

# Exposure to Dioxin and Nonneoplastic Mortality in the Expanded IARC International Cohort Study of Phenoxy Herbicide and Chlorophenol Production Workers and Sprayers

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The authors studied noncancer mortality among phenoxyacid herbicide and chlorophenol production workers and sprayers included in an international study comprising 36 cohorts from 12 countries followed from 1939 to 1992. Exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin or higher chlorinated dioxins (TCDD/HCD) was discerned from job records and company questionnaires with validation by biologic and environmental measures. Standard mortality ratio analyses suggested a moderate healthy worker effect for all circulatory diseases, especially ischemic heart disease, among both those exposed and those not exposed to TCDD/HCD. In Poisson regression analyses, exposure to TCDD/HCD was not associated with increased mortality from cerebrovascular disease. However, an increased risk for circulatory disease, especially ischemic heart disease (rate ratio [RR] 1.67, 95% confidence interval [CI] 1.23–2.26) and possibly diabetes (RR 2.25, 95% CI 0.53–9.50), was present among TCDD/HCD-exposed workers. Risks tended to be higher 10 to 19 years after first exposure and for those exposed for a duration of 10 to 19 years. Mortality from suicide was comparable to that for the general population for all workers exposed to herbicides or chlorophenols and was associated with short latency and duration of exposure. More refined investigations of the ischemic heart disease and TCDD/HCD exposure association are warranted. — *Environ Health Perspect* 106(Suppl 2):645–653 (1998). <http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-2/645-653vena/abstract.html>

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## Introduction

Workers exposed to phenoxyacid herbicides and chlorophenols known to be contaminated with dioxins, including the 2,3,7,8-tetrachlorodibenzo-*p*-dioxin

(TCDD) congener, consistently have been shown to be at increased risk for all cancers combined and, although less consistently, for specific neoplasms such as lung cancer,

soft-tissue sarcoma, and non-Hodgkin's lymphoma (1). TCDD exposure also has been associated with numerous acute and chronic adverse health effects among humans (1,2). There is a complex network of responses to dioxin exposure in animals and humans accompanied by modulation of numerous biochemical responses in target tissues and organs (1). Biochemical and toxic effects are mediated by the intracellular aryl hydrocarbon receptor (3,4). There is evidence that TCDD potently induces transcription of a distinct network of target genes encoding xenobiotic-metabolizing genes (5,6), affects expression of growth modulating genes (7), interacts with thyroid hormones (8), and modulates protein phosphorylation (9), glucose metabolism and transport (10,11), and estrogen responses (12).

The most informative epidemiologic studies of chronic effects of TCDD exposure were conducted among U.S. Air Force personnel exposed to TCDD-contaminated pesticides (13–16), pesticide users and chemical production workers, including groups of workers involved in industrial accidents (17–26), and populations of contaminated communities in Missouri in the United States and Seveso, Italy (27–30). Possible long-term nonneoplastic consequences of TCDD exposure appear to be altered male reproductive hormone levels, lipid metabolism, and thyroid function, chronic elevated levels of the hepatic enzyme  $\gamma$ -glutamyl transferase, persistent chloracne, reproductive toxicity, increased risk of diabetes, and immunologic, renal, respiratory, and cardiovascular disorders (1,2).

Occupational cohorts known to have high exposure to TCDD have had inconsistent but suggestive findings with regard to cardiovascular mortality. A large U.S.

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Abbreviations used: CI, confidence interval(s); HCD, higher chlorinated dioxin(s); NIOSH, National Institute for Occupational Safety and Health; RR, rate ratio(s); SMR, standardized mortality ratio(s); 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

cohort (18) did not show an excess of heart disease (standard mortality ratio [SMR] = 0.96) when compared to the general population. In an international study (19), the SMR for all circulatory disease was 0.90. However, the English component of the study showed a slight increase in circulatory disease (SMR = 1.17) (31). The small German accident cohort studied by Ott and Zober (24) also did not show an excess of heart disease. However, for another German cohort of chemical workers, Flesch-Janys et al. (21) recently reported mortality for all cardiovascular diseases and ischemic heart disease to be positively related to estimated TCDD exposure levels when exposed workers were

compared to other industrial workers. More detailed and thorough analysis of cardiovascular disease risk clearly is warranted given the potential for increased risk of diabetes and altered lipid metabolism among TCDD-exposed workers.

The international study of workers who produced or sprayed phenoxy herbicides (6) was recently updated and enlarged to include cohorts from the United States and Germany and offered an opportunity to evaluate the long-term consequences and chronic outcomes of TCDD exposure with some statistical precision because of the large sample size and longer latency periods. Results for cancer mortality were recently reported (20). An assessment of noncancer

outcomes is presented here, with particular emphasis on cardiovascular disease mortality in relation to TCDD exposure.

**Methods**

The International Agency for Research on Cancer multicentric mortality study is an international cohort study of 26,976 workers producing or spraying phenoxyacid herbicides and chlorophenols and employed in 36 cohorts from 12 countries (Table 1). In eight countries, 4160 workers employed in the same companies but not exposed to phenoxyacid herbicides and chlorophenols were also enrolled in the study. These workers, together with 592 workers with unknown exposure rates and 361 workers

**Table 1.** Description of the cohorts in the IARC international mortality study, 1939 to 1992.

Cohort no, country, type	Gender	Workers, no.		Date of follow-up	Lost to follow-up, %	Deaths, no.	Serum TCDD samples, no.	Main herbicides produced, formulated, or sprayed
		Exposed to TCDD/HCD	Minimally or not exposed to TCDD/HCD					
1 Australia, S	M	1840	0	1951-1983	3.3	620	37	2,4-D; 2,4,5-T
2 Austria, P	M, F	159	0	1971-1991	3.1	21	47	2,4-D; 2,4,5-T; MCPA; 2,4,5-TCP; 2,4-DCP
3 Canada, S	M	1142	81	1950-1992	3.4	152	0	2,4-D; 2,4,5-T
4 Denmark, P	M, F	0	1920	1947-1992	5.0	397	0	2,4-DP; MCPA; MCPP
5 Denmark, P	M, F	0	198	1951-1992	2.0	28	0	2,4-DP; MCPA
6 Finland, P	M, F	62	0	1939-1991	9.7	19	0	2,3,4,6-TeCP
7 Italy, P	M, F	205	0	1970-1991	1.5	22	0	2,4,5-TCP
8 Italy, P	M, F	0	60	1967-1991	10.0	4	0	2,4-D; MCPA
9 Netherlands, P	M, F	524	38	1955-1991	5.5	140	31	2,4,5-T; 2,4,5-TCP
10 Netherlands, P	M, F	0	419	1965-1991	1.7	31	0	2,4-D; MCPA; MCPP
11 New Zealand, P	M, F	782	0	1969-1990	14.8	70	0	2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP
12 New Zealand, S	M, F	699	0	1973-1990	4.1	35	9	2,4-D; 2,4,5-T; MCPA
13 Sweden, P	M, F	244	0	1965-1990	1.6	24	5	2,4-D; 2,4,5-T; MCPA; MCPP; 2,4,6-TCP
14 United Kingdom, P	M	0	1565	1947-1990	10.1	392	0	MCPA
15 United Kingdom, P	M	145	0	1960-1989	1.4	49	0	PCP
16 United Kingdom, P	M	572	369	1975-1991	3.6	83	0	2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DB; 2,4-DP
17 United Kingdom, P	M	0	345	1963-1991	2.0	29	0	MCPB; PBA
18 United Kingdom, P	M	0	271	1969-1991	5.2	19	0	MCPA; MCPP; 2,4-DB; 2,4-DP
19 United Kingdom, P	M		479 <sup>a</sup>	1969-1991	5.4	64	0	2,4-D; MCPA; MCPP; 2,4-DP
20 United Kingdom, S	M	0	1992	1947-1990	8.6	418	0	MCPA
21 Germany, P	M, F	576	59	1956-1989	0.9	89	19	2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP
22 Germany, P	M, F	1307	42	1952-1989	0.5	358	190	2,4,5-T; 2,5-DCP; 2,4,5-TCP
23 Germany, P	M, F	313	179	1965-1989	13.4	21	0	2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP
24 Germany, P	M, F	126	15	1951-1992	2.1	24	20	2,4,5-TCP
25 United States, P	M	437	0	1951-1987	1.6	128	253 <sup>b</sup>	2,4-D; 2,4,5-T; 2,4,5-TCP
26 United States, P	M	96	0	1968-1987	0.0	11	0	2,4,5-T; 2,4,5-TCP; HCP
27 United States, P	M	691	0	1961-1987	1.7	58	0	2,4-D; 2,4,5-T; 2,4,5-TCP
28 United States, P	M	354	0	1957-1987	1.4	50	0	2,4-D; 2,4,5-T; 2,4,5-TCP; 2,4,5-TP
29 United States, P	M	113	0	1961-1987	0.0	25	0	2,4-D; 2,4,5-T; 2,4,5-TCP
30 United States, P	M	121	0	1957-1987	5.0	28	0	2,4-D; 2,4,5-T; 2,4,5-TCP
31 United States, P	M	96	0	1960-1987	1.0	21	0	2,4-D; 2,4,5-T; DCP; PCP
32 United States, P	M	452	0	1948-1987	4.4	121	0	2,4,5-T; 2,4,5-TCP
33 United States, P	M	2089	0	1942-1987	0.3	425	0	2,4-D; 2,4,5-T; 2,4,5-TCP; DCP; PCP; 2,4,5-TP; 2,4,6-TCP; TECP
34 United States, P	M	265	0	1949-1987	2.3	94	0	2,4,5-TCP
35 United States, P	M	163	0	1957-1987	0.6	27	0	HCP
36 United States, P	M	258	0	1953-1987	1.9	62	0	2,4-D; 2,4,5-T; 2,4,5-TP

Abbreviations: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DB, 2,4-dichlorophenoxybutyric acid; 2,4-DCP, 2,4-dichlorophenol; 2,4-DP, 2,4-dichlorophenoxypropionic acid; F, female; HCP, hexachlorophenol; IARC, International Agency for Research on Cancer; M, male; MCPA, 4-chloro-2-methylphenoxyacetic acid; MCPP, 4-chloro-2-methylphenoxypropionic acid; P, production; PCP, pentachlorophenol; S, sprayer; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TCP, 2,4,5-trichlorophenol; 2,4,6-TCP, 2,4,6-trichlorophenol; 2,3,4,6-TeCP, 2,3,4,6-tetrachlorophenol; 2,4,5-TP, 2,4,5-trichlorophenoxypropionic acid. <sup>a</sup>Workers exposed to phenoxy herbicides or chlorophenols but with unknown exposure to TCDD/HCD. <sup>b</sup>Also from cohort 26.

with exposure information missing from their medical histories were excluded from the current analysis, which therefore is based on 21,863 workers exposed to phenoxyacid herbicides and chlorophenols. The cohort includes any workers ever employed in production or spraying of phenoxyacid herbicides except those in selected cohorts for which minimum employment periods were specified. Detailed information on each cohort is provided in Table 1 and in previous publications (17,19–21). The follow-up was conducted according to a similar methodology in the different countries and extended from 1939 to 1992 but varied by cohort. Only 4.4% of the entire cohort was lost to follow-up ( $n=970$ ), with less than 10% lost to follow-up in 33 of the 36 cohorts. Those workers lost to follow-up were eliminated from the study at the time of loss. Cohort members accumulated a total of 488 and 482 person-years of follow-up.

Individual worker exposure estimates were reconstructed using job records, company exposure questionnaires, and, in some cohorts, measurements of TCDD and other congeners in serum or adipose tissue and in the workplace environment. The plant exposure questionnaire was completed by factory personnel in the presence of an industrial hygienist or the principal investigator for each study (32). Information was elicited on procedures and products by time period and volume, number of workers, and contamination of products with dioxins. An extensive industrial hygiene review was done for U.S. cohorts by the National Institute for Occupational Safety and Health (NIOSH) (18).

For this analysis workers were classified by exposure to TCDD or higher chlorinated dioxin(s) (HCD) into three categories: those exposed to TCDD or HCD (TCDD/HCD) ( $n=13,831$ ); those not exposed to TCDD/HCD ( $n=7553$ ); and those having unknown amounts of exposure to TCDD/HCD ( $n=479$ ). The grouping of TCDD with other HCD was done because exposures often occurred concomitantly and the compounds have similar mechanisms of action and relatively similar toxicity. Two criteria had to be fulfilled for workers to classify as exposed to TCDD/HCD. First, workers must have been employed during the period of production, formulation, or spraying of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), 2,4,5-trichlorophenoxy propionic acid, 2,4,5-trichlorophenol, hexachlorophene, pentachlorophenol, or

2,3,4,6-tetrachlorophenol, because TCDD/HCD contamination was highest in these chemicals. Second, workers must have been employed in plants with documented exposure to TCDD/HCD at levels above background based on biologic or environmental measurements; or, in the absence of TCDD/HCD measurements, plants involved in production, formulation, or spraying of more than 10 tons/year of those compounds listed above. Estimation of duration of exposure took into account the exact dates and time periods of production or spraying of each chemical. Serum TCDD measurements were available for 573 workers from 10 cohorts (Table 1). Sampling policy for the selection of these workers varied by cohort and was in most cases nonrandom. There was also variation among cohorts in the time elapsed between TCDD exposure and blood sample collection: mean TCDD serum levels were below 20 pg/g in the cohorts from Sweden and Australia (sprayers) and one German cohort ( $n=21$ ), close to 50 pg/g lipid in the Dutch cohort ( $n=9$ ) and the New Zealand cohort (sprayers) and higher than 100 pg/g lipid in the cohorts of production workers from Austria, the United States, and Germany ( $n=22, 23$ ); the highest mean (402 pg/g) was found in a group of twenty 2,4,5-T production workers with chloracne or other symptoms from cohort 23 (Germany). So, the available evidence suggests that production workers have higher serum TCDD levels than sprayers and substantially higher serum TCDD levels than in the general population.

SMR were calculated, with 95% confidence interval(s) (CI) based on the Poisson distribution, using the Person-Years program (33). Expected numbers of deaths were calculated by multiplying the appropriate person-years by the country-, gender-, age-, calendar period-, and cause-specific national death rates using the World Health Organization Mortality Data Bank.

Gender-specific analyses for the major causes of death were conducted for all workers exposed to phenoxy herbicides or chlorophenols. However, all subsequent findings by exposure group are presented for males and females combined because there was no gender effect modification and the number of observed deaths among females was small in most cases. Underlying cause of death was retrieved from the death certificate records in each country and coded according to the revision of the *International Classification of Diseases*

(World Health Organization, Geneva) in effect at the time of death.

Internal cohort comparisons examining mortality from selected causes of death according to exposure to phenoxy herbicides and chlorophenols and to TCDD/HCD were made using Poisson multiple regression models. Rate ratio(s) (RR) and 95% CI derived from the analysis were adjusted for country, age (10-year groups), gender, calendar period, and employment status (i.e., whether workers were employed in the companies included in the study or had left employment). The Generalized Linear Interactive Modeling statistical package (34) was used for the regression analysis.

## Results

A total of 4159 deaths occurred during the follow-up. Cause was known for 96.4% of the deaths. Cause-specific mortality by gender is presented in Table 2. The all-cause mortality for both men and women was comparable to that expected from national mortality rates, illustrating the lack of an apparent healthy worker effect for all causes combined. Among the smaller cohort of women with only 133 observed deaths, none of the specific categories of cause of death were significantly different from expected. Cardiovascular disease deaths for women were not lower than expected, as one might suspect for an industrial cohort, and the ischemic heart disease SMR was 1.07 (95% CI 0.68–1.59). A 50% nonsignificant excess mortality was observed for external causes, accounted for partly by the high SMR for suicide (1.46, 95% CI 0.59–3.00).

Significant excess mortality for men was observed for all malignant neoplasms combined (SMR 1.07, 95% CI 1.01–1.13) and for symptoms and ill-defined conditions (SMR 1.60, 95% CI 1.27–1.98). Mortality from accidents, poisoning, and violence (SMR 1.09, 95% CI 0.98–1.19) was also elevated, and there were 114 deaths from suicides (SMR 1.02, 95% CI 0.84–1.22). A significant deficit in mortality was observed for all diseases of the circulatory system because of lower than expected mortality for ischemic heart disease and cerebrovascular disease; this suggested a moderate healthy worker selection for circulatory diseases among men. The only other causes of death significantly lower than expected were diseases of the respiratory and digestive systems.

Detailed results of cancer mortality for specific cancers and by exposure subgroups

**Table 2.** Standardized mortality ratios for major causes of death by gender among workers in the IARC international cohort study exposed to phenoxy herbicides or chlorophenols, 1939 to 1992.

Cause of death	ICD-9 classification	Males			Females		
		Obs	SMR	95% CI	Obs	SMR	95% CI
All causes	—	4026	0.97	0.94–1.00	133	0.98	0.82–1.17
All malignant neoplasms	140–208	1083	1.07	1.01–1.13	44	0.93	0.68–1.25
Benign neoplasms	210–239	18	1.16	0.69–1.84	0 <sup>a</sup>	0	0–2.95
Diseases of the endocrine system and blood	240–289	64	0.79	0.61–1.01	1	0.27	0.10–1.48
Mental disorders	290–319	30	0.97	0.66–1.39	0 <sup>b</sup>	0	0–3.88
Diseases of the nervous system	320–389	40	0.77	0.55–1.05	1	0.44	0.10–2.47
Diseases of the circulatory system	390–459	1738	0.91	0.87–0.95	48	1.00	0.73–1.32
Ischemic heart disease	410–414	1179	0.92	0.87–0.98	24	1.07	0.68–1.59
Cerebrovascular disease	430–438	254	0.86	0.76–0.97	9	0.73	0.33–1.38
Other diseases of the heart	415–429	166	1.11	0.95–1.29	6	0.92	0.34–2.00
Diseases of the respiratory system	460–519	252	0.82	0.72–0.92	7	1.06	0.43–2.19
Diseases of the digestive system	520–579	139	0.80	0.67–0.95	8	1.28	0.55–2.53
Liver cirrhosis	571	70	0.90	0.70–1.14	3	1.27	0.26–3.70
Diseases of the genitourinary system	580–629	40	0.75	0.54–1.02	2	0.81	0.10–2.94
Symptoms and ill-defined conditions	780–799	82	1.60	1.27–1.98	5	1.36	0.44–3.16
Accidents, poisoning, and violence	E800–E999	429	1.09	0.98–1.19	15	1.50	0.84–2.48
Suicide	E950–E959	114	1.02	0.84–1.22	7	1.46	0.59–3.00
Unknown cause	—	113	—	—	4	—	—

Abbreviations: ICD-9, *International Classification of Diseases, Ninth Revision* (World Health Organization, Geneva); Obs, observed deaths. <sup>a</sup>1.25 expected deaths. <sup>b</sup>0.95 expected deaths.

**Table 3.** Standardized mortality ratios (1939–1992) for specific causes among workers in the IARC international cohort study exposed to phenoxy herbicides or chlorophenols by exposure to TCDD or HCD.<sup>a</sup>

Cause of death	ICD-9 classification	Workers exposed to TCDD/HCD (n=13,831)			Workers not exposed to TCDD/HCD (n=7553)		
		Obs	SMR	95% CI	Obs	SMR	95% CI
All causes	—	2728	1.00	0.97–1.04	1367	0.91	0.86–0.96
All malignant neoplasms	140–208	710	1.12	1.04–1.21	398	0.96	0.87–1.06
Benign neoplasms	210–239	11	1.03	0.51–1.84	7	1.20	0.48–2.47
Diseases of the endocrine system and blood	240–289	47	0.78	0.57–1.04	17	0.71	0.41–1.14
Mental disorders	290–319	13	0.57	0.30–0.97	17	1.97	1.15–3.16
Diseases of the nervous system	320–389	28	0.86	0.57–1.24	12	0.59	0.30–1.03
Diseases of the circulatory system	390–459	1170	0.94	0.88–0.99	588	0.86	0.79–0.93
Ischemic heart disease	410–414	789	0.97	0.90–1.04	394	0.85	0.77–0.94
Cerebrovascular disease	430–438	162	0.84	0.71–0.98	96	0.86	0.70–1.05
Other diseases of the heart	415–429	138	1.20	1.01–1.42	32	0.80	0.55–1.13
Diseases of the respiratory system	460–519	151	0.86	0.73–1.01	102	0.76	0.62–0.92
Diseases of the digestive system	520–579	96	0.73	0.59–0.89	47	1.00	0.74–1.33
Liver cirrhosis	571	53	0.82	0.61–1.07	19	1.28	0.77–1.99
Diseases of the genitourinary system	580–629	27	0.73	0.48–1.07	15	0.81	0.45–1.34
Symptoms and ill-defined conditions	780–799	65	1.83	1.42–2.34	22	1.13	0.71–1.71
Accidents, poisoning, and violence	E800–E999	322	1.10	0.98–1.22	117	1.10	0.91–1.31
Suicide	E950–E959	78	1.01	0.80–1.27	42	1.09	0.79–1.48
Unknown cause	—	86	—	—	25	—	—

<sup>a</sup>Excluded are 479 workers exposed to phenoxy herbicides or chlorophenols and with unknown TCDD/HCD exposure.

have already been reported (20). Table 3 shows noncancer mortality for specific causes for both genders combined, stratified by exposure subgroup: those exposed to phenoxy acids or chlorophenols contaminated with TCDD/HCD and those exposed to phenoxyacids or chlorophenols but with minimal or no exposure to TCDD/HCD.

The SMR for circulatory diseases were below 1 in both groups. However, workers exposed to TCDD/HCD had somewhat higher SMR than unexposed

workers; their SMR for other diseases of the heart were significantly increased and could be attributed predominantly to acute pericarditis (36% of observations) and heart failure (23%). Mortality from respiratory diseases was below expectation in both groups ( $p < 0.05$  in the TCDD/HCD unexposed group), whereas mortality from digestive diseases was significantly reduced in the TCDD/HCD-exposed group and close to expectation in the TCDD/HCD-unexposed group. There was a 10% excess mortality from

external causes and the SMR for suicide were similar in both TCDD/HCD-exposed and -unexposed groups.

### Internal Comparisons

Poisson regression was done to assess risk for selected causes by measures of exposure to TCDD/HCD. As shown in Table 4, risks of mortality for all circulatory diseases combined and ischemic heart disease were significantly related to indices of exposure to TCDD/HCD. The adjusted RR for exposure to TCDD/HCD were 1.51 (95%

**Table 4.** Poisson regression analyses of mortality from selected causes among workers in the IARC international cohort study and indices of exposure to TCDD or HCD, 1939 to 1992.<sup>a</sup>

Variables in the model	All circulatory disease			Ischemic heart disease			Cerebrovascular disease			Diabetes		
	RR	95% CI	Obs	RR	95% CI	Obs	RR	95% CI	Obs	RR	95% CI	Obs
Exposure to TCDD/HCD <sup>b</sup>												
No (reference category)	1.00	—	582	1.00	—	391	1.00	—	95	1.00	—	11
Yes	1.51	1.17–1.96	1151	1.67	1.23–2.26	775	1.54	0.83–2.88	161	2.25	0.53–9.50	33
Years since first TCDD/HCD exposure <sup>c</sup>												
0–9 (reference category)	1.00	—	173	1.00	—	113	1.00	—	27	1.00	—	3
10–19	1.09	0.88–1.34	393	1.16	0.90–1.48	273	0.96	0.56–1.64	61	2.34	0.56–9.83	14
20+	1.07	0.85–1.35	585	1.10	0.84–1.45	389	0.73	0.39–1.36	73	1.54	0.30–7.82	16
Trend <sup>d</sup>	0.69			0.71			0.22			0.96		
Duration of TCDD/HCD exposure, years <sup>e</sup>												
Less than 1 (reference category)	1.00	—	248	1.00	—	187	1.00	—	31	1.00	—	8
1–4	1.16	0.98–1.38	370	1.05	0.86–1.29	236	1.13	0.70–1.82	54	1.07	0.39–2.94	9
5–9	1.32	1.08–1.60	220	1.17	0.92–1.48	135	1.39	0.83–2.32	38	1.01	0.28–3.62	4
10–19	1.28	1.05–1.55	233	1.21	0.96–1.53	158	1.22	0.72–2.08	34	2.52	0.89–7.11	10
20+	0.96	0.73–1.27	80	0.98	0.70–1.36	59	0.30	0.10–0.91	4	1.13	0.20–6.43	2
Trend <sup>d</sup>	0.19			0.29			0.51			0.18		
Year of first TCDD/HCD exposure <sup>c</sup>												
Before 1955 (reference category)	1.00	—	564	1.00	—	373	1.00	—	81	1.00	—	16
1955–1964	1.07	0.93–1.23	380	1.13	0.95–1.33	266	1.03	0.70–1.51	49	0.97	0.41–2.30	10
1965+	1.07	0.87–1.30	207	1.03	0.81–1.32	136	1.18	0.68–2.07	31	1.76	0.58–5.31	7
Trend <sup>d</sup>	0.40			0.47			0.61			0.42		

<sup>a</sup>The analysis was limited to workers with known durations of exposure and known employment status. Internal comparisons were made using Poisson regression analysis. <sup>b</sup>RR values are adjusted for age, gender, country, calendar period, employment status, and years since first exposure and duration of exposure to phenoxy herbicides or chlorophenols. The group exposed to TCDD/HCD is compared to the group exposed to phenoxy herbicides or chlorophenols not contaminated with TCDD/HCD. <sup>c</sup>RR values are adjusted for age, gender, country, calendar period, employment status, and years since first exposure and duration of exposure to phenoxy herbicides or chlorophenols. Analysis is limited to workers classified as exposed to TCDD/HCD. <sup>d</sup>p-value of test for linear trend.

CI 1.17–1.96) for all circulatory diseases and 1.67 (95% CI 1.23–2.26) for ischemic heart disease. Risks did not differ across latency categories or by year of first exposure but increased slightly by duration of exposure except for those with 20 or more years of exposure. Exposed workers had a 50% excess of cerebrovascular diseases (RR 1.54, 95% CI 0.83–2.88) and the findings for latency, duration, and time period of TCDD/HCD exposure were unremarkable. There was an approximately 2-fold risk for mortality from diabetes, but the CI was wide. The point estimate of the risk was higher for 10 to 19 years latency, 10 to 19 years duration of exposure, and exposure after 1966. Further analyses were conducted for the inactive stratum of employment status separately, but most findings did not change, although the association between exposure to TCDD/HCD and ischemic heart disease was slightly attenuated (RR for any exposure 1.52, 95% CI 1.07–2.15).

The risk of suicide did not differ by exposure group (RR in the internal comparison: 0.98, 95% CI 0.41–2.36), suggesting that suicide was not exclusively related to exposure to TCDD/HCD. Therefore, an analysis of suicide was conducted for the entire cohort exposed to phenoxy herbicides

or chlorophenols (Table 5); suicide risk was slightly lower in the longest latency category and slightly higher for latency 10 to 19 years, duration of phenoxy herbicide and chlorophenol exposure less than 1 year, and year of first exposure after 1964. Other causes of death, namely diseases of the endocrine system and the blood combined and diseases of the nervous system, were not associated with indices of exposure to either phenoxy herbicides and chlorophenols or TCDD/HCD.

### Discussion

The major focus of epidemiologic studies assessing the long-term consequences of exposure to TCDD has necessarily been risks for malignant neoplasms given the potent carcinogenicity of this compound in experimental systems. Recent evidence concerning mechanisms of action, TCDD's influence on biochemical and endocrine pathways, and morbidity effects in cross-sectional studies has highlighted the importance for also evaluating the noncancer consequences from TCDD exposure. This international cohort of phenoxyacid herbicide- and chlorophenol-exposed workers from 36 cohorts in 12 countries represents the largest study group of its kind ever assembled, and allowed classification of

**Table 5.** Poisson regression analysis of mortality from suicide among workers in the IARC international cohort study exposed to phenoxyacid herbicides or chlorophenols, 1939 to 1992.<sup>a</sup>

Variables in the model	RR	95% CI	Obs
Years since first exposure to herbicides			
0–9 (RC)	1.00	—	51
10–19	1.10	0.69–1.74	44
20 or more	0.75	0.38–1.45	24
Years of exposure to herbicides			
Less than 1 (RC)	1.00	—	58
1–4	0.81	0.53–1.25	36
5–9	0.85	0.45–1.59	14
10–19	0.92	0.45–1.90	11
20 or more	—	—	0
Year of first exposure to herbicides			
Before 1955 (RC)	1.00	—	34
1955–1964	1.52	0.90–2.56	36
1965 or after	2.30	1.24–4.27	49

RC, reference category. <sup>a</sup>The analysis was limited to those workers with known durations of exposure and employment status. RR values are adjusted for age, gender, country, calendar period, and employment status.

subgroups with and without substantial exposure to TCDD/HCD. Mortality from all malignant neoplasms combined was increased for all male workers and especially for workers exposed to TCDD/HCD.

This association and cancer site-specific analyses are presented and evaluated in Kogevinas et al. (20).

SMR analyses suggested a moderate healthy worker effect for all circulatory and ischemic heart diseases for workers both exposed and unexposed to TCDD/HCD. Therefore there was no absolute excess in ischemic heart disease when exposed workers were compared to the general population. However, for those exposed to TCDD/HCD, SMR were higher 10 years after exposure and for exposures after 1955. For those not exposed to TCDD/HCD, the SMR for ischemic heart disease, even after 20 years since first exposure, was 0.82 (95% CI 0.72–0.93). An association of increased risk for ischemic heart disease with TCDD/HCD exposure was found through internal analysis, where confounding by age, employment status, and other time-related variables could be controlled. Similarly, diabetes appeared to be independently related to TCDD/HCD when assessed by Poisson regression (Table 4). The difference in the results between the internal analysis (RR 1.51) and the analysis based on external references (ratio of the SMR 0.94/0.86 = 1.09, Table 3) is because of incomparability of SMR rather than to the confounding effect of variables controlled for in the internal analysis; a Poisson regression model including only age, country, gender, and calendar period resulted in a RR of 1.46. Higher suicide rates than expected for a working population were observed for all workers exposed to any phenoxyacid herbicide or chlorophenol. Suicide mortality is usually lower among workers compared to the general population, which includes the unemployed and mentally ill (35,36). Suicide risk was highest with latency of 10 to 19 years and short duration of employment. No increase was found for other causes of death.

This retrospective cohort mortality study was hampered by the reliance on mortality and the crudeness and inaccuracies of death certificate diagnoses. Diseases of interest such as endocrine and neurologic outcomes likely were underdiagnosed. This likely affected precision, not validity of risk estimates. Also, possible confounding effects from important risk factors for ischemic heart disease such as cigarette smoking, high fat diet, blood pressure, obesity, physical inactivity, and serum lipids cannot be ruled out. However, excess risk from nonmalignant respiratory disease was not observed and the internal analysis

may have, at least in part, controlled for confounding from known risk factors.

There is sufficient information in both the experimental and epidemiologic literature in support of the biologic plausibility of the association found between TCDD exposure and ischemic heart disease and diabetes. In animal studies, reported effects include disturbances in lipid metabolism (1,2,37), functional cardiovascular disturbances (38–40), and morphologic changes in peripheral vessels (41,42). Cross-sectional epidemiologic studies of highly exposed selected populations, although methodologically limited, suggest that TCDD exposure might be associated with increased prevalence of ischemic heart disease (16,23,27,30), hypertension (16,27), diabetes (43,44), and abnormal serum lipids (16,27,45,46). An increase in diabetes mortality has been shown among women in Seveso (47). Recent evidence from the study of U.S. Air Force personnel shows an inverse trend between serum dioxin level and high density lipoprotein and a positive trend with cholesterol (48).

Diabetes among the U.S. Air Force personnel cohort was recently studied by Henriksen et al. (49). Dioxin exposure increased risk of glucose abnormalities, diabetes prevalence and the use of oral medications to control diabetes, and decreased time-to-onset of diabetes. Our findings of higher risk of diabetes among TCDD/HCD-exposed workers, especially with 10 or more years of latency and duration of exposure, are confirmatory. However, our results are limited by the death certificate diagnoses and small number of observations.

Recent evidence suggests that inflammation may be more important in the pathogenesis of atherothrombosis than originally thought (50). C-reactive protein, a marker for systemic inflammation that predicts risk for a first myocardial infarction (50), may be a surrogate for interleukin-6, a cellular cytokine (51). TCDD/HCD elicits an inflammatory response. TCDD/HCD apparently alters gene expression in human cells of cytokine interleukin-1 $\beta$  and plasminogen activator inhibitor-2, both of which are involved in the physiologic and pathologic process of inflammation (52).

Most of the early mortality studies of populations exposed to TCDD or TCDD/HCD, including analyses of subcohorts in the present study (18,19,21,53), did not consistently assess ischemic heart disease mortality and most did not undertake

specific exposure assessments for TCDD. For example, in the NIOSH cohort study (18), the SMR for diseases of the heart, including ischemic heart disease, was 0.96 (95% CI 0.87–1.06) based on 393 observed deaths. No detailed exposure-related analysis for ischemic heart disease was provided. Previous studies of cohorts included in the NIOSH study (54–56) did not report elevated SMR. The more recent update by Collins et al. (25) of the Nitro, West Virginia, cohort reported only an SMR for all circulatory disease (SMR 0.90, 95% CI 0.8–1.0). Ott et al. (56) reported cause-specific mortality for the Dow Chemical Company (Midland, MI) cohort of phenol production workers overall and for both TCDD and heptooctachlorinated dioxin indices of exposure. For the entire cohort followed to 1982, the SMR for diabetes was 0.73 (95% CI 0.20–1.86) and for diseases of the circulatory system it was 0.93 (95% CI 0.79–1.08) based on 157 deaths. For diseases of the circulatory system, the trend tests for SMR across intensity score categories of TCDD were not significant. Internal cohort analyses were not conducted. Bond et al. (57) updated the cohort to 1984 to study cause-specific mortality among the subgroup with chloracne. The SMR for arteriosclerotic heart disease was 0.95 (95% CI 0.53–1.56) for workers with chloracne.

In another small cohort ( $n = 243$ ) exposed in an industrial accident (53), circulatory system mortality was not elevated in the highest exposed subgroup (SMR 0.91, 95% CI 0.51–1.50) but was higher among all cohort members with chloracne (SMR 1.21, 95% CI 0.83–1.70). Ott and Zober (24) updated the follow-up to 1992 and assessed SMR by estimated TCDD dose groups. No evidence of an effect of TCDD on deaths from all diseases of the circulatory system ( $n = 37$ ) or ischemic heart disease ( $n = 16$ ) was observed.

In an early report of this study limited to a smaller number of cohorts (19), we reported only the SMRs for all diseases of the circulatory system combined. The SMR for those exposed to chlorophenoxy herbicides or chlorophenols was 0.90 (95% CI 0.84–0.97). Reports of individual cohorts included in this early study include four British plants studied by Coggon et al. (31), a cohort of Canadian sprayers (58), and two Dutch plants (59). The SMR for circulatory disease among British workers with greater than background exposure to herbicides or chlorophenols was 1.17, but the excess appeared to be confined to plant A workers (SMR 1.66) (31). Green (58)

reported an SMR of 0.92 (95% CI 0.61–1.34) for all diseases of the circulatory system in a Canadian cohort of public utility forestry workers who applied herbicides. Among the Dutch workers the RR for circulatory disease mortality was 1.70 (95% CI 0.90–3.20) comparing workers exposed to phenoxy herbicides or chlorophenols and nonexposed subjects. None of these studies assessed TCDD exposure. However, a cohort of German chemical workers included in the present study who manufactured 2,4,5-trichlorophenol and 2,4,5-T as well as chemicals contaminated with dioxins was compared to gas workers using a quantitative measure of dioxin exposure (21). All cardiovascular disease and ischemic heart disease showed a dose-dependent relationship with TCDD and all dioxins/furans combined. The relative risk for ischemic heart disease in the highest TCDD/HCD exposure group was 2.48 (95% CI 1.32–4.66).

The most recent update of the U.S. Air Force personnel study (60) shows an increase of ischemic heart disease among nonflying enlisted men (SMR 1.49, 95% CI 0.98–2.19,  $n = 24$ ), although not in other subgroups using a comparison group of nonexposed servicemen. The largest subgroup and also the highest dioxin exposure based on serum levels is nonflying enlisted men. The most recent 15-year follow-up of

the Seveso population showed a significant increase in circulatory disease among males (RR 1.6, 95% CI 1.1–2.5,  $n = 21$ ) and ischemic heart disease among males (RR 1.5, 95% CI 0.3–4.5,  $n = 9$ ) in the highest exposure zone (zone A), although females showed no elevation in zone A (61).

The higher-than-expected SMRs for suicide for an employed population (35,36) in this cohort of workers exposed to phenoxyacid herbicides and chlorophenols confirms the previous observations of Green (58,62) and Becher et al. (22). Green (62) postulated that the neurologic toxicity of phenoxyacid herbicide exposure might have psychiatric manifestations such as suicide. The documented neurologic toxicity of phenoxyacid herbicides (63) and their exposure-associated personality changes, neurologic disturbances (64), and depression (65) have been hypothesized as considerations in the evaluation of suicide risk among exposed cohorts (58). The higher rates of suicide among workers with short durations of exposure in the present study suggest that perhaps those susceptible to psychiatric manifestations of exposure are at risk during the first few years of exposure. Alternatively, the excess may have occurred by chance or as a consequence of nonoccupational confounding factors. Further study of the biologic and clinical basis for suicide among phenoxyacid herbicide-exposed workers is warranted.

The results of this cohort study reinforce the hypothesis that exposure to TCDD/HCD increases the risk for ischemic heart disease and perhaps diabetes. It seems somewhat paradoxical that investigations of a few subcohorts with previous TCDD/HCD exposure estimates, which comprise this expanded international cohort, did not reveal an association with circulatory disease. However, the cohort reported by Ott et al. (56) was followed only to 1982 and the Badische Anilin- und Sodafabrik (Ludwigshafen, Germany) cohort had a small number of observed events (24). The present investigation had the advantages of a systematic and consistent TCDD/HCD exposure assessment that was validated with biologic and environmental sampling (20), substantial sample size, and extended latency periods. Nonetheless, the current study had important limitations, including reliance on mortality measures, lack of specific quantitative measures of exposure to TCDD/HCD for each worker, and the inability to authoritatively rule out confounding from other occupational and lifestyle exposures. Refined risk estimates based on more explicit exposure estimates would be informative and important given the ubiquitous environmental contamination of food, soil, and water with TCDD/HCD.

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