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## Cancer Mortality in Workers Exposed to Phenoxy Herbicides, Chlorophenols, and Dioxins

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## ORIGINAL CONTRIBUTIONS

### Cancer Mortality in Workers Exposed to Phenoxy Herbicides, Chlorophenols, and Dioxins

#### An Expanded and Updated International Cohort Study

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The authors examined cancer mortality in a historical cohort study of 21,863 male and female workers in 36 cohorts exposed to phenoxy herbicides, chlorophenols, and dioxins in 12 countries. Subjects in this updated and expanded multinational study coordinated by the International Agency for Research on Cancer were followed from 1939 to 1992. Exposure was reconstructed using job records, company exposure questionnaires, and serum and adipose tissue dioxin levels. Among workers exposed to phenoxy herbicides contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) or higher chlorinated dioxins, mortality from soft-tissue sarcoma (6 deaths; standardized mortality ratio (SMR) = 2.03, 95% confidence interval (CI) 0.75–4.43) was higher than expected from national mortality rates. Mortality from all malignant neoplasms (710 deaths; SMR = 1.12, 95% CI 1.04–1.21), non-Hodgkin's lymphoma (24 deaths; SMR = 1.39, 95% CI 0.89–2.06), and lung cancer (225 deaths; SMR = 1.12, 95% CI 0.98–1.28) was slightly elevated. Risks for all neoplasms, for sarcomas, and for lymphomas increased with time since first exposure. In workers exposed to phenoxy herbicides with minimal or no contamination by TCDD and higher chlorinated dioxins, mortality from all neoplasms (398 deaths; SMR = 0.96, 95% CI 0.87–1.06), non-Hodgkin's lymphoma (9 deaths; SMR = 1.00), and lung cancer (148 deaths; SMR = 1.03) was similar to that expected, and mortality from soft-tissue sarcoma was slightly elevated (2 deaths; SMR = 1.35). In a Poisson regression analysis, workers exposed to TCDD or higher chlorinated dioxins had an increased risk for all neoplasms (rate ratio = 1.29, 95% CI 0.94–1.76) compared with workers from the same cohort exposed to phenoxy herbicides and chlorophenols but with minimal or no exposure to TCDD and higher chlorinated dioxins. These findings indicate that exposure to herbicides contaminated with TCDD and higher chlorinated dioxins may be associated with a small increase in overall cancer risk and in risk for specific cancers. *Am J Epidemiol* 1997;145:1061–75.

chlorophenols; cohort studies; dioxins; herbicides; mortality; neoplasms; occupational exposure; tetrachlorodibenzodioxin

Phenoxy herbicides are used extensively worldwide. Some of these herbicides (2,4,5-trichlorophenoxyacetic acid and its derivatives) have been banned in some

countries because of contamination with polychlorinated dioxins, including the most toxic dioxin congener, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (1).

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Abbreviations: CI, confidence interval; IARC, International Agency for Research on Cancer; ICD-9, *International Classification of Diseases, Ninth Revision*; NIOSH, National Institute of Occupational Safety and Health; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin.

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Dioxins and related compounds such as furans and polychlorinated biphenyls are acutely toxic in all species examined, and are among the most potent carcinogens in experimental animals (2). In humans, exposure to phenoxy herbicides, chlorophenols, and dioxins has been linked with excess overall cancer risk and excess risks of soft-tissue sarcoma, non-Hodgkin's lymphoma, and other cancers (3, 4). However, the evidence, particularly from case-control studies, is inconsistent (5). Frequent use of phenoxy herbicides has been associated with increased risk of non-Hodgkin's lymphoma in case-control studies conducted in Sweden (6, 7), the US state of Kansas (8), the US state of Nebraska (9), and Saskatchewan, Canada (10). No excess risk was found, however, in case-control studies carried out in New Zealand (11), the US state of Washington (12), and the US states of Iowa and Minnesota (13). Excess risk of soft-tissue sarcoma has been identified in case-control studies in Italy (14), Washington State (12), and a series of studies conducted in Sweden (15, 16), while results of other studies carried out in New Zealand (17) and the United States (8) were negative. Recent cohort studies of herbicide production workers with high exposure to dioxins, including studies of cohorts that form part of the international multicenter cohort described in this paper, have found excess risks for overall cancer (18–22), respiratory cancers (18, 22), soft-tissue sarcomas (22–26), non-Hodgkin's lymphoma (18, 27), and other fairly rare tumors (18, 25). In the population of Seveso, Italy, which was accidentally exposed to TCDD in 1976, excess risk was observed for hepatobiliary cancer, soft-tissue sarcoma, and hematologic neoplasms (28).

In 1980, the International Agency for Research on Cancer (IARC) established an international cohort study of people whose jobs involved producing or

spraying phenoxy herbicides (25). The study initially included workers from 10 countries. Results from the first follow-up of the IARC cohort (25), from a nested case-control study of soft-tissue sarcoma and non-Hodgkin's lymphoma (26), and from studies of five national subcohorts (23, 24, 29–31) were published previously. The IARC study has since been enlarged, incorporating additional cohorts of herbicide production workers from 12 plants in the United States (22) and four plants in Germany (18, 20, 21), and it now includes practically all of the phenoxy herbicide production workers who have ever been studied. In addition, mortality follow-up has been updated for most of the cohorts. In parallel, dioxin levels have been determined in serum samples obtained from some workers in seven of the 12 countries included in the study. Results on cancer mortality for the updated and enlarged IARC cohort are reported here.

## MATERIALS AND METHODS

The centers participating in the study were selected following a worldwide search for appropriate study populations of workers producing or spraying phenoxy herbicides or chlorophenols (32). All national studies followed the same core protocol developed jointly by the participating countries. The study was coordinated by IARC, and the international study group met on several occasions to secure a common implementation of the protocol at all centers and a common interpretation of results.

### Subjects

The 26,976 workers enrolled in the IARC cohort were employed in specific departments of plants producing phenoxy herbicides or chlorophenols, or in companies spraying phenoxy herbicides. In eight countries, workers employed in the same companies but not directly involved in production or spraying of herbicides were also enrolled. We excluded 361 workers from the analysis because of a lack of information on date of birth ( $n = 228$ ) or date of first employment ( $n = 84$ ) or for other reasons ( $n = 49$ ), leaving 26,615 workers for the analysis. Of those, 21,863 workers were classified as being exposed to phenoxy herbicides or chlorophenols on the basis of information abstracted from individual job records and company exposure questionnaires; 4,160 workers were classified as nonexposed; and 592 were classified as having unknown exposure to phenoxy herbicides or chlorophenols. Because the nonexposed workers were mainly from Denmark and the Netherlands (3,259 workers, or 78 percent of all nonexposed workers), information on the nonexposed workers is not pre-

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sented in this paper and has been used only in national analyses (24, 27). Analyses of the international cohort reported here were limited to the 21,863 workers (20,851 men and 1,012 women) exposed to phenoxy herbicides or chlorophenols. The cohort included workers ever employed in production or spraying, except cohorts from New Zealand, in which a minimum employment period of 1 month was specified, Australia (minimum period of 1 year), Canada (6 months), and Germany (1 month in three cohorts and 3 months in one cohort (cohort 22)). The follow-up period varied in each cohort; overall, it extended from 1939 to 1992, accumulating a total of 488,482 person-years of follow-up (table 1). Production of herbicides/chlorophenols had started in some cohorts before the beginning of follow-up. During the study period, 970 subjects (4.4 percent) were lost to follow-up (they emigrated or vital status was unknown at the end of follow-up); in only three of the 36 cohorts were more than 10 percent of the subjects lost to follow-up (table 1). The procedures for follow-up varied by country. In Italy, active follow-up was conducted for all subjects by contacting municipal death registries. In Germany, information was retrieved from the records of the participating plants, from insurance companies, and from contacts with physicians, workers, and their families. In the remaining 10 countries, national death registration and emigration schemes were used (combined, in the case of New Zealand, with active follow-up).

### Exposure assessment

Exposure was reconstructed using individual job records, company exposure questionnaires developed specifically for the study, and, in some cohorts, measurements of TCDD and other dioxin and furan congeners in serum and adipose tissue and in the workplace. Information was retrieved for all jobs held by the workers during the study period, using 21 job codes for production workers and 10 codes for sprayers. Workers were classified by longest-held exposed job, and the job codes of exposed workers were aggregated into five groups: 1) "main production" ( $n = 8,608$ ), including workers in synthesis, formulation, packaging, and chemical effluent/waste; 2) "maintenance" ( $n = 3,297$ ), including workers involved in maintenance, cleaning, and cleaning up during or after an accident; 3) "other exposed jobs" ( $n = 3,186$ ), including workers in storage, laboratory work, and transporting; 4) "unspecified tasks" ( $n = 1,018$ ), including workers with rotating jobs, those for whom only the initial job title was available, and those in various other exposed jobs; and 5) "sprayers" ( $n = 5,754$ ), including all spraying-related exposed job po-

sitions such as sprayer, applicator, sprayer's field assistant, and sprayer's field supervisor. Exposure information was retrieved from each plant using a questionnaire which was completed by factory personnel in the presence of an industrial hygienist or of the principal investigator in each study (33, 34). Information was collected on procedures; types of products, including period of production and volumes produced; numbers of workers; accidents; and contamination of products and of the working environment with dioxins and other related substances. An extended industrial hygiene review was carried out for the US National Institute of Occupational Safety and Health (NIOSH) cohorts (34).

Each of the 21,863 workers exposed to phenoxy herbicides or chlorophenols was classified into one of three categories: 1) those exposed to TCDD or higher (penta-, hexa-, etc.) chlorinated dioxins ( $n = 13,831$ ); 2) those not exposed to TCDD or higher chlorinated dioxins ( $n = 7,553$ ); and 3) those with unknown exposure to TCDD or higher chlorinated dioxins ( $n = 479$ ). The latter category included all workers in one British cohort (cohort 19) for which production history, particularly for 2,4,5-trichlorophenoxyacetic acid, was incomplete. The grouping of TCDD with other higher chlorinated dioxins was done because these compounds have similar mechanisms of action and relatively similar toxicities, and also because these exposures sometimes occur concomitantly.

Three criteria were used to classify workers as exposed to TCDD or higher chlorinated dioxins: 1) employment during the period of production, formulation, or spraying of 2,4,5-trichlorophenoxyacetic acid, 2,4,5-trichlorophenoxypropionic acid, 2,4,5-trichlorophenol, hexachlorophene, Erbon [2-(2,4,5-trichlorophenoxy)-ethyl 2,2-dichloropropionate], Ronnel [*o,o*-dimethyl-*o*-(2,4,5-trichlorophenyl)-phosphorothioate], pentachlorophenol, or 2,3,4,6-tetrachlorophenol; 2) employment in plants with documented (through serum, adipose tissue, or environmental measurements) exposure to TCDD or higher chlorinated dioxins at levels above background levels; and 3) in the absence of dioxin measurements, employment in plants or companies with documented large-scale production, formulation, or spraying of the above phenoxy herbicides and chlorophenols. An average level of production of these chemicals of 10 tons per year was chosen a priori, below which the probability of contamination and significant exposure to TCDD and higher chlorinated dioxins was considered to be minimal for most workers in a given cohort (25). Contamination with TCDD or higher dioxins does not occur in production of other major phenoxy herbicides such

TABLE 1. Cohorts in the international study of workers exposed to phenoxy herbicides, chlorophenols, and dioxins, International Agency for Research on Cancer, 1939-1992

Cohort no. and country	Type of cohort*	Sex of workers*	No. of workers†				Period of follow-up	% lost to follow-up‡	Deaths among exposed workers#		Main herbicides produced, formulated, or sprayed§
			Not exposed or unknown exposure to phenoxy herbicides or chlorophenol¶	Exposed to herbicides or chlorophenols, and to TCDD§ or higher chlorinated dioxins	Exposed to phenoxy herbicides or chlorophenols, but not to TCDD or higher chlorinated dioxins	All causes			All cancers		
1, Australia	S	M	233	1,840	0	1951-1983	3.3	620	133	2,4-D; 2,4,5-T	
2, Austria	P	M and F	0	159	0	1971-1991	3.1	21	5	2,4-D; 2,4,5-T; MCPA; 2,4,5-TCP; 2,4-DGP	
3, Canada	S	M	0	1,142	81	1950-1982	3.4	152	43	2,4-D; 2,4,5-T	
4, Denmark	P	M and F	1,923	0	1,920	1947-1992	5.0	397	111	2,4-DP; MCPA; MCPP	
5, Denmark	P	M and F	418	0	198	1951-1982	2.0	28	8	2,4-DGP; MCPA	
6, Finland	P	M and F	0	62	0	1939-1991	9.7	19	5	2,3,4,6-TeCP	
7, Italy	P	M and F	120	205	0	1970-1991	1.5	22	9	2,4,5-TCP	
8, Italy	P	M and F	21	0	60	1967-1991	10.0	4	1	2,4-D; MCPA	
9, The Netherlands	P	M and F	594	524	38	1955-1991	5.5	140	51	2,4,5-T; 2,4,5-TCP	
10, The Netherlands	P	M and F	723	0	419	1965-1991	1.7	31	10	2,4-D; MCPA; MCPP	
11, New Zealand	P	M and F	244	782	0	1969-1990	14.8	70	21	2,4-D; 2,4,5-T; MCPA; MCPB; 2,4,5-TCP	
12, New Zealand	S	M and F	4	699	0	1973-1990	4.1	35	14	2,4-D; 2,4,5-T; MCPA	
13, Sweden	P	M and F	25	244	0	1965-1990	1.6	24	6	2,4-D; 2,4,5-T; MCPA; MCPP; 2,4,6-TCP	
14, United Kingdom	P	M	0	0	1,565	1947-1990	10.1	392	109	MCPA	
15, United Kingdom	P	M	0	145	0	1960-1989	1.4	49	12	2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DB; 2,4-DP	
16, United Kingdom	P	M	189	572	369	1975-1991	3.6	83	17	MCPB; PBA	
17, United Kingdom	P	M	0	0	345	1963-1991	2.0	29	7	MCPA; MCPP; 2,4-DB; 2,4-DP	
18, United Kingdom	P	M	0	0	271	1969-1991	5.2	19	7	2,4-D; MCPA; MCPP; 2,4-DP	
19, United Kingdom††	P	M	6	0	0	1969-1991	5.4	64	19	2,4-D; MCPA; MCPP; 2,4-DP	
20, United Kingdom	S	M	0	0	1,992	1947-1990	8.6	418	133	MCPA	
21, Germany	P	M and F	53	576	59	1956-1989	0.9	89	24	2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP	
22, Germany	P	M and F	189	1,307	42	1952-1989	0.5	358	103	2,4,5-T; 2,5-DGP; 2,4,5-TCP	
23, Germany	P	M and F	0	313	179	1965-1989	13.4	21	4	2,4-D; 2,4,5-T; MCPA; MCPP; 2,4-DP	
24, Germany	P	M and F	0	128	15	1951-1992	2.1	24	9	2,4,5-TCP	
25, United States	P	M	0	437	0	1951-1987	1.6	128	32	2,4-D; 2,4,5-T; 2,4,5-TCP	
26, United States	P	M	0	96	0	1968-1987	0	11	2	2,4,5-T; 2,4,5-TCP; HCP	
27, United States	P	M	0	691	0	1961-1987	1.7	58	10	2,4-D; 2,4,5-T; 2,4,5-TCP	
28, United States	P	M	0	354	0	1957-1987	1.4	50	7	2,4-D; 2,4,5-T; 2,4,5-TCP; 2,4,5-TP	
29, United States	P	M	0	113	0	1961-1987	0	25	7	2,4-D; 2,4,5-T; 2,4,5-TCP	
30, United States	P	M	0	121	0	1957-1987	5.0	28	7	2,4-D; 2,4,5-T; 2,4,5-TCP	
31, United States	P	M	0	96	0	1960-1987	1.0	21	3	2,4-D; 2,4,5-T; DCP; PCP	
32, United States	P	M	0	452	0	1948-1987	4.4	121	35	2,4,5-T; 2,4,5-TCP	
33, United States	P	M	0	2,089	0	1942-1987	0.3	425	106	2,4-D; 2,4,5-T; 2,4,5-TCP; DCP; PCP; 2,4,5-TP; 2,4,6-TCP; TECP; Ronnel; Erbon	
34, United States	P	M	0	265	0	1949-1987	2.3	94	30	2,4,5-TCP	
35, United States	P	M	0	163	0	1957-1987	0.6	27	11	HCP	
36, United States	P	M	0	258	0	1953-1987	1.9	62	16	2,4-D; 2,4,5-T; 2,4,5-TP	

\* P, production workers; S, sprayers; M, male; F, female.  
 † Number of workers after exclusion of 361 workers missing information on date of birth or date of first employment or excluded for other reasons.  
 ‡ Workers not included in this analysis.  
 § TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, 2,4-dichlorophenoxypropionic acid; 2,4-DB, 2,4-dichlorophenoxybutyric acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TP, 2,4,5-trichlorophenoxypropionic acid; MCPA, 4-chloro-2-methyl-phenoxyacetic acid; MCPP, 4-chloro-2-methyl-phenoxypropionic acid; MCPB, 4-chloro-2-methyl-phenoxybutyric acid; 2,4-DGP, 2,4-dichlorophenoxypropionic acid; 2,4,5-TCP, 2,4,5-trichlorophenoxypropionic acid; 2,3,4,6-TeCP, 2,3,4,6-tetrachlorophenol; PCP, pentachlorophenol; MCA, monochloroacetic acid; PCOC, p-chloro-o-cresol; TeCB, tetrachlorobenzene; HCP, hexachlorophenol; Ronnel, o,o-dimethyl-o-(2,4,5-trichlorophenoxy)-phosphorothioate; Erbon, 2-(2,4,5-trichlorophenoxy)-ethyl 2,2-dichloropropionate.

¶ Workers emigrated or vital status was unknown.

# Deaths in the 21,863 workers included in the analysis.

†† A total of 479 workers were exposed to phenoxy herbicides or chlorophenols but their exposure to TCDD was unknown.

as 2,4-dichlorophenoxyacetic acid and 4-chloro-2-methyl-phenoxyacetic acid. Estimation of duration of exposure to chemicals took into account the department in which production occurred and the dates of production or spraying of each chemical.

TCDD serum levels were measured in 573 workers from 10 companies in seven countries (table 2) (21, 22, 30, 35–40; Mariette Hooiveld, Wageningen Agricultural University (Wageningen, The Netherlands), personal communication, 1996). Sampling policy for the selection of workers providing blood samples differed by cohort. There was variation among cohorts in terms of the time elapsed between the last day of

occupational TCDD exposure and the drawing of blood for serum analysis. Mean TCDD levels at the time of measurement ranged from 3.2 pg/g in a German cohort to 402 pg/g in another German cohort (table 2). Because TCDD has a long half-life, estimated at 7–12 years (41, 42), the wide variation in mean TCDD levels measured at the time of blood drawing may not accurately reflect the differences that existed on the last day of occupational exposure to TCDD. The levels do indicate, however, that production workers have higher serum TCDD levels than sprayers, and substantially higher levels than the general population (table 2).

TABLE 2. Exposure to TCDD\* among 573 workers in 10 cohorts included in the IARC\* International cohort study, 1939–1992

Cohort no. and country (reference)	Exposed workers				Comments
	No. of samples and sampling scheme	Work history	Year of blood drawing	Measured mean TCDD levels (pg/g)†,‡	
1, Australia (35)	37, random stratified	Sprayers, minimum spraying of 12 months, first employed from before 1965 until 1990	1990	NA* (2–34)§	Highest mean exposure rate was estimated at 2.7 ppt* per month for subjects spraying before 1965
2, Austria (36)	9, nonrandom	Production workers with chloracne, exposed about 17 years earlier	1990	389 (98–659)	Median TCDD level in four white-collar workers at the same plant was ~18 pg/g; in 17 workers not at the same plant, it was ~14 pg/g
9, The Netherlands¶	31, nonrandom	Production workers, first employed before 1975 for more than 1 year; workers present at industrial accident in 1963	1993	53 (1.9–194)	Mean in 16 nonexposed workers at the same plant was 8 pg/g; mean for 14 accident workers (a subset of the 31 exposed workers) was 96 pg/g (15.8–194)§
12, New Zealand (37)	9, nonrandom	Sprayers, first employed before 1960, mean duration of 2,4,5-T* spraying of 16 years	1988	53.3 (3.0–131)	Mean TCDD level in nine exposed subjects was 5.8 ppt
13, Sweden (30)	5, nonrandom	Production workers, employed 16–21 years earlier	1992	17 (9–37)	Mean TCDD level in five unexposed workers not working in the plant was 2 pg/g
21, Germany (40)	19, random stratified	Production workers	1996	3.2# (1.3–6.49)	Elevated values for some higher chlorinated dioxins and furans. Synthesis workers had highest levels (median TCDD = 3.8 ppt; median I-TEQ* = 35.4)
22, Germany (20, 21)	190, nonrandom	Production workers	1985–1994	141# (3–2,252)	Estimated mean level for total cohort of about 1,500 workers at end of employment (adipose tissue, 48 subjects; blood, 142 subjects)
24, Germany (38, 39)	20, nonrandom	Production workers with chloracne or other clinical symptoms, exposed between 1953 and 1976	1989–1992	401.7# (23–1,935)	
25 and 26, United States (22, 34)	253, all surviving members participating in medical study	Production workers, exposed 15–37 years earlier	1987–1988	233 (2–3,400)	Estimated mean on last day of occupational exposure was 2,000 ppt (range, up to 36,000). Mean in 79 unexposed neighbors in medical study from the same plants was 7 pg/g

\* TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; IARC, International Agency for Research on Cancer; NA, not available; ppt, parts per trillion; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; I-TEQ, International Toxic Equivalents.

† All values are pg/g lipid (equivalent to ppt).

‡ Measured level (not back-calculated). Levels are not strictly comparable between cohorts because of differences in time elapsed between last occupational exposure and drawing of blood.

§ Numbers in parentheses, range.

¶ Personal communication (Mariette Hooiveld, Wageningen Agricultural University, Wageningen, The Netherlands, 1996).

# Estimate.

### Statistical analysis

For external comparisons, standardized mortality ratios were calculated, with 95 percent confidence intervals based on the Poisson distribution, using the Person-Years computer program (43). The World Health Organization mortality data bank was used to compute national mortality rates by sex, age (in 5-year groups), and calendar period (in 5-year intervals, except when periods coincided with a revision of the *International Classification of Diseases*), from which expected numbers of deaths were derived. Underlying cause of death for deceased cohort members was retrieved from death certificate records in each country. Most soft-tissue sarcomas are coded on death certificates under the rubric "malignant neoplasms of connective and other soft tissue" (*International Classification of Diseases*, Ninth Revision (ICD-9) (44), code 171).

Within-cohort comparisons examining mortality from all neoplasms according to exposure to TCDD or higher chlorinated dioxins used Poisson multiple regression models. Rate ratios and 95 percent confidence intervals derived from this analysis were adjusted for country, age, sex, calendar period, time since first exposure, duration of exposure, and employment status. The GLIM statistical package (45) was used for this analysis.

### RESULTS

#### Workers exposed to any phenoxy herbicide or chlorophenol

In the total cohort of workers exposed to phenoxy herbicides or chlorophenols ( $n = 21,863$ ), all-cause mortality (table 3) was slightly lower than expected from national mortality rates in both men (4,026 deaths; standardized mortality ratio (SMR) = 0.97) and women (133 deaths; SMR = 0.98). This was mainly due to low mortality from circulatory and respiratory diseases.

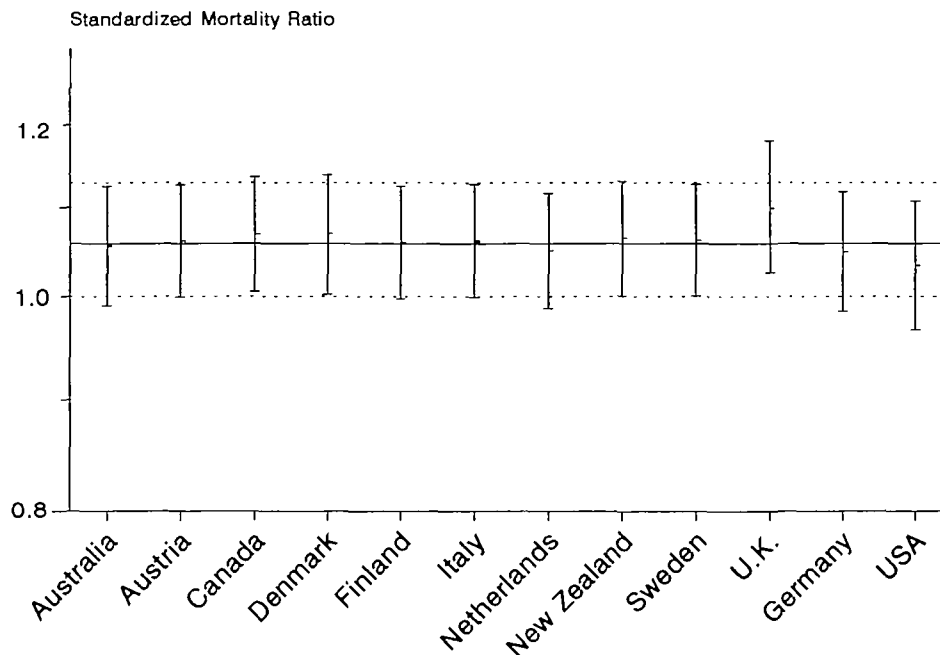
A small, statistically significant excess mortality from all neoplasms was observed in men (1,083 deaths; SMR = 1.07) but not in women (44 deaths; SMR = 0.93). Greater than 10 percent excess mortality from all neoplasms was observed in 15 cohorts from eight countries. The influence that the cohorts from each single country had on the joint risk estimates for all neoplasms was examined by consecutively omitting each country from the pooled results (figure 1). (Thus, each risk estimate shown on figure 1 was computed using data from 11 countries.) The joint risk estimate changed little from country to country when the cohorts of any particular country were omitted. The widest increases in the joint estimate were

**TABLE 3. Standardized mortality ratios among 21,863 international workers exposed to phenoxy herbicides or chlorophenols, by cause of death and sex, 1939–1992**

Cause of death (ICD-9* codes)	Males			Females		
	Observed no. of deaths	SMR*	95% CI*	Observed no. of deaths	SMR	95% CI
All causes	4,026	0.97	0.94–1.00	133	0.98	0.82–1.17
All malignant neoplasms (140–208)	1,083	1.07	1.01–1.13	44	0.93	0.68–1.25
Diseases of the endocrine system and the blood (240–289)	64	0.79	0.61–1.01	1	0.27	0.01–1.48
Mental disorders (290–319)	30	0.97	0.66–1.39	0	0	0–3.88
Diseases of the nervous system (320–389)	40	0.77	0.55–1.05	1	0.44	0.01–2.47
Diseases of the circulatory system (390–459)	1,738	0.91	0.87–0.95	48	1.00	0.73–1.32
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
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
Unknown cause	109			2		

\* ICD-9, *International Classification of Diseases*, Ninth Revision; SMR, standardized mortality ratio; CI, confidence interval.





**FIGURE 1.** Standardized mortality ratio (—) and 95% confidence interval (---) from pooled analysis of 36 cohorts of workers exposed to phenoxy herbicides, chlorophenols, and dioxins in 12 countries, 1939–1992. The vertical bars show the standardized mortality ratio (—) and 95% confidence interval (I) computed by consecutively omitting from the pooled results each country in turn.

seen with omission of the Danish and (particularly) British cohorts, and the widest decreases were seen with omission of the Dutch, German, and US cohorts. This pattern suggests that there are differences between those cohorts with a high percentage of workers exposed to TCDD or higher chlorinated dioxins and those without.

Twofold excess mortality (9 deaths; SMR = 2.00) was observed for soft-tissue sarcoma (table 4). The deaths occurred in Australia (one death), Denmark (one death in cohort 4), New Zealand (one death in cohort 12), the United Kingdom (two deaths in cohorts 19 and 20), and the United States (four deaths (two each in cohorts 32 and 33)). Lower excess risk was seen for non-Hodgkin's lymphoma (34 deaths; SMR = 1.27), with deaths occurring in Australia (two deaths), Canada (one death), Denmark (four deaths in cohort 4), the Netherlands (three deaths in cohort 9 and one death in cohort 10), New Zealand (one death in cohort 12), Sweden (one death), the United Kingdom (two deaths in cohort 14 and one death each in cohorts 17, 19, and 20), Germany (four deaths in cohort 22 and 2 deaths in cohort 24), and the United States (one death each in cohorts 25, 28, and 30, and seven deaths in cohort 33). Statistically significant excess mortality was observed from neoplasms of the respiratory system (SMR = 1.13), particularly from cancer of the larynx and from neoplasms in the cate-

gory "other respiratory organs" (ICD-9 codes 163–165), comprising the mediastinum, pleura, and undefined respiratory organs. Mortality from lung cancer was slightly increased (SMR = 1.09). Mortality from smoking-related cancers (cancers of the oral cavity, esophagus, pancreas, larynx, lung, urinary bladder, and kidney) was only slightly higher (565 deaths; SMR = 1.08, 95 percent confidence interval (CI) 0.99–1.17) than mortality from cancer at all other sites (562 deaths; SMR = 1.05, 95 percent CI 0.96–1.14). Finally, statistically significant excess mortality was observed from neoplasms of "other endocrine organs" (ICD-9 code 194) (SMR = 3.60), all five deaths being tumors of the suprarenal gland.

#### Workers exposed to TCDD or higher chlorinated dioxins

In the subgroup of 13,831 workers exposed to phenoxy herbicides contaminated with TCDD or higher chlorinated dioxins, statistically significant excess mortality was observed from all malignant neoplasms (710 deaths; SMR = 1.12). Mortality from all neoplasms increased slightly with time since first exposure to dioxins, while there was no consistent pattern of risk by calendar period or duration of exposure (table 5).

A twofold excess risk was seen for soft-tissue sarcoma (table 5). All deaths from soft-tissue sarcoma

**TABLE 4. Standardized mortality ratios for specific tumors in 21,863 international workers exposed to phenoxy herbicides or chlorophenols, by exposure to TCDD\* or higher chlorinated dioxins, 1939–1992**

Cause of death (ICD-9* code(s))	Workers exposed to TCDD or higher chlorinated dioxins			Workers not exposed to TCDD or higher chlorinated dioxins			All workers exposed to any phenoxy herbicide or chlorophenol†		
	No. of deaths	SMR*	95% CI*	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI
All causes	2,728	1.00	0.97–1.04	1,367	0.91	0.86–0.96	4,159	0.97	0.94–1.00
All malignant neoplasms	710	1.12	1.04–1.21	398	0.96	0.87–1.06	1,127	1.06	1.00–1.13
Oral cavity and pharynx (140–149)	22	1.30	0.82–1.97	3	0.45	0.09–1.31	26	1.09	0.71–1.60
Esophagus (150)	20	1.25	0.76–1.93	6	0.49	0.18–1.07	28	0.97	0.65–1.41
Stomach (151)	42	0.90	0.65–1.22	30	0.88	0.59–1.26	72	0.88	0.69–1.11
Colon (152–153)	52	1.00	0.75–1.31	33	1.16	0.80–1.63	86	1.06	0.85–1.31
Rectum (154)	29	1.32	0.88–1.89	14	0.74	0.41–1.24	44	1.06	0.77–1.42
Liver and biliary tract (155–156)	12	0.87	0.45–1.52	3	0.42	0.09–1.22	15	0.71	0.40–1.17
Pancreas (157)	30	0.98	0.66–1.39	16	0.86	0.49–1.39	47	0.94	0.69–1.25
Peritoneum and unspecific digestive organs (158–159)	5	1.23	0.40–2.88	4	1.83	0.50–4.68	10	1.58	0.76–2.91
Nose and nasal sinuses (160)	0	0	0.00–3.48	3	3.80	0.78–11.10	3	1.60	0.33–4.66
Larynx (161)	15	1.72	0.96–2.84	5	1.22	0.40–2.85	21	1.62	1.00–2.48
Lung (162)	225	1.12	0.98–1.28	148	1.03	0.87–1.21	380	1.09	0.98–1.20
Other respiratory organs (163–165)	9	3.20	1.46–6.08	3	1.24	0.26–3.62	12	2.25	1.16–3.93
Bone (170)	3	1.08	0.22–3.14	2	1.43	0.17–5.16	5	1.18	0.38–2.76
Connective tissue and other soft tissue (171)	6	2.03	0.75–4.43	2	1.35	0.16–4.88	9	2.00	0.91–3.79
Malignant melanoma (172)	5	0.48	0.16–3.21	4	0.95	0.26–2.42	9	0.61	0.28–1.16
Skin, other (173)	4	1.25	0.34–3.21	0	0	0.00–3.35	4	0.92	0.25–2.35
Breast, female (174)	9	2.16	0.99–4.10	3	0.53	0.11–1.56	12	1.23	0.63–2.14
Breast, male (175)	2	2.56	0.31–9.26	0	0	0.00–7.69	2	1.55	0.19–5.60
Cervix uteri (180)	0	0	0.00–3.84	3	1.79	0.37–5.22	3	1.14	0.23–3.32
Endometrium and uterus (179, 181–182)	3	3.41	0.70–9.96	1	1.16	0.03–6.48	4	2.30	0.63–5.89
Ovary (183)	0	0	0.00–2.62	1	0.45	0.01–2.51	1	0.28	0.01–1.53
Prostate (185)	43	1.11	0.81–1.50	25	1.10	0.71–1.62	68	1.10	0.85–1.39
Testis (186)	4	1.31	0.36–3.35	3	1.33	0.28–3.90	7	1.30	0.52–2.68
Other male genital organs (187)	1	1.27	0.03–7.05	1	1.69	0.04–9.44	2	1.42	0.17–5.12
Bladder (188)	24	1.42	0.91–2.11	10	0.65	0.31–1.20	34	1.04	0.72–1.45
Kidney (189)	26	1.60	1.05–2.35	3	0.31	0.06–0.91	29	1.10	0.74–1.59
Brain (191–192)	12	0.63	0.33–1.10	10	0.81	0.39–1.48	22	0.69	0.43–1.04
Thyroid (193)	2	1.36	0.16–4.91	2	2.17	0.26–7.85	4	1.65	0.45–4.23
Other endocrine organs (194)	2	2.25	0.27–8.12	3	6.38	1.32–18.65	5	3.60	1.17–8.39
Ill-defined and unspecified neoplasms (195–199)	41	1.34	0.96–1.82	19	1.04	0.63–1.63	60	1.21	0.92–1.56
Non-Hodgkin's lymphoma (200, 202)	24	1.39	0.89–2.06	9	1.00	0.46–1.90	34	1.27	0.88–1.78
Hodgkin's lymphoma (201)	8	1.29	0.56–2.53	1	0.27	0.01–1.51	10	0.99	0.48–1.82
Multiple myeloma (203)	9	1.21	0.55–2.29	8	1.59	0.69–3.13	17	1.34	0.78–2.14
Leukemia (204–208)	16	0.73	0.42–1.19	17	1.44	0.84–2.30	34	1.00	0.69–1.39

\* TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; ICD-9, *International Classification of Diseases*, Ninth Revision; SMR, standardized mortality ratio; CI, confidence interval.

† Exposure to TCDD or higher chlorinated dioxins could not be evaluated for 479 workers in one plant producing phenoxy herbicides, who are included in this column together with those shown in the two middle columns. In this plant, there were 64 deaths, including one death from soft tissue sarcoma and one from non-Hodgkin's lymphoma.

occurred 10 or more years after first exposure, and the risk appeared to be higher among subjects with a long duration of exposure and among persons first employed before 1965. Four additional soft-tissue sarco-

mas (three deaths in the United States (46) and one case in New Zealand) were registered among workers who either were alive at the end of follow-up or had a different cause of death given on the death certificate.

TABLE 5. Standardized mortality ratios for selected neoplasms in 13,831 international workers exposed to TCDD\* or higher chlorinated dioxins, by time since first exposure, duration of exposure, year of first exposure, and job title, 1939-1992

	All neoplasms			Lung cancer			Non-Hodgkin's lymphoma			Soft-tissue sarcoma		
	No. of deaths	SMR*	95% CI*	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI
Years since first exposure												
0-9	100	0.96	0.78-1.17	34	1.22	0.85-1.71	2	0.63	0.08-2.26	0	[0.59]†	0.00-6.25
10-19	216	1.08	0.94-1.24	64	1.04	0.80-1.32	8	1.45	0.63-2.87	3	3.13	0.64-9.13
≥20	394	1.20	1.09-1.33	127	1.15	0.96-1.37	14	1.63	0.89-2.73	3	2.27	0.47-6.64
Duration of exposure (years)‡												
<1	170	1.14	0.98-1.33	54	1.12	0.84-1.47	11	2.43	1.21-4.35	0	[0.85]	0.00-4.34
1-4	222	1.23	1.07-1.40	70	1.27	0.99-1.61	6	1.20	0.44-2.62	1	1.18	0.03-6.56
5-9	113	1.09	0.90-1.31	36	1.15	0.80-1.59	3	1.14	0.23-3.32	2	4.76	0.58-17.20
10-19	135	1.13	0.95-1.34	44	1.13	0.82-1.52	2	0.66	0.08-2.37	3	6.52	1.35-19.06
≥20	59	0.92	0.70-1.19	20	0.90	0.55-1.40	2	1.21	0.15-4.38	0	[0.27]	0.00-13.66
Year of first exposure												
<1955	335	1.12	1.00-1.25	107	1.13	0.92-1.36	12	1.49	0.77-2.60	3	2.52	0.52-7.37
1955-1964	242	1.17	1.03-1.33	81	1.20	0.96-1.50	9	1.65	0.75-3.12	2	2.15	0.26-7.77
1965-1974	109	1.03	0.84-1.24	31	0.97	0.66-1.38	3	0.96	0.20-2.80	1	1.52	0.04-8.44
≥1975	24	1.23	0.78-1.92	6	1.05	0.38-2.28	0	[0.62]	0.00-5.95	0	[0.14]	0.00-28.35
Job title												
Main production	286	1.17	1.04-1.31	93	1.20	0.97-1.47	9	1.33	0.61-2.52	2	1.61	0.20-5.83
Maintenance	99	1.23	1.00-1.49	38	1.39	0.98-1.91	1	0.46	0.01-2.56	1	2.78	0.07-15.48
Other exposed job	100	1.22	0.99-1.48	21	0.80	0.50-1.23	10	4.85	2.33-8.93	1	2.78	0.07-15.48
Unspecified task	35	0.93	0.65-1.29	15	1.16	0.65-1.92	0	[0.85]	0.00-4.34	0	[0.14]	0.00-26.35
Sprayer	190	1.02	0.88-1.18	58	1.03	0.78-1.34	4	0.73	0.20-1.88	2	2.47	0.30-8.92
Total	710	1.12	1.04-1.21	225	1.12	0.98-1.28	24	1.39	0.89-2.06	6	2.03	0.75-4.43

\* TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; SMR, standardized mortality ratio; CI, confidence interval.

† In cells with no observed deaths, the number of expected deaths is shown in square brackets instead of the SMR.

‡ Information on 11 workers was missing.

Mortality from non-Hodgkin's lymphoma (24 deaths; SMR = 1.39) was slightly elevated, and it increased with time since first exposure (table 5). The highest risks were observed among workers with less than 1 year's duration of exposure, among workers first employed before 1965, and among workers in "other exposed jobs."

Mortality from lung cancer was only slightly elevated (SMR = 1.12). It was not associated with any of the time-related exposure variables, and was highest among maintenance workers and cleaners (table 5). Statistically significant excess mortality was observed from all respiratory neoplasms, a category which, excluding lung cancer, includes cancers of the nose and larynx and "other respiratory neoplasms" (table 4). All nine deaths in this latter category were coded as neoplasms of the pleura (five deaths in Germany, two deaths in the Netherlands, and one death each in Australia and New Zealand). Mortality from "other respiratory neoplasms" increased with time since first exposure and was highest in maintenance workers (4 deaths; SMR = 9.52).

A statistically significant excess risk was observed for kidney cancer (table 4). However, there was no trend by latency (at 0–9 years since first exposure, SMR = 1.61; at 10–19 years, SMR = 1.55; and at  $\geq 20$  years, SMR = 1.64) or by duration of exposure. The highest risk was observed among workers in "other exposed jobs" (8 deaths; SMR = 3.74). Elevated risks were observed for breast cancer in both women and men and for endometrial cancer. The increased mortality from breast cancer was confined to female workers in cohort 22 in Germany (9 deaths; SMR = 2.84, 95 percent CI 1.30–5.39). Similarly, two of three deaths from endometrial cancer occurred in this plant. Finally, an excess risk was seen for cancer of "other endocrine organs," both deaths being due to tumors of the suprarenal glands.

We could distinguish three cohorts with exposure to higher chlorinated dioxins but not to TCDD (cohorts 6, 15, and 21), including a total of 842 exposed workers. Mortality from all neoplasms was slightly lower in these three cohorts (41 deaths; SMR = 1.02, 95 percent CI 0.74–1.39) compared with mortality in the entire group of workers exposed to TCDD or higher chlorinated dioxins (table 5). No deaths from soft-tissue sarcoma (0.17 expected) or non-Hodgkin's lymphoma (0.70 expected) were registered in these three cohorts, while mortality from lung cancer was higher (19 deaths; SMR = 1.48, 95 percent CI 0.89–2.31) than that in TCDD-exposed workers.

#### **Workers not exposed to TCDD or higher chlorinated dioxins**

In the subgroup of 7,553 workers with exposure to phenoxy herbicides and chlorophenols but with mini-

mal or no exposure to TCDD or higher chlorinated dioxins, mortality from all neoplasms (398 deaths; SMR = 0.96), non-Hodgkin's lymphoma (SMR = 1.00), and lung cancer (SMR = 1.03) was close to that expected, while there was a slight elevation for soft-tissue sarcoma (SMR = 1.35, based on two deaths) (table 4). For none of these neoplasms was there a consistent trend in risk observed by time since first exposure, duration of exposure, or calendar period of first exposure (table 6). Three additional cases of soft-tissue sarcoma (among persons alive at the end of follow-up) were registered in Denmark based on the combination of topography and morphology codes in the national cancer registry. Statistically significant excess risk was seen only for the category "other endocrine tumors," all three deaths being due to tumors of the suprarenal glands. High risks, although not statistically significant, were seen for sinonasal and thyroid cancers.

#### **Internal comparisons using Poisson regression modeling**

In the Poisson regression analysis, workers exposed to TCDD or higher chlorinated dioxins had an increased risk of mortality from all neoplasms (rate ratio = 1.29, 95 percent confidence interval 0.94–1.76) compared with workers in the same cohort with no exposure to TCDD or higher chlorinated dioxins (table 7). An important problem encountered when fitting this model was the existing collinearity between "country" and "exposure to TCDD or higher chlorinated dioxins." This occurred because, in some countries, the majority of workers were characterized either as exposed or as nonexposed to TCDD or higher chlorinated dioxins. Therefore, although the effect estimate (rate ratio) was likely to be more valid than the standardized mortality ratios, it became less precise. The effect of the collinearity on the confidence intervals of the rate ratios can be seen when the results shown in table 7 are compared with those of a regression model not including country (rate ratio = 1.16, 95 percent CI 1.02–1.32). The latter result is similar to the ratio of the standardized mortality ratios shown in table 4 ( $1.12/0.96 = 1.17$ ).

#### **DISCUSSION**

Chronic bioassays and mechanistic data have shown that dioxins and furans, particularly TCDD, are extremely potent carcinogens, but the epidemiologic evidence is not consistent. The findings of this international study of 36 cohorts from 12 countries indicate that exposure to herbicides contaminated with dioxins is associated with a small increase in overall cancer

TABLE 6. Standardized mortality ratios for selected neoplasms in 7,553 international workers who were not exposed to TCDD\* or higher chlorinated dioxins, by time since first exposure, duration of exposure, year of first exposure, and job title, 1939-1992

	All neoplasms			Lung cancer			Non-Hodgkin's lymphoma			Soft-tissue sarcoma		
	No. of deaths	SMR*	95% CI*	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI
Years since first exposure												
0-9	55	1.02	0.77-1.33	25	1.49	0.96-2.20	0	[1.46]†	0.00-2.53	0	[0.30]	0.00-12.30
10-19	95	0.96	0.77-1.17	34	1.00	0.69-1.39	4	1.79	0.49-4.57	2	5.41	0.65-19.53
≥20	248	0.95	0.84-1.08	89	0.96	0.77-1.18	5	0.94	0.31-2.20	0	[0.75]	0.00-4.92
Duration of exposure (years)‡												
<1	200	1.08	0.93-1.24	75	1.17	0.92-1.46	6	1.45	0.53-3.15	2	2.90	0.35-10.47
1-4	104	0.89	0.73-1.08	43	1.05	0.76-1.41	0	[2.63]	0.00-1.40	0	[0.43]	0.00-6.58
5-9	36	0.74	0.52-1.03	11	0.65	0.33-1.17	1	0.88	0.02-5.46	0	[0.15]	0.00-24.59
10-19	33	0.88	0.61-1.24	9	0.70	0.32-1.33	2	2.74	0.33-9.90	0	[0.11]	0.00-33.54
≥20	23	1.04	0.66-1.57	9	1.20	0.55-2.28	0	[0.41]	0.00-9.00	0	[0.05]	0.00-73.78
Year of first exposure												
<1955	227	0.98	0.86-1.12	90	1.05	0.85-1.30	4	0.89	0.24-2.28	0	[0.88]	0.00-5.43
1955-1964	94	0.96	0.77-1.17	30	1.02	0.70-1.44	3	1.40	0.29-4.08	1	3.03	0.08-16.88
1965-1974	62	0.91	0.70-1.17	18	0.88	0.57-1.44	2	1.10	0.13-3.99	1	3.23	0.08-17.97
≥1975	15	0.90	0.51-1.49	5	1.03	0.33-2.35	0	[0.53]	0.00-6.96	0	[0.10]	0.00-36.89
Job title												
Main production	103	1.07	0.87-1.29	39	1.32	0.94-1.81	1	0.46	0.01-2.58	0	[0.35]	0.00-10.54
Maintenance	98	0.87	0.71-1.07	33	0.83	0.57-1.17	4	1.81	0.49-4.63	0	[0.33]	0.00-11.16
Other exposed job	55	0.79	0.59-1.02	11	0.48	0.24-0.86	3	1.90	0.39-5.55	1	3.85	0.10-21.43
Unspecified task	9	1.16	0.53-2.20	5	1.99	0.65-4.65	0	[0.19]	0.00-19.42	0	[0.04]	0.00-92.23
Sprayer	133	1.04	0.87-1.23	60	1.22	0.93-1.57	1	0.35	0.01-1.94	1	2.13	0.05-11.86
Total	398	0.96	0.87-1.06	148	1.03	0.87-1.21	9	1.00	0.46-1.90	2	1.35	0.16-4.88

\* TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; SMR, standardized mortality ratio; CI, confidence interval.

† In cells with no observed deaths, the number of expected deaths is shown in square brackets instead of the SMR.

‡ Information on nine workers was missing.

**TABLE 7. Mortality from all neoplasms (1,091 deaths) among workers in the IARC\* international cohort study, by exposure to TCDD\* or higher chlorinated dioxins, 1939–1992†,‡**

Variables in the model	RR*,§	95% CI*
Exposure to TCDD or higher chlorinated dioxins		
No¶	1.0	
Yes	1.29	0.94–1.76
Years since first exposure#		
0–9¶	1.0	
10–19	1.04	0.84–1.30
≥20	1.26	0.99–1.60
Duration of exposure (years)#		
<1¶	1.0	
1–4	1.01	0.86–1.18
5–9	0.96	0.79–1.17
10–19	1.06	0.87–1.30
≥20	0.99	0.75–1.29
Year of first exposure#		
<1960¶	1.0	
1960–1969	1.23	0.83–1.49
1970–1979	1.28	0.87–1.90
≥1980	1.14	0.76–1.70

\* IARC, International Agency for Research on Cancer; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; RR, rate ratio; CI, confidence interval.

† Analysis was limited to workers exposed to phenoxy herbicides or chlorophenols in the 35 cohorts characterized with regard to exposure to TCDD or higher chlorinated dioxins, and to those workers with known durations of exposure and known employment status.

‡ Internal comparisons using Poisson regression analysis.

§ Adjusted for the variables in the table and for age, sex, country, and employment status.

¶ Reference category.

# Exposure to TCDD or higher chlorinated dioxins or (for the comparison group) to phenoxy herbicides or chlorophenols not contaminated with TCDD.

risk and in risk for specific cancers. Several observations support this statement. First, the group of workers exposed to TCDD or higher chlorinated dioxins had, on average, clearly higher exposure to these chemicals than the general population. Second, in the subgroup of workers exposed to phenoxy herbicides and chlorophenols contaminated with TCDD or higher chlorinated dioxins, the mortality increases were more pronounced and more consistently associated with exposure than were those in workers exposed to uncontaminated phenoxy herbicides and chlorophenols. Finally, the increases in overall and specific cancer mortality were observed in several cohorts from different countries.

The validity of epidemiologic studies addressing the carcinogenicity of phenoxy herbicides and their contaminants has been questioned. Doubts have been expressed about the evaluation of exposure to herbicides and dioxins, particularly the evaluation of exposure to dioxins in case-control studies (5, 37), the potentially

confounding effects of other occupational exposures (5, 47) and of lifestyle factors such as smoking (48), and outcome misclassification resulting from use of death certificate information (46). The most important consideration when interpreting the findings of this international study is exposure misclassification, which, if anything, has probably led to an underestimation of the true risk. The validity of our results may also have been influenced, to a lesser extent, by inaccuracy of diagnoses from death certificates and by confounding by other workplace chemical exposures or lifestyle factors.

The dichotomous classification of exposure used in this analysis distinguished two groups of workers: those with and those without substantial exposure to TCDD or higher chlorinated dioxins. However, this categorization has undoubtedly led to some misclassification of exposure between the two groups and to considerable variability of exposure within groups, particularly in the TCDD-exposed group. TCDD levels were determined in 574 workers from 10 plants, but the available information did not allow for quantitative evaluation of levels of exposure to TCDD for the entire international cohort. Average estimated TCDD levels in production workers at the time of blood drawing ranged from a low of 3.2 pg per gram of extracted fat in a German cohort (a cohort in which elevated levels of higher chlorinated dioxins were found, however (40)) to a mean of 233 pg/g from two NIOSH cohorts (34) (estimated as 2,000 parts per trillion at the end of employment, ranging to 36,000 parts per trillion) and 402 pg/g among workers with chloracne in another German cohort (36). These values should be compared with the average levels below 5 pg/g seen in the general population of most industrialized countries. Furthermore, TCDD and other polychlorinated dioxins and furans have been detected in the end products, reactor products, and waste streams of many plants producing contaminated herbicides (33, 34). The group of workers classified as not exposed or minimally exposed to TCDD undoubtedly included some workers who had been professionally exposed to dioxins, but it is unlikely that, on average, their level of exposure was as high as that in the exposed group. The cutoff point of average production of 10 tons per year of herbicides or chlorophenols known to be contaminated with TCDD or higher dioxins is low relative to the normal yearly production volumes in these plants of hundreds or thousands of tons of herbicides and chlorophenols (33). This definition of substantial exposure to TCDD was set a priori in the first follow-up of the IARC cohort (25), and classifies as nonexposed to TCDD and higher chlorinated dioxins those workers who produced

or sprayed predominantly 2,4-dichlorophenoxyacetic acid or 4-chloro-2-methyl-phenoxyacetic acid, herbicides known not to contain TCDD. The few measurements of TCDD in workers classified in this analysis as nonexposed to this compound show that they had lower levels than those measured in workers classified as exposed (table 2).

The identification of soft-tissue sarcoma in epidemiologic studies using death certificates has been shown to be inaccurate (46). Most sarcomas are likely to be coded under the rubric "malignant neoplasms of connective and other soft tissue" (ICD-9 code 171), but errors may be as high as 50 percent (46). Given the small number of deaths from soft-tissue sarcoma in this study, these errors may have had a considerable impact on the magnitude of the risk estimates, and results should be interpreted with caution. However, the pattern of higher mortality from soft-tissue sarcoma in the cohort overall and of a higher risk in the TCDD-exposed subgroup seems to hold true irrespective of errors in diagnosis. In this cohort, a pathology review was available for eight out of nine deaths from soft-tissue sarcoma. The death certificate diagnosis of two soft-tissue sarcomas occurring in workers exposed to TCDD was not confirmed when slides of the tumors were reviewed independently by two pathologists (22). It is unlikely that such false-positive diagnoses occurred at a higher rate in the cohort than in the general population, especially since seven out of nine deaths from soft-tissue sarcoma occurred before 1980, the time period when an association between this malignancy and exposure to phenoxy herbicides and chlorophenols was first suggested in an epidemiologic study (49). Apart from the nine soft-tissue sarcomas identified from death certificates among workers exposed to phenoxy herbicides and contaminants, another three deaths (two confirmed pathologically and one through medical records) were identified through a review of selected diagnoses in death certification in the NIOSH cohorts (46); three further cases were identified in Denmark on the basis of the combination of topography and morphology codes in the cancer registry, and one was identified in New Zealand from cancer registration records. Of those seven additional deaths/cases, four occurred among workers exposed to phenoxy herbicides contaminated with TCDD and higher chlorinated dioxins and three in workers exposed to uncontaminated phenoxy herbicides.

Confounding by other occupational carcinogenic exposures such as 4-aminobiphenyl, 2-naphthylamine (47), and other pesticides (5) has been proposed as one explanation for the increased risk of soft-tissue sarcoma among production workers or sprayers. In a nested case-control study carried out in part of this

cohort (excluding the NIOSH cohorts and the latest years of follow-up in the remaining cohorts), it was shown that other exposures occurring in the workplace were not important determinants of the risk of soft-tissue sarcoma or of non-Hodgkin's lymphoma (26). Furthermore, excess cancer mortality was found in many workforces making up the international cohort, each exposed to a different range of chemicals. This makes confounding by an unidentified chemical exposure unlikely. It is probable that exposure to asbestos occurred in some plants, given the excess mortality from "other respiratory" neoplasms. This disease group may include pleural mesothelioma but also unrecognized soft-tissue sarcoma or secondary tumors. However, any effect of exposure to asbestos in this cohort could be expected to be minimal given the small number of deaths in this category and in the category "neoplasms of the peritoneum and other digestive organs"—even if it is assumed that all of these deaths were due to mesothelioma.

The generalized increases in cancer risk in the TCDD-exposed group are unusual in occupational cohorts because of the healthy worker effect and because most carcinogens precipitate specific cancers. However, this pattern of excess mortality is consistent with evidence from animal experiments in which TCDD has been demonstrated to cause cancer at multiple sites (2). While the possible confounding effects of lifestyle factors cannot be ruled out, there is some evidence here to suggest that they have not played a major role in the excesses that were observed. There was no evidence in this cohort of excess risk from nonmalignant respiratory disease or liver cirrhosis; and where information on smoking was available, the data suggested that smoking had a minimal effect on the overall risk pattern (18, 22). Finally, a potentially confounding effect by general lifestyle factors should, in part, be controlled in the internal comparisons of workers producing phenoxy herbicides with or without contamination by dioxins.

Mortality from all neoplasms, soft-tissue sarcoma, and non-Hodgkin's lymphoma increased with time since first exposure to herbicides contaminated with dioxins. Mortality from soft-tissue sarcoma and non-Hodgkin's lymphoma tended to be highest in workers first employed before 1970, when exposures were probably highest. Kidney cancer was among the cancers showing an overall statistically significant increase in mortality, but there was no clear association with any of the time-related exposure variables. The increase in breast cancer among women was solely due to the observed increase in a German cohort (20, 21) which included most of the TCDD-exposed female production workers in the international study, and

which was not included in the previous follow-up of the IARC study (25). This finding is in contrast with results from the Seveso population (28), which was accidentally exposed to high levels of dioxin but which has been followed for a shorter period than the German cohort. It is also in contrast with results of the previous follow-up of the IARC cohort, which included fewer female production workers (50). Exposure to organochlorine compounds with estrogenic activity, such as dichlorodiphenyltrichloroethane, has been associated with excess breast cancer risk (51), but the epidemiologic evidence is contradictory (52). It has been postulated, however, that dioxin-like compounds have an antiestrogenic effect (53), and in some of the chronic bioassays TCDD inhibited the development of spontaneous mammary and uterine tumors in female rats (54).

In conclusion, the latest findings from this international study of 36 cohorts from 12 participating countries indicate that exposure to herbicides contaminated with dioxins may be associated with a small increase in overall cancer risk and in the risk for specific cancers. Any evaluation of these findings must be balanced by the knowledge that these risks were associated with considerably higher levels of exposure to TCDD and higher chlorinated dioxins than those typically experienced by the general population.

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