkin's disease,[5] non-Hodgkin's lymphoma,[1,3,6] stomach cancer,[1,6] nasal cancer,[1] and cancer of the liver.[1,3] In other studies of these cancers, no significant associations with TCDD exposure were found.[7-9] The carcinogenicity of TCDD has been demonstrated in studies of rats, mice, and hamsters; histiocytic lymphomas, fibrosarcomas, and tumors of liver, skin, lung, thyroid, tongue, hard palate, and nasal turbinates have been found.[10-13] TCDD acts as a promoter[14,15] and may also initiate carcinogenesis.[15,16] To evaluate the effect of occupational exposure to TCDD, particularly with respect to the cancers listed above, we conducted a retrospective cohort study of mortality among U.S. chemical workers assigned to the production of substances contaminated with TCDD.

METHODS

Identification of Companies

In 1978 the National Institute for Occupational Safety and Health began an effort that would eventually identify the exposed workers at all U.S. chemical companies that had made TCDD-contaminated products between 1942 and 1984. TCDD was generated as a contaminant in the production of 2,4,5-trichlorophenol and was carried into subsequent production processes.[17] One derivative, 2,4,5-trichlorophenoxyacetic acid, was widely used in the United States to kill brush and was a component of 4:4 (1:1 mixture of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid) and other herbicides such as Agent Orange. Other derivatives included the herbicides 2-(2,4,5-trichlorophenoxy propionic acid (Silvex) and 2-(2,4,5-trichlorophenoxy) ethyl 2,2-dichloropropionate (Erbon), the insecticide *O,O*-dimethyl *O*-(2,4,5-trichlorophenyl) phosphorothioate (Ronnel), and the bactericide 2,2'-methylene-bis(3,4,6-trichlorophenol) (hexachlorophene).

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Identification of Exposed Workers

Workers from 12 companies were included in the study cohort if they were employed for a total duration of at least 1 month in specified production or maintenance jobs in a process involving TCDD contamination (n = 5000), or if they had been identified in a previously published study on the basis of exposure to TCDD (n = 172).[3] Personnel records for 202 workers did not reveal the duration of their assignment to processes involving TCDD contamination; they were therefore included in the analysis of overall mortality but excluded from analyses according to duration of exposure. Sixty-seven women are not included in this report; there were 10 deaths among them, including a single death from cancer (lung cancer).

At each plant, we made a thorough review of operating conditions, work histories, and records of TCDD levels in industrial-hygiene samples, intermediate reactants, products, and wastes. This review provided clear evidence of potential daily exposure to TCDD. The production of TCDD-contaminated substances at the various plants involved similar raw materials, processes, and job duties. However, there were differences between jobs and between plants in the extent of TCDD exposures. Occupational exposure to substances contaminated with TCDD was confirmed by measuring serum TCDD levels, as adjusted for lipids, in 253 surviving members of the study cohort from two plants who were also participants in a related cross-sectional medical study.[18]

Life-Table Analysis

Vital status was determined as of December 31, 1987, from records of the Social Security Administration or Internal Revenue Service, or from the National Death Index. All death certificates

were independently classified by two nosologists according to the rules of the revision of the *International Classification of Diseases* (ICD) in effect at the date of death.[7]

Life-table analysis was used to evaluate mortality in the cohort.[8] At each plant, the number of person-years at risk was calculated as the interval between the first systematically documented assignment to a process involving TCDD contamination and the date of death or December 31, 1987, whichever occurred first. Those whose vital status was unknown were assumed to be alive at the end of the study. Standardized mortality ratios (SMRs) were computed by dividing the observed number of deaths by the expected number and multiplying by 100, after stratification to adjust for [illegible] and calendar period. Two-sided 95 percent confidence intervals were computed for each cause-specific SMR [illegible] for approximation for [illegible] deaths or more and Fisher's exact method for fewer than eight deaths.[9] The U.S. population was used as the reference group, because the 12 plants were located in 11 states throughout the country.

Analyses According to Duration of Exposure and Employment

[illegible] duration of exposure as a surrogate for cumulative exposure to TCDD on the basis of the high correlation of the logarithm of serum TCDD levels with the logarithm of the number of years assigned to processes involving TCDD contamination in our sample of 253 workers. Pearson's [illegible] (adjusted $r = 0.72$; [illegible]) [illegible] similar in the 12 plants.

Because of the concentration of person-years in the short-duration [illegible] into categories of <1, 1 to <5, 5 to <15, and ≥15 years. Table 1. Mortality was also examined according to time since first exposure (latency), in periods of 0 to <10, 10 to <20, and ≥20 years since first exposure. To examine mortality in a subgroup with substantial exposure and adequate time for cancer to develop, we identified a group of workers who had 1 year or more of exposure to processes involving TCDD contamination and at least 20 years of latency. One year was chosen as a cutoff point for this high-exposure subcohort because in the sample of workers whose serum TCDD levels were measured, 100 percent of those exposed for more than one year had serum TCDD [illegible] than the mean level in the [illegible] of such workers. [illegible] risk [illegible] [illegible] [illegible] [illegible] worker's exposures was impossible. A separate measure called "duration of employment," defined as the total time that each worker was employed at a study plant, was therefore used. Because [illegible] duration of employment at the plants, analyses according to duration of employment were stratified into periods of <5, 5 to <10, 10 to <15, 15 to <20, 20 to <25, 25 to <30, and ≥30 years (Table 1). For these analyses, latency was defined as time since first [illegible].

When the SMR [illegible] was used, [illegible] and when the observed number [illegible] [illegible] [illegible] [illegible]

(393 deaths; SMR, 90; 95 percent confidence interval, 87 to 106). There were significant reductions in the mortality rates for diseases of the circulatory system (467 deaths; SMR, 77; 95 percent confidence interval, 60 to 98), primarily because of fewer deaths from stroke, and for diseases of the digestive system (48 deaths; SMR, 70; 95 percent confidence interval, 49 to 96), primarily because of fewer deaths from cirrhosis. There were also significantly fewer deaths from alcoholism and personality disorders (2 deaths; SMR, 23; 95 percent confidence interval, 3 to 87). The low mortality from circulatory disease may be a reflection of the "healthy worker" effect — cohorts of workers die at lower rates than the general population, particularly of causes other than cancer.[11] The reduced number of deaths from cirrhosis and alcoholism implies that this cohort consumed less alcohol than the general population. Reduction may also have occurred simply by chance, since numerous comparisons were made between the cohort and the U.S. population. Fatal injuries were significantly more frequent in the cohort (106 deaths; SMR, 128; 95 percent confidence interval, 104 to 154; data not shown). Deaths appear to be associated particularly with exposure to TCDD. Mortality from all cancers combined (265 deaths; SMR, 115; 95 percent confidence interval, 102 to 130) was significantly elevated in the cohort.

Cancers of a Priori Interest

The term "soft-tissue sarcoma" describes the group of rare malignant neoplasms arising from supporting tissue other than bone.[32] We restricted our analysis of mortality due to soft-tissue sarcoma to cases of soft-tissue sarcoma listed as the *underlying* cause of death

Table 2 Cancer Mortality in the Entire Cohort and in Workers with More Than 20 Years of Latency

SITE OF CANCER	ICD CODE*	ENTIRE COHORT (N = 5172)†			SUBCOHORT WITH >20 YR OF LATENCY (N = 3066)					
					>1 YR OF EXPOSURE (N = 3161)‡			>3 YR OF EXPOSURE (N = 1520)§		
		Deaths observed	Deaths expected	SMR‖	Deaths observed	Deaths expected	SMR‖	Deaths observed	Deaths expected	SMR‖
All cancers	140–208	265	229.9	115 (102–130)**	48	46.8	102 (76–136)	114	78.0	146 (121–176)**
Buccal and pharynx	140–149	5	7.0	70 (23–166)	2	1.4	145 (18–524)	2	2.2	90 (11–325)
Pharynx	146–149	3	3.4	88 (18–259)	2	0.7	298 (36–1080)	0	1.2	0 (—)
Other parts	142–145	2	1.9	105 (13–379)	0	0.4	0 (—)	2	0.6	329 (40–1190)
Digestive organs	150–159	67	59.7	112 (87–143)	13	11.8	111 (59–189)	28	20.1	140 (93–202)
Esophagus	150	9	5.9	152 (70–290)	2	1.2	165 (20–602)	4	2.0	200 (55–513)
Stomach	151	10	9.7	103 (50–190)	3	1.7	178 (37–521)	4	2.9	138 (38–353)
Small intestine and colon	152–153	25	20.4	122 (79–181)	5	4.3	117 (38–274)	13	7.3	178 (95–304)
Rectum	154	5	4.6	99 (32–230)	1	1.0	100 (3–557)	2	1.7	115 (14–415)
Liver and biliary	155–156	6	5.2	116 (42–252)	1	1.0	100 (3–557)	1	1.7	59 (1–327)
Pancreas	157	10	11.9	84 (40–155)	1	2.4	41 (1–232)	4	4.0	100 (27–253)
Peritoneum and unspecified	158, 159	2	1.1	184 (22–666)	0	0.2	0 (—)	0	0.4	0 (—)
Respiratory system	160–165	46	34.5	113 (92–139)	19	18.4	103 (62–161)	43	30.2	142 (103–192)
Larynx	161	2	3.3	211 (84–434)	2	0.7	297 (36–1074)	3	1.1	268 (55–783)
Trachea, bronchus, and lung	162	39	30.1	111 (89–137)	17	17.5	96 (56–155)	40	28.8	139 (99–189)
Male genital organs	185–187	17	15.3	111 (65–177)	2	3.2	63 (8–229)	9	6.1	149 (68–283)
Prostate	185	17	13.9	122 (71–196)	2	3.0	67 (8–239)	9	5.9	152 (70–290)
Urinary organs	188–189	7	7.4	95 (38–196)	3	2.4	125 (26–365)	7	4.0	175 (70–361)
Kidney	189.0–189.2	3	3.7	80 (16–234)	1	1.2	85 (2–473)	2	1.9	106 (13–384)
Bladder and other	188, 189.3–189.9	4	3.7	107 (29–275)	2	1.2	169 (20–610)	5	2.2	227 (74–530)
Lymphatic and hematopoietic tissue	200–208	24	22.1	109 (70–162)	4	3.9	102 (28–260)	8	6.4	125 (54–247)
Hodgkin's disease	201	3	2.5	119 (25–349)	0	0.2	0 (—)	1	0.4	276 (7–1534)
Non-Hodgkin's lymphoma††	200, 202	10	7.3	137 (66–254)	2	1.5	135 (16–488)	2	2.1	93 (11–335)
Lymphosarcoma and reticulosarcoma††	200	5	3.5	142 (46–332)	0	0.6	0 (—)	1	0.9	107 (3–594)
Other lymphatic††	202	5	3.7	135 (43–315)	2	0.9	215 (26–776)	1	1.4	71 (2–395)
Multiple myeloma††	203	5	3.0	164 (53–385)	0	0.6	0 (—)	3	1.1	262 (54–766)
Leukemia and aleukemia	204–208	6	8.9	67 (24–146)	2	1.6	126 (15–455)	2	2.6	77 (9–277)
Other sites	190–199	20	15.1	132 (81–204)	5	5.6	89 (29–207)	18	9.0	201 (118–316)**
Skin	172, 173	4	4.9	82 (22–211)	0	0.9	0 (—)	2	1.3	155 (19–559)
Brain and nervous system	191–192	5	3.3	150 (49–350)	0	0.7	0 (—)	2	1.9	106 (13–384)
Bone	170	2	0.9	225 (27–814)	0	0.2	0 (—)	1	0.2	521 (13–2903)
Connective tissue and soft tissue	171	4	1.2	336 (92–865)	0	0.2	0 (—)	3	0.3	922 (190–2695)**
Other and unspecified	194–199	24	14.8	162 (104–241)**	5	3.1	159 (52–372)	10	5.1	196 (94–361)

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

†Mean number of years exposed, 2.7; mean number of years employed, 12.6.

‡Excludes 292 workers for whom the duration of assessment to processes involving TCDD contamination was not available from work records.

§Mean number of years exposed, 0.3; mean number of years employed, 10.7; 32,299 person-years at risk.

‖Mean number of years exposed, 6.5; mean number of years employed, 19.2; 15,536 person-years at risk.

SMR equals deaths observed divided by deaths expected and multiplied by 100. Slight differences are due to rounding. Values in parentheses are 95 percent confidence intervals.

**$P < 0.05$.

††Person-years at risk and observed deaths are computed from 1964; no deaths occurred before that year.

on death certificates and assigned to the ICD category "malignant neoplasms of connective and other soft tissue." In the cohort, mortality from soft-tissue sarcoma was nonsignificantly higher than in the reference population (four deaths; SMR, 338; 95 percent confidence interval, 92 to 865) (Table 2). The deaths occurred at 2 of the 12 plants, with a significant increase at 1 plant (two deaths; SMR, 1512; 95 percent confidence interval, 183 to 5462). A review of tissue specimens from the four men whose deaths were attributed to soft-tissue sarcoma showed that only two were in fact soft-tissue sarcomas (Cases 1 and 4, Table 3).[13] Mortality from soft-tissue sarcomas was increased significantly in the subcohort of 1520 workers with 1 year or more of exposure and at least 20 years of latency (the high-exposure subcohort) (three deaths; SMR, 922; 95 percent confidence interval, 190 to 2695). Two other deaths in the cohort (Cases 5 and 6) were attributed to soft-tissue sarcoma according to hospital records, and one of them (Case 5) was confirmed by review of a tissue specimen. These two deaths did not contribute to mortality due to soft-tissue sarcoma in our life-table analysis, because the deaths were assigned other ICD codes. We are aware of a seventh death from soft-tissue sarcoma, which occurred in a group of 139 workers with chloracne who were excluded from the cohort because they did not meet the entry criteria.

In the cohort, the SMRs for the other cancers of a priori interest were nonsignificantly increased (Table 2). There were no deaths from nasal cancer, although approximately one was expected. In the high-exposure subcohort, the SMRs were nonsignificantly higher for Hodgkin's disease and stomach cancer and lower for non-Hodgkin's lymphoma and cancer of the liver, biliary passages, and gallbladder (Table 2).

A Posteriori Findings

A small but significant increase in mortality due to all cancers combined was observed in the entire cohort (SMR, 115; 95 percent confidence interval, 102 to 130). In the high-exposure subcohort the SMR was 146 (95 percent confidence interval, 121 to 176) (Table 2). At 9 of the 12 plants, mortality from all cancers combined was increased; at one of these plants the increase was statistically significant. Mortality was significantly higher than expected in the category of cancers of unspecified sites, which included those of rare sites not included in a category of the life-table analysis and those for which no primary site was listed on the death certificate. Hospital records, which were obtained for 96 percent of these cancers, revealed no particular clustering according to site.

The cohort had a nonsignificant increase in mortality from cancers of the trachea, bronchus, and lung (ICD code 162; SMR, 111; 95 percent confidence interval, 89 to 137). Mortality from cancers of the respiratory system (ICD codes 160 to 165) was significantly higher than expected in the high-exposure subcohort (SMR, 142; 95 percent confidence interval, 103 to 192) (Table 2). To estimate the effect of smoking on the increase in lung cancer, the expected number of lung cancers was adjusted according to the smoking prevalence found in lifetime histories obtained in 1987 by interviewing 223 workers from two plants.[25] This adjustment increased the expected number of lung cancers in the overall cohort by 5 percent and in the high-exposure subcohort by 1 percent, which reduced the SMR in the full cohort to 105 (95 percent confidence interval, 85 to 130) and in the high-exposure subcohort to 137 (95 percent confidence interval, 98 to 187).

Analyses According to Duration of Exposure and Employment

The study cohort worked a mean of 2.7 years in processes involving TCDD contamination and 12.6 years at the plants. The high-exposure subcohort worked a mean of 6.8 years in processes involving TCDD contamination and a mean of 19.2 years in total employment at the plants.

The numbers of deaths due to the rare cancers of

Table 3. Deaths from Soft-Tissue Sarcoma among Workers in the Cohort.*

Case No.	Years Employed	Type of Exposure	Year First Exposed	Years Exposed	Year of Death	Latency (yr)†	Cause of Death: Death [illegible]	Cause of Death: [illegible]	Cause of Death: [illegible]
1	1946–1978	TCP and 2,4,5-T	1950	8.8	1978	28	MFH	MFH	MFH
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible] differentiated‡
3	1950–1975	TCP	1963	1.2	1975	12	Fibrosarcoma	Fibrosarcoma	Renal carcinoma§
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	MFH	MFH	MFH
5¶	[illegible]	TCP or 2,4,5-T	intermittent	Unknown	[illegible]	Unknown	[illegible]	[illegible] nic sarcoma	[illegible]
6¶	[illegible]	TCP	[illegible]	[illegible]	[illegible]	[illegible]	[illegible] sarcoma§	[illegible]	Not available

*Cases 1 through 5 have been previously described. †For other previously described cases, records of exposure to TCDD were not available, and the cases were not included in this cohort study. Some information differs slightly from that reported earlier, since additional records were reviewed. Few details about exposure were available for Cases 5 and 6. TCP denotes 2,4,5-trichlorophenol, 4,5-T, 2,4,5-trichlorophenoxyacetic acid, and MFH, malignant fibrous histiocytoma.

†Time from first exposure to death.

‡Conducted at the Armed Forces Institute of Pathology.

§Not a soft-tissue sarcoma.

¶Death was not attributed to soft-tissue sarcoma in the life-table analysis.

Table 4. Mortality from All Cancers and from Cancers of the Trachea, Bronchus, and Lung, According to Latency Period and Duration of Exposure to Processes Involving TCDD Contamination.*

[illegible]	<1		1 to <5		5 to <10		≥10		[illegible]	
	deaths observed	SMR	deaths observed	SMR	deaths observed	SMR	deaths observed	SMR	deaths observed	SMR
All cancers										
<10 Yr	10	68	8	71	3	71	0	0	21	70
10 to <20 Yr	28	109	16	87	18	122	7	340†	69	113
≥20 Yr	48	102	59	155†	37	138	18	114	162	129†
Total	86	98	83	127†	58	126	25	141	252	116†
SRR		100		127		123		129		0.3
Trachea, bronchus, and lung										
<10 Yr	3	77	3	95	1	79	0	0	7	84
10 to <20 Yr	6	69	5	79	9	180	1	137	21	101
≥20 Yr	17	96	17	126	14	146	9	156	57	123
Total	26	86	25	109	24	151	10	154	85	112
SRR		100		100		166		136		0.2

*Excludes 202 workers for whom the duration of assignment to processes involving TCDD contamination was not available from work records. The number of observed deaths and the SMRs therefore differ slightly from those in Table 2. SRR denotes standardized rate ratio. [illegible]

†P<0.05

a priori interest were too small to permit meaningful analyses according to duration. For all cancers combined and for cancers of the trachea, bronchus, and lung, Table 4 shows the distribution of mortality with increasing duration of exposure to products contaminated with TCDD. The standardized rate ratios were increased in the strata of longer duration for both these categories, but significant linear trends were not found. Mortality increased with increasing latency for both these categories of cancer. Table 5 shows the distribution of mortality for the same categories with increasing duration of employment. Significant linear trends were not observed for either category with increasing length of employment, although standardized rate ratios were higher than expected in several strata of employment ≥20 years. Mortality increased with increasing latency for both categories of cancer.

Serum Levels of TCDD

The mean serum TCDD level, as adjusted for lipids, in the sample of 253 workers from two plants was 233 pg per gram of lipid (range, 2 to 3400) (Fig. 1). A mean level of 7 pg per gram was found in the comparison group of 79 unexposed persons, all of whose levels were under 20, a range found in other unexposed populations.[14] The mean for 119 workers with one year or more of exposure was 418 pg per gram. All the workers had received their last occupational exposures 15 to 37 years earlier.

Discussion

TCDD, widely known as dioxin, has acquired the reputation of a potent carcinogen. Our study, although limited in its ability to detect increased numbers of rare cancers, found little increase in mortality from the cancers associated with TCDD in previous studies in humans. The exception was an increase in soft-tissue sarcoma. The difficulties of evaluating soft-tissue sarcomas in a cohort study of mortality have been described.[15] These include variability in pathological diagnosis and misclassification on death certificates. Consequently, the interpretation of the increased mortality from soft-tissue sarcoma in our study is limited by the small number of cases and the fact that the cause of death was sometimes misclassified on the death certificates of the workers (Table 3) and in the U.S. comparison population.[16]

Several case–control studies have found significant fourfold increases in non-Hodgkin's lymphoma in persons reporting exposure to phenoxy herbicides or chlorophenols, some of which contained TCDD.[17] The magnitude of the increase in mortality in the cohort described here (SMR, 137; 95 percent confidence interval, 66 to 254) suggests a smaller increase in this risk, or no increase at all. Mortality was not significantly higher than expected for other cancers of a priori interest — liver and stomach cancers and Hodgkin's disease. No deaths from nasal cancer were observed. The inconsistency between the results reported here and those of earlier epidemiologic studies is accentuated by the longer and probably greater exposure of this cohort to phenoxy herbicides and chlorophenols contaminated with TCDD.

Mortality from cancers of the trachea, bronchus, and lung was nonsignificantly higher in the cohort. Among the workers with 20 years or more of latency, mortality from respiratory cancer was significantly increased in the high-exposure subcohort, which had 1 year or more of exposure (SMR, 142; 95 percent confidence interval, 103 to 192) but not in the subcohort with less than 1 year of exposure (SMR, 103; 95 percent confidence interval, 62 to 161). Table 2). SMRs for lung cancer are known to be somewhat higher in blue-collar groups than in the general U.S. population because of more cigarette smoking in the blue-collar groups.[18] However, the increased number of lung cancers in the high-exposure subcohort was probably not due to confounding by smoking, for several reasons. First, other diseases related to smoking were not more common than expected in this subco-

Table 5 **Mortality** from All **Cancers** and from Cancers of the Trachea, Bronchus, and **Lung**, According to **Latency** Period and Duration of **Employment** at the Study Plants*

Cause, Latency Period	Duration of Employment (yr)														Test for Trend
	<1		1 to <5		5 to <10		10 to <15		15 to <20		20 to <25		≥25		
	deaths observed	SMR	deaths observed	SMR	deaths observed	SMR	deaths observed	SMR	deaths observed	SMR	deaths observed	SMR	deaths observed	SMR	
All cancers															
<10 Yr	10	85	7	78	0	0	0	0	0	0	0	0	0	0	
10 to <20 Yr	21	114	5	126	12	103	8	80	0	0	0	0	0	0	
≥20 Yr	40	138	15	140	6	70	15	98	34	134	31	116	54	135†	195
Total	71	120	27	134	18	91	23	87	34	132	31	116	54	135†	252
SRR		100		99		91		76		128		84		115	
Trachea, bronchus, and lung															
<10 Yr	3	103	1	74	0	0	0	0	0	0	0	0	0	0	
10 to <20 Yr	5	82	0	0	5	139	4	122	0	0	0	0	0	0	
≥20 Yr	11	102	2	51	2	65	3	55	12	133	18	180†	19	126	67
Total	19	96	3	46	7	105	7	81	12	133	18	180†	19	126	85
SRR		100		65		91		89		171		147		98	

All cancers															
<10 Yr	10	85	7	78	0	0	0	0	0	0	0	0	0	0	27	82	
10 to <20 Yr	21	114	5	126	12	103	8	80	0	0	0	0	0	0	46	105	
≥20 Yr	40	138	15	140	6	70	15	98	34	134	31	116	54	135†	195	125†	
Total	71	120	27	134	18	91	23	87	34	132	31	116	54	135†	252	116	
SRR		100		99		91		76		128		84		115			0.9
Trachea, bronchus, and lung																	
<10 Yr	3	103	1	74	0	0	0	0	0	0	0	0	0	0	4	94	
10 to <20 Yr	5	82	0	0	5	139	4	122	0	0	0	0	0	0	14	98	
≥20 Yr	11	102	2	51	2	65	3	55	12	133	18	180†	19	126	67	117	
Total	19	96	3	46	7	105	7	81	12	133	18	180†	19	126	85	112	
SRR		100		65		91		89		171		147		98			0.6

*[illegible] from [illegible] the duration of employment in [illegible] involving TCDD-contaminated [illegible] and not available from [illegible] records. SRR denotes standardized rate ratio.

†P < 0.05 ‡P < 0.01

[illegible] mortality from nonmalignant respiratory disease (ICD codes 470 to 478 and 490 to 519), which is often associated with smoking, was lower than expected (15 deaths; SMR, 96; 95 percent confidence interval, 54 to 158). Second, in the exposed population with 20 years of latency, whose members presumably shared similar smoking habits, the increase was confined to the high-exposure subcohort. Third, on the basis of empirical evidence from other studies, Siemiatycki et al.[36] have shown that between a blue-collar population and the general U.S. population, confounding by smoking is unlikely to account for an excess risk of more than 10 to 20 percent. Finally, a limited adjustment in the risk of lung cancer,[37,38] based on the smoking prevalence of surviving workers at only two plants, did not substantially change our results.[25] Although confounding by smoking is unlikely to explain the higher rate of respiratory cancer in the high-exposure subcohort, it remains possible that the increase was due to confounding by [illegible] exposures other than TCDD. For example, asbestos may have contributed to mortality from lung cancer in the cohort, since two deaths were due to mesotheliomas.

An unexpected finding was the small but significant increase in mortality from all cancers combined. The observed increase is consistent with a carcinogenic effect of TCDD. For all cancers combined, mortality was significantly higher than expected in the entire cohort, more pronounced in the high-exposure subcohort, and increased at 9 of 12 plants. With mortality from cancers of the trachea, bronchus, and lung excluded, mortality from all remaining cancers combined was still higher than expected in the entire cohort (SMR, 117; 95 percent confidence interval, 100 to 136) and in the high-exposure subcohort (SMR, 120; 95 percent confidence interval, 66 to 199). Consequently, the increased risk for all cancers combined is not explained by smoking or by increased mortality due to cancer of the trachea, bronchus, and lung. The generation of tumors in a number of organs in animals exposed to TCDD[1–4] and the demonstration that TCDD promoted tumors in two organs[5,6] make it biologically plausible that TCDD may produce tumors in more than one organ in humans. Moreover, a significantly increased SMR for all cancers combined is unusual in occupational studies of chemical workers. Results similar to ours were observed in a study of German workers exposed to TCDD after a 2,4,5-trichlorophenol reactor accident in 1953. A subgroup of workers with chloracne (used as a surrogate for exposure) and at least 20 years of latency had an SMR of 201 (90 percent confidence interval, 122 to 315) for all cancers combined, based on 14 deaths.[39] This is the only other industrial cohort with both substantial exposure to TCDD and a long period of latency during which mortality was examined. Workers from U.S. production cohorts described in previous studies were included in the current study if they met our entry criteria.[7–9]

Two observations argue against a carcinogenic effect of TCDD. First, there was not a significant linear trend of increasing mortality with increasing duration of exposure to products contaminated with TCDD (Table 4). However, our use of duration of exposure may have misclassified the cumulative dose of some workers. In addition, a dose–response relation is generally viewed as strong evidence for an association when it is present, but as fairly weak evidence against an association when it is absent.[41] Second, our study did not directly assess the effect of exposure to TCDD alone. The workers were exposed concurrently to the chlorophenols and phenoxy herbicides that were contaminated with TCDD. In addition, they may have been exposed to numerous other chemicals while employed at the plants.

Because the [illegible] ly higher than that of most nonoccupational populations, the estimates of effect in this study may provide an upper level of risk to be anticipated in humans. For several types of cancer previously associated with

TCDD, we found no increases above expected levels. Soft-tissue sarcoma was an exception; a ninefold increase was found among workers who were exposed for 1 year or more and who had at least 20 years of latency. Interpretation of the increased SMR is limited, however, by the small number of cases and because this cause of death was sometimes misclassified on the death certificates of the workers and in the national comparison population. Continued surveillance of the cohort may provide a firmer estimate of risk.

Mortality from all cancers combined was 15 percent higher than expected in the overall cohort. The subcohort with 1 year or more of exposure and 20 years or more of latency had a 46 percent increase in all cancers combined and a 42 percent increase in cancers of the respiratory tract. Although the study could not completely exclude the possible contribution of other occupational carcinogens or smoking, the increased mortality, especially in the subcohort with one year or more of exposure, is consistent with the status of TCDD as a carcinogen.

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