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Cancer mortality in workers exposed to chlorophenoxy herbicides and chlorophenols

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Epidemiological studies have revealed an increased risk of cancer, notably soft-tisuesarcomas and non-Hodgkin's lymphomas, in people occupationally exposed to chlorophenoxy herbicides, including those contaminated by 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin (TCDD). We report here a historical cohort study of mortality in an international register of 18 910 production workers or sprayers from ten countries

Exposure was reconstructed through questionnaires. factory or spraying records. and job histories Cause-specific national death rates were used as reference. No excess was observed in all-cause mortality for all neoplasms. for tre most common epithelial cancers, or for lymphomas. A statistically non-significant two-fold excess risk. based on 4 observed deaths, was noted for soft-tissue sarcoma with a standardised mortality ratio (SMR) of 196 and 95% confidence interval (CI) 53–502; this was concentrated as a six-fold statistically significant excess. occurring 10–19 years from first exposure in the cohort as a whole (SMR = 606 [165–1552]) and. for the same time period as a nine-fold excess among sprayers (SMR = 882 [182 2578]). Risks appeared to be increased for cancers of the testicle. thyroid. other endocrine glands and nose and nasal cavity, based on small numbers of deaths

The excess of soft-tissue sarcomas among sprayers is compatible with a causal role oi chlorophenoxy herbicides but the excess does not seem to be specifically associated with those herbicides probably contaminated by TCDD.

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Introduction

Chlorophenoxy herbicides have been used extensively since the mid-1950s for control of weeds and for removing unwanted brush on non-crop land.' In the 1960s an equal mixture of 2,4-dichloro and 2,4,5-trichloro phenoxyacetic acids agent orange) was heavily used in South Vietnam and Cambodia for defoliation by the US armed forces. Since 1969 in several industrialised countries, production and use of some compounds. and especially of 2,4,5-trichlorophenoxyacetic and 2,4,5-T and its derivatives hair been reduced or banned Chlorinated phenols are

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intermediates in the production of these chlorophenoxy herbicides and are also used directly for wood preservation. Both groups of compounds may be contaminated during the production process with polychlorinated dioxins and furans, including tetrachlorodibenzo-*p*-dioxin (dioxin, TCDD), which is a widespread contaminant of the general environment.[1]

Studies of cancer risks have revealed excesses for soft-tissue sarcoma and non-Hodgkin's lymphoma in populations exposed to chlorophenoxy herbicides, chlorinated phenols, dioxins, and furans during manufacture and spraying or after accidents.[2-26] In 1987 an International Agency for Research on Cancer (IARC) working group concluded that there was "limited" evidence of human carcinogenicity for chlorophenoxy herbicides and chlorinated phenols.[27] A recent paper,[16] focusing on exposure in chemical plants to "dioxin", reported excesses for cancer of the respiratory tract and soft-tissue sarcoma, but could not exclude the contribution of smoking and other exposures in the workplace. We present here the first detailed mortality analysis of a large international cohort of workers (the International Register of Workers Exposed to Phenoxy Herbicides and their Contaminants) set up by the IARC in association with the US National Institute of Environmental Health Sciences (NIEHS). Results for some cohorts in the register have been reported earlier[4,8,9,13] but for different follow-up periods.

Material and methods

Study population

The register incorporates information on 17 372 male workers, 1537 female workers, and 1 of unknown sex, distributed among twenty cohorts from ten countries (table 1). Since publication of the register population[28] minor corrections have led to the exclusion of 62 workers found to be ineligible. Workers from one British company which both produced and sprayed herbicides have been separated here into two cohorts (14 and 20).

The register includes workers ever employed in production or spraying, except in the cohorts from Australia, Canada, and New Zealand, in which minimum employment periods of 1 year, 6 months, and 1 month, respectively, were specified. Eligibility of cohorts depended on the completeness at company level of records identifying workers and on the ability to ensure tracing rates of 95% or more. Follow-up for mortality was based either on computerised national record systems or on active follow-up procedures. Additional information on cases of soft-tissue sarcoma and non-Hodgkin's lymphoma cases was sought from medical records and cancer registries. Denmark, New Zealand, Finland, and Sweden provided incidence data from population-based cancer registries. Person-years at risk were calculated from 1955 onwards since only from that year were cancer-specific mortality rates available for all participating countries. Excluded from the analysis were 220 workers who either died or were lost to follow-up before 1955, 105 workers with unknown year of first exposure, 131 with unknown year of birth, 1 with unknown sex, and 63 with other missing information. The 18 390 workers included comprise 16 863 males and 1527 females, and 307 488 person-years at risk were accumulated, with an average follow-up of 17 years. Workers lost to follow-up constituted 5% of the total cohort, and in no individual cohort did this proportion exceed 10%.

Exposure assessment

Questionnaires were constructed for factories producing chlorophenoxy herbicides or chlorinated phenols and for spraying cohorts. These were completed with the assistance of industrial hygienists, workers, and/or factory personnel. Industry and other production records were also used. Job histories were examined when available. Workers were classified as exposed, probably exposed, exposure unknown, or non-exposed:

TABLE I—DESCRIPTION OF COHORTS IN INTERNATIONAL REGISTER

Cohort	No of subjects	Type of cohort	Sex	Period at risk	Main chemicals sprayed or produced
1. Australia	2177	S	M	1955–83	2,4,5-T 2,4-D
2. Austria	159	PC	B	1971–88	2,4,5-T 2,4-D MCPA 2,4,5-TCP 2,4-DCP
3. Canada	1222	S	M	1955–82	2,4,5-T 2,4-D
4. Denmark*	3843	P	B	1955–82	MCPA MCPP 2,4-DP
5. Denmark	616	P	B	1955–82	2,4-DP MCPA
6. Finland	62	P	B	1955–85	2,3,4,6-TeCP
7. Italy	325	P	B	1970–86	2,4,5-TCP
8. Italy	81	P	B	1967–86	2,4-D MCPA
9. Netherlands	1167	P	B	1955–85	2,4,5-T 2,4,5-TCP
10. Netherlands	1143	?	B	1955–88	MCPA MCPP 2,4-D
11. New Zealand	1938	P	B	1955–87	2,4,5-T 2,4-D MCPA MCPB 2,4,5-TCP
12. New Zealand	780	S	B	1973–87	2,4,5-T MCPA 2,4-D
13. Sweden	270	P	B	1965–86	2,4-D MCPA MCPP 2,4,6-TCP
14. UK*	1531	P	M	1955–87	MCPA
15. UK	145	P	M	1960–85	PCP
16. UK	1147	P	M	1975–87	2,4-DB MCPA MCPP 2,4-D 2,4-DP 2,4,5-T
17. UK	353	P	M	?–87	MCPB PBA
18. UK	275	P	M	1969–87	2,4-DP 2,4-DB MCPA MCPP
19. UK	528	P	M	1969–87	MCPA MCPP 2,4-D 2,4-DP
20. UK	2013	S	M	1955–87	MCPA

S = sprayers, P = production, PC = chloracne cases in production
M = males, B = both sexes
2,4-D = 2,4-dichlorophenoxyacetic acid, 2,4-DP = 2-(2,4-dichlorophenoxy)-propanoic acid, 2,4-DB = 4-(2,4-dichlorophenoxy)-butanoic acid, 2,4,5-T = (2,4,5-trichlorophenoxy) acetic acid, 2,4,5-TP = 2-(2,4,5-trichlorophenoxy)-propanoic acid, MCPA = (4-chloro-2-methyl-phenoxy)-acetic acid, MCPP = 2-(4-chloro-2-methyl-phenoxy)propanoic acid, MCPB = 4-(4-chloro-2-methyl-phenoxy) butanoic acid, 2,4-DCP = 2,4-dichlorophenol, 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, PCP = pentachlorophenol, PBA = phenoxybutyric acid
*35 additional subjects from Denmark and the United Kingdom were exposed during both production and spraying.
†Formulators and packers 1982–87, handymen 1967–87, process workers 1963–87.

Exposed workers (n = 13 482) comprise all known to have sprayed chlorophenoxy herbicides and all who had worked in any of the following departments at factories producing chlorophenoxy herbicides or chlorinated phenols: synthesis, finishing, formulation, packing, maintenance, repair, laboratory, chemical effluent/waste, cleaning, shipping, transportation, stores, warehouse, plant supervision, clearing during accident, and other and unclassified exposure.

Probably exposed workers (n = 416) comprise all workers in cohorts 15 and 18, no job titles were available but it was judged that most workers would have been exposed. Exposed and probably exposed are aggregated for some analyses, as indicated in the text.

Workers with unknown exposure (n = 541) had no information on exposure status.

Non-exposed workers (n = 3951) were those never employed in the parts of factories which produced chlorophenoxy herbicides or chlorinated phenols and who never sprayed chlorophenoxy herbicides came mainly from Australia, Denmark, Netherlands, New Zealand, and UK (224, 1966, 1283, 214, and 180, respectively). Although not exposed to chlorophenoxy herbicides they were exposed to other chemicals, such as dyes and rodenticides.

Workers were also categorised as producers (12 492) and sprayers (5898).

Exposed and probably exposed workers were also classified by groups of chemicals produced or sprayed (9377 chlorophenoxy herbicides, 408 chlorinated phenols, and 4113 both) and within the manufacturing cohorts by department (3034 main production, 1522

TABLE II—MORTALITY BY DETAILED CAUSE AND EXPOSURE TO CHLOROPHENOXY HERBICIDES AND/OR CHLOROPUENOLS. BOTH SEXES

Cause of death (ICD 8)	SMR (95% CI) (no of observed deaths)			
	Exposed	Probably exposed	Non-exposed	Unknown
uses	92* (88–96) *1870*	122 (93–158) *58*	103 (93–114) *392*	157* (119–203)
nant neoplasms (140–207)	101 (92–110) *499*	129 (74–210) *16*	99 (81–120) *100*	135 (72–231) *11*
cal cavity and pharynx (140–149)	116 (58–207) *11*	0 (0–1942) *0*	59 (2–330) *1*	667 (17–3714)
ophagus (150)	60 (26–119) *8*	0 (0–971) *0*	255 (83–595) *5*	0 (0–2170) *0*
nach (151)	89 (64–121) *40*	0 (0–305) *0*	85 (34–175) *7*	0 (0–492) *0*
stine, except rectum (152–153	113 (81–154) *41*	0 (0–479) *0*	67 (22–156) *5*	164 (4–913) *1*
tum (154	110 (70–163) *24*	179 (5–995) *1*	43 (5–156) *2*	238 (6–1327) *1*
er, gallbladder and bileduct (155–156	44 (12–113) *4*	0 (0–2170) *0*	53 (10–300) *2*	435 (11–2423)
creas (157	112 (73–164) *26*	185 (5–1032) *1*	61 (13–177) *3*	0 (0–820) *0*
roneum (158)	156 (19–564) *2*	0 (0–12 296) *0*	0 (0–1085) *0*	3333 (84–18 572)
recified digestive organs (159)	331 (90–846) *4*	0 (0–12 296) *0*	870* (105–3141) *2*	0 (0–18 444)
e & nasal cavities (160)	241 (6–1343) *1*	0 (0–12 296) *0*	0 (0–217) *0*	0 (0–369)
rnx (161)	145 (63–285) *8*	0 (0–3074) *0*	90 (2–502) *1*	0 (0–3074) *0*
ches, bronchus and lung (162)	102 (87–118) *173*	221* (110–395) *11*	140 (100–190) *40*	110 (23–320) *3*
nective and other soft tissue (171	201 (55–515) *4*	0 (0–7378) *0*	0 (0–878) *0*	0 (0–12296) *0*
(172–173)	32* (7–94) *3*	0 (0–2838) *0*	144 (30–422) *3*	0 (0–2049) *0*
e breast (174)	345 (42–1246) *2*	0 (0–36 889) *0*	0 (0–3689) *0*	0 (0–36 889) *0*
ale breast (174)	30 (1–166) *1*	— —	114 (31–293) *4*	0 (0–1537) *0*
ale genital organs (180–184)	94 (19–274) *3*	— —	89 (18–260) *3*	0 (0–753) *0*
state (185)	111 (75–158) *30*	0 (0–671) *0*	40 (5–143) *2*	217 (6–1211) *1*
ns (186)	225 (90–464) *7*	0 (0–5270) *0*	0 (0–444) *0*	0 (0–3074) *0*
lder (188)	80 (42–136) *13*	227 (6–1266) *1*	56 (7–202) *2*	0 (0–1085) *0*
ney (189)	97 (48–173) *11*	0 (0–1537) *0*	35 (1–197) *1*	0 (0–1366) *0*
ain (191–192)	38* (14–82) *6*	0 (0–1025) *0*	96 (18–250) *3*	556 (67–2007)
Thyroid gland (193)	147 (30–430) *3*	0 (0–12 296) *0*	0 (0–1230) *0*	0 (0–18 444) *0*
Other endocrine gland (194	362 (98–928) *7*	0 (0–36 889) *0*	0 (0–1942) *0*	0 (0–36 889) *0*
Ill-defined sites (195–199)	131 (83–197) *23*	0 (0–802) *0*	153 (50–357) *5*	323 (8–1797) *1*
Lymphosarcoma (200, 202)	97 (48–173) *11*	0 (0–1476) *0*	178 (46–455) *4*	0 (0–1757) *0*
Hodgkins disease (201)	39 (5–141) *2*	769 (19–4286) *1*	0 (0–332) *0*	0 (0–3353) *0*
Multiple myeloma (203)	69 (19–178) *4*	0 (0–2838) *0*	160 (19–578) *2*	0 (0–3074) *0*
Leukaemia and aleukaemia (204–207)	117 (70–186) *18*	0 (0–1118) *0*	88 (18–256) *3*	0 (0–1025) *0*
Benign and unspecified neoplasms (210–239)	199* (103–348) *12*	*0* (0–2459) *0*	317* (103–739) *5*	0 (0–2306) *0*
Circulatory system (390–458)	90* (84–97) *857*	111 (72–165) *25*	99 (84–116) *162*	113 (64–183) *16*
Respiratory system (460–519)	72* (53–96) *125*	94 (31–221) *5*	106 (69–156) *25*	191 (52–490) *4*
Accidents, poisonings, violence (E800–E999)	100 (86–116) *174*	169 (55–394) *5*	108 (77–146) *31*	319* (152–587) *16*
Unknown causes	— *50*	— *0*	— *11*	— *1*

*p<0·05

maintenance and cleaning, 1665 other, 1907 unclassifiable). A substantial number of workers producing chlorophenoxy herbicides may also have exposed to chlorophenols (eg, *p*-chloro-*o*-cresol) which are used as raw materials in the synthesis of chlorophenoxy acids. Exposure to the most toxic dioxin congener (2,3,7,8,-TCDD) may occur during production of 2,4,5-TCP and 2,4,5-T, and during spraying of herbicides containing 2,4,5-T or its derivatives.[5] Factories 1,5,6,8,10,14,15,17,18, and 20 in [illegible]845 had either not produced 2,4,5-T or had produced very little of it around 10 tonnes per year during the study period. Workers in these factories were exposed to various chlorophenoxy herbicides, [illegible]

regarded as statistically significant at $p < 0{\cdot}05$ (two-tail) when the CI does not include 100. The WHO Mortality Data Bank was used to compute national mortality reference rates for sex, age (in 5-year age groups), and calendar period (in 5-year periods, except when such a period coincides with an ICD revision). Duration of exposure was treated as a time-dependent variable in the allocation of person-years at risk. Poisson regression analysis was applied for selected sites.[10]

Coding

Coding of underlying cause of death was done nationally. A

TABLE III—MORTALITY FOR ALL MALIGNANT NEOPLASMS AND FOR SOFT-TISSUE SARCOMA AND NON-HODGKIN'S LYMPHOMA SEPARATELY BOTH SEXES

	All malignant neoplasms			Soft-tissue sarcomas			Non-Hodgkin's lymphomas		
	Obs	Exp	SMR (95% CI)	Obs	Exp	SMR (95% CI)	Obs	Exp	SMR (95% CI)
Exposure									
Exposed and probably exposed	515	508·55	101 (93–110)	4	2·04	196 (53–502)	11	11·04	99 (47–169)
Non-exposed	100	101·38	99 (81–120)	0	0·42	0 (0–878)	4	2·25	178 (48–455)
*Type of cohort**									
Production	253	258·01	98 (86–111)	1	1·03	97 (3–541)	8	5·36	149 (64–294)
Sprayers	262	249·94	105 (93–118)	3	1·01	297 (61–868)	3	6·28	49 (10–140)
*Chemicals produced or sprayed**									
Both	112	106·70	105 (86–126)	1	0·48	208 (5–1161)	4	2·37	169 (46–432)
Phenoxy	384	385·28	100 (90–110)	3	1·50	200 (41–585)	7	8·96	78 (32–161)
Chlorophenols	19	16·82	113 (68–176)	0	0·06	0 (0–6148)	0	0·31	0 (0–1190)
*TCDD exposure**									
Probable	236	215·12	110 (96–125)	2	1·00	200 (24–723)	5	5·76	87 (28–203)
Unlikely	279	293·76	95 (84–107)	3	1·04	193 (23–695)	6	5·88	102 (37–222)
*Years since first exposure**									
30 +	74	88·60	84 (66–105)	0	0·24	0 (0–1537)		1·68	119 (14–430)
20–29	171	159·19	107 (92–125)	0	0·52	0 (0–709)	3	3·38	89 (18–259)
10–19	170	166·19	102 (87–119)	4	0·66	606 (165–1552)		3·94	127 (41–296)
0–9	100	94·53	106 (86–129)	0	0·50	0 (0–738)	1	2·67	38 (1–209)
Duration of exposure (yr)*									
20 +	36	42·17	85 (60–119)	0	0·15	0 (0–2459)	1	1·02	98 (3–546)
10–19	74	76·16	97 (76–122)	2	0·29	690 (84–2491)	1	1·81	55 (1–308)
1–9	234	230·54	102 (89–115)	0	0·89	0 (0–415)	3	5·36	56 (12–164)
< 1	168	155·68	108 (92–126)	2	0·59	339 (41–1125)	6	3·35	179 (66–390)
*Department**									
Production	62	60·38	103 (79–132)	0	0·29	0 (0–1272)	2	1·40	143 (17–516)
Maintenance	40	42·02	95 (68–130)	0	0·15	0 (0–2459)	1	0·91	110 (3–612)
Other exposure	42	39·65	106 (76–143)	1	0·16	625 (16–3482)	1	0·90	333 (69–974)
Unclassified	107	114·10	94 (77–113)	0	0·15	0 (0–10541)		2·08	96 (12–347)

*Exposed and probably exposed workers are grouped together

exposure status had high all-auw mortality (table II), especially for accidents, poisoning, and violence including suicide (SMR = 319 [182–518]).

Table II gives SMRs (and 95% CIs) and observed deaths for major causes of death and for malignant neoplasms by site and exposure for both sexes combined since only 10 deaths from cancer were available for analysis among exposed females. Significant excesses were observed among males for malignant thyroid and benign and unspecified neoplasms in the exposed category, malignant neoplasms of trachea, bronchus and lung in the probably exposed category, and malignant neoplasms of unspecified digestive organs and benign and unspecified neoplasms in the non-exposed category; significant deficits were observed for malignant neoplasms of skin and of brain.

Exposed workers had SMRs above 200 for neoplasms of unspecified digestive organs, neoplasms of the nose and nasal cavity, soft-tissue sarcoma, breast cancer (in males) and for neoplasms of the testis, other endocrine glands and thyroid.

Table III gives combined SMRs for exposed and probably exposed workers of both sexes, for all neoplasms, soft-tissue sarcomas and non-Hodgkin's lymphomas. The pattern of risk for all neoplasms by time first exposure did not indicate a strong healthy worker effect, and mortality did not vary substantially between the groups examined.

Soft tissue sarcoma

4 deaths were observed, all among exposed male workers (table III). So increased risk was observed among production workers (1 death), whereas mortality appeared to be increased among sprayers (3 deaths, SMR = 297 [61–868]). All deaths occurred 10–19 years after first exposure, giving rise, for this time interval, to a six-fold excess risk in the cohort as a whole (table III) and an even greater excess among exposed sprayers (3 deaths, SMR = 882 [182–2579]). No differentiation in risk was observed in relation to duration of exposure or probable TCDD exposure. 5 additional cases of soft-tissue sarcoma were recorded in cohort members who were alive at the end of follow-up or who had died with a certified cause of death other than ICD 171. These included 1 non-fatal case in the non-exposed group. Details of all 9 cases are given in table IV.

Malignant lymphoma

14 deaths from non-Hodgkin's lymphoma (ICD 200, 202, 8th and 9th revision) were observed among men and 1 among women. 11 deaths were in exposed workers, all men. Mortality for exposed probably exposed workers was close to expected (SMR = 95) with production workers having a small statistically insignificant increase in mortality (5 deaths, SMR = 149; table III). 10 out of 11 deaths occurred more than 10 years after first exposure. 6 deaths occurred among workers exposed for less than a year, and no difference in risk could be seen in relation to exposure to TCDD or type of chemical produced. The highest SMR among production workers was for those in "other jobs" (transport, storage, laboratory workers, plant supervisors; 4 deaths from non-Hodgkin's lymphoma were observed among non-exposed workers in one Danish factory cohort [4]). Mortality for non-exposed workers was higher than that of all exposed

TABLE IV—DESCRIPTION OF 9 CASES OF SOFT TISSUE SARCOMAS

Case*	Sex, age	Year of death†	Cause of death	Histology‡	Longest held job	Years since first exposure	Years of exposure
1, Australia	M, 46	< 1980	Connective tissue lower limb (ICD 171)	Fibrosarcoma of the hip	Sprayer	16	16
2, Denmark	M, 32	< 1980	Connective tissue lower limb ICD 171	Neurofibrosarcoma, lower limb	Production, transportation storage	10	< 1
3, Denmark	M, 34	Alive, Jan. 1984		Mesenchymal sarcoma, possible liposarcoma, retroperitoneum	Production unspecified	14	< 1
4, Denmark	M, 47	< 1980	Ill-defined cancer	Haemangiopericytoma, back	Production transportation storage	21	8
5, Denmark	M, 64	< 1980	Prostate cancer	Leiomyosarcoma, prostate	Production, transportation storage	17	2
6, New Zealand	M, 35	Alive, Jan. 1988		Fibrous histiocytoma, lower limb	Sprayer	12	12
7, New Zealand	M, 55	1980 +	Connective tissue upper limb (ICD 171)	Neurilemmoma	Sprayer	14	12
8, UK	M, 43	< 1980	Connective tissue unspecified (ICD 171)	Spindle cell neurilemmomal sarcoma	Sprayer	18	< 1
9, Denmark	M, 56	Alive, Jan. 1984		Leiomyosarcoma, larynx	Non-exposed	26	< 1

1 additional incident case occurred after the end of follow-up in New Zealand
*Cases 2, 3, 4, 5, 8, and 9 previously reported [2,4,7]
†Precise year of death not provided for reasons of confidentiality
‡Histology from cancer registration or medical records. Histology record not retrieved for case 1

workers, and similar to that of production workers (table III). The cases arose in seven countries. Six included in table III are 3 cases in cohort members who were alive at the end of follow-up or whose certified underlying cause of death was not ICD 200 or 202.

Mortality from Hodgkin's disease was below expectation.

Other neoplasms

More than two-fold increases in risk were noted among exposed workers for several less common neoplasms, most of which have not been previously associated with exposure to chlorophenoxy herbicides. 7 deaths from testicular cancer were recorded, with at least a two-fold increase in mortality for the combined group of exposed workers (SMR = 220 [89–454]) and for the production workers (5 deaths, SMR = 278 [90–648]). 5 deaths occurred 5 or more years after first exposure, and risk was higher in workers probably exposed to TCDD (SMR = 296) compared to those probably not exposed (SMR = 164). Thyroid cancer mortality was increased for the combined group of exposed workers (4 deaths, SMR = 357 [97–914]), the excess applying both to sprayers and production workers, with deaths registered in three countries. 3 deaths from thyroid cancer occurred 10 or more years after first exposure, and risk was higher for workers probably exposed to TCDD (SMR = 426) compared to those probably no exposed (SMR = 308). 3 deaths from neoplasms of other endocrine glands occurred in the UK with increased mortality for the combined group of exposed workers (SMR = 454 [94–1328]), and separately in sprayers and production workers. Increased mortality from neoplasms of nose and nasal cavity (3 deaths, SMR = 283 [58–827]) was similarly observed only in the UK, with the highest risk in sprayers.

The mortality of cases exposed through accidents was not increased either for all cancers (33 deaths, SMR = 96 [67–137]) or for all neoplasms (13 deaths, SMR = 120 [64–205]). Similarly, no increased risk was seen for [illegible] (13 deaths, SMR = 90 [55–113]) or for all neoplasms (5 deaths, SMR = 98 [32–228]). No deaths from soft-tissue sarcoma or non-Hodgkin's lymphoma were observed in these groups, but the expected numbers were very low.

Results were virtually unchanged when analyses were repeated with exclusion of all workers with less than one year exposure. Analyses by time since first exposure and duration of exposure for workers probably exposed to TCDD did not show any trends. Analysis using Poisson regression for all cause mortality, all neoplasms, soft-tissue sarcoma, and non-Hodgkin's lymphoma, did not reveal different pattern of risk than that shown in the SMR analysis.

Discussion

The IARC register provides an opportunity to study, with a common protocol, the mortality experience of workers producing and spraying chlorophenoxy herbicides and/or chlorinated phenols in ten countries. This cohort study is the largest to have been done on these categories of workers. Nonetheless the attempt to associate risks with specific agents was only partly successful because there was often simultaneous exposure to several different chlorophenoxy herbicides or chlorophenols (table I) and to other pesticides, raw materials, intermediates, and processing chemicals. The risk specifically related to chlorophenoxy herbicides is best evaluated by looking at sprayers, who are exposed mainly to these compounds and, in smaller amounts, to other herbicides, and only to negligible amounts of chlorophenol impurities. Workers producing chlorophenoxy herbicides may also have been exposed to chlorophenols during the production process. It was not possible to identify a large group of workers exposed solely to chlorophenols. The most toxic dioxin (TCDD) can be formed during production of 2,4,5-T or 2,4,5-TCP so the identification of factories which did not produce 2,4,5-T or produced only very small amounts and of sprayers not using 2,4,5-T allowed a population to be distinguished in which exposure to TCDD was unlikely (with the caveat that [illegible] of TCDD may lead to accumulation of high tissue burdens [...].

A non-significant increased risk was observed for soft tissue sarcoma, the excess being significant for sprayers in an analysis by time since first exposure. All 4 cases in four countries occurred 10–19 years after first exposure, a time shorter than that observed in Sweden[7] or the USA.[6] The increased risk was not confined to workers probably exposed

to TCDD. Of the 5 additional registered cases of soft-tissue sarcoma, identified from other morbidity or mortality [illegible] was in a worker probably exposed to TCDD.

A small, non-significant increase in mortality from [illegible] workers, most deaths occurring more than 10 years after first exposure. 6 out of the 11 deaths were in workers exposed for less than one year. Other studies[14-22] have, however, shown risks associated with exposure to chlorophenoxy herbicides higher for non-Hodgkin's lymphomas than for soft-tissue sarcomas. There was no increase in mortality from Hodgkin's disease, and the evidence for an association of with exposure to chlorophenoxy herbicides has been weaker than that for non-Hodgkin's lymphoma.

We found increased risks for some uncommon neoplasms but these results are difficult to interpret because of the small numbers. Neoplasms of the thyroid and other endocrine glands have not been previously linked with chlorophenoxy herbicides in man but exposure to TCDD and chlorophenols have been associated with neoplasms of the thyroid and the adrenals in mice and rats.[35]

Interpretation of our findings will be easier when follow-up of this large cohort is longer—ie, when the number of recorded deaths is greater. The pattern so far indicates no increased mortality for neoplasms in general for the most common epithelial cancers, and no clearly detectable excess for non-Hodgkin's or for Hodgkin's lymphoma. The significant six-fold excess of soft-tissue sarcomas occurring in the period 10–19 years since first exposure in the whole cohort, rising to a nine-fold excess in sprayers, is compatible with a causal role for chlorophenoxy herbicides, though not specifically for those probably contaminated with TCDD.

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