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Mortality of workers exposed to 2 methyl-4 chlorophenoxyacetic acid

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COGGO D, PANNETT B, WINTER PD, ACHESON ED, BONSALL J. Mortality of workers exposed to 2 methyl-4 chlorophenoxyacetic acid. *Scand J Work Environ Health* 12 (1986) 448—454. The authors examined the mortality and cancer incidence of employees at a company which has manufactured, formulated, and sprayed 2 methyl-4 chlorophenoxyacetic acid (MCPA) and other phenoxy acid herbicides. Ninety-eight percent of the 5 784 men employed by the company during 1947—1975 was traced to the end of 1983. The overall mortality of the cohort was less than that of the national population, as was mortality from cancer. When allowance was made for rural residence, the deficit of cancer deaths became a slight excess, but not statistically significantly so. Among workers whose jobs entailed potential exposure to MCPA, there was one death from soft tissue sarcoma (0.6 expected). No further cases of soft tissue sarcoma were registered among living members of the cohort. Three potentially exposed workers died from nasal carcinoma, but this tumor has not previously been associated with phenoxy herbicides and the cluster of cases may have occurred by chance. The findings do not exclude the possibility that MCPA is a human carcinogen, but they suggest that any risk of soft tissue sarcoma is less than that indicated by earlier studies of 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) and 2,4,5-trichlorophenol and is small in absolute terms.

Key terms: phenoxy acids, 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid, soft tissue sarcoma, lymphoma, nasal carcinoma.

Since their discovery in the early 1940s, the phenoxy acid herbicides have found wide use in many countries, both in agriculture and in forestry. They have also been sold for use in gardens, mainly as lawn weedkillers. Among the compounds in the group are 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), 2,4-dichlorophenoxyacetic acid (2,4-D), and 2 methyl-4 chlorophenoxyacetic acid (MCPA). Commercial preparations of 2,4,5-T have in the past contained traces of 2,3,7,8-tetrachlorodibenzo-para-dioxin (2,3,7,8-TCDD), a substance which is highly toxic in several animal species (11) and which is also an animal carcinogen (12, 17). Other phenoxy acids may be contaminated by less toxic dioxin isomers, but not by 2,3,7,8-TCDD.

Epidemiologic studies have linked exposure to phenoxy acids and structurally related chlorophenols with the occurrence of soft tissue sarcomas and lymphomas (1). However, almost all the published data concern subjects exposed to 2,4,5-T or its precursor in the manufacture of 2,4,5-trichlorophenol. It is

unclear whether the hazard, if any, extends to products other than those contaminated by 2,3,7,8-TCDD. To explore this question, we have carried out a retrospective survey of mortality and cancer incidence among the workforce of a British company which has both manufactured and sprayed MCPA.

Subjects and methods

The company under study manufactured MCPA from 1947 until 1982. The process entailed the condensation of orthocresol with sodium monochloroacetate to form sodium cresoxyacetate, which was then acidified and reacted with gaseous chlorine to give MCPA. Production was carried out at a single site with most of the workforce drawn from the local rural population. Several other agricultural chemicals were made at the factory during the same period, the most important being copper oxychloride (1943—1972), dinitro-orthocresol (1943—1962), and a variety of organophosphorus insecticides (1948 on) and chlortriazine herbicides (1964 on). In addition many other products were bought in and formulated, including, at times, 2,4,5-T and other phenoxy acids. However, in comparison with MCPA, 2,4,5-T was handled on only a small scale.

Until 1972 the company also operated an aerial and tractor-mounted spraying service from depots scattered over a wide area of rural Britain. The range of chemi-

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cals sprayed was similar to that handled in production and formulation, but their use was seasonal. Phenoxy acids (principally MCPA) were applied extensively during the months from March to August, but 2,4,5-T was virtually never used. Because the work was seasonal, many of the spray operatives were employed for periods of less than six months.

The study cohort comprised all men employed by the company at its factory or spray depots between 1 January 1947 and 31 December 1975. We identified the cohort from personnel records, and for each employee abstracted the full name, date of birth, address, dates of starting and finishing work, and details of jobs held. On the basis of recorded job title (and in the case of spray operatives, dates of employment), we then classified workers according to their potential exposure to phenoxy acids. Three grades of exposure were distinguished — “high,” “low,” and “background.” Jobs entailing high exposure comprised principally chemical process workers, spray operatives, and certain laboratory occupations. Those with low exposure included maintenance staff and workers in chemical stores and transport. Background exposure was assigned to clerical and sales staff and to managers who did not normally enter the chemical production area. In spraying operations exposure would only have occurred during the spring and summer. Occasionally, where workers had changed their job in the course of their employment, only the most recent occupation was available from the personnel records. When assigning exposure, we assumed that earlier jobs held by these men were similar (in terms of exposure) to the occupation that was known.

Members of the cohort were traced through the National Health Service (NHS) Central Register at Southport (supplemented if necessary by reference to the National Insurance Index at Newcastle Upon Tyne), and their vital status on 31 December 1983 was determined. The Office of Population Censuses and Surveys provided us with copies of the death certificates of those men who had died, with the underlying cause of death coded to the ninth revision of the International Classification of Diseases (ICD). In addition, we obtained details of any cancers that had been registered among the cohort members during the period of follow-up.

Expected numbers of deaths by cause were calculated by the person-years method using national (England and Wales) death rates for men by age and calendar period. As a large proportion of workers were resident in rural areas at the time of their employment, we derived a second set of expected numbers adjusted by the cause-specific standardized mortality ratio (SMR) for aggregated rural areas of England and Wales during the period 1968–1978. Neither of these reference sets is ideal, but in the context of cancer mortality the most appropriate comparison is likely to lie somewhere between the two. Tests of statistical significance and confidence limits were calculated by the usual methods based on the Poisson distribution.

Results

A total of 5 784 employees satisfied the entry criteria for the study, but 30 (0.5 %) could not be included in the analysis because either their date of birth or date of joining the company was not available from the personnel records. A further 98 men (1.7 %) could not be traced in the NHS Central Register, and could only be followed to the date on which they left the company. Two hundred and fifty-six subjects emigrated during the period of follow-up and were followed to their date of embarkation.

Of the 5 754 employees included in the analysis, 4 078 were considered to have greater than “background” exposure to phenoxy acids (table 1). More than half of these men had worked in potentially exposed jobs for at least six months.

Overall mortality in the cohort was less than that expected from national rates, as was mortality from all neoplasms, from heart disease, and from disease of the respiratory system (table 2). Death rates from injury and poisoning and from gastrointestinal disorders were slightly elevated, but not to the point of statistical significance. On application of the rural correction factor, the deficit of deaths from cancer became a slight excess, but again it was not statistically significant.

More detailed analysis showed that most of the common types of cancer occurred less frequently in the workforce than in the general population (table 3). Small excesses of prostatic carcinoma (18 deaths observed, 13.5 expected) and brain cancer (11 deaths observed, 8.7 expected) were not statistically significant. The observation of 14 deaths from leukemia (8.0 expected) was more striking, but five of the cases occurred in men with only background exposure to phenoxy acids, and a breakdown of the leukemias by histological type was unremarkable (four chronic lymphatic leukemia, four acute myeloid leukemia, three chronic myeloid leukemia, two acute monocytic leukemia, and one unspecified leukemia). There were three deaths from nasal cancer (0.7 expected), all in men with probable exposure to phenoxy acids. Two had worked as spray operatives (for two and three months, respectively), and the third had been employed for six months as a process operator in chemical manufacture. One of the spray operatives was recorded

Table 1. Potential exposure to phenoxy acids among subjects included in the analysis of mortality and cancer incidence.

Type of potential exposure	<1 month	1–6 months	>6 months	Total
Manufacture and formulation	137	388	1 020	1 545
Application	322	1 128	1 111	2 561
Any ^a	450	1 502	2 126	4 078

^a Twenty-eight men were potentially exposed both in manufacture and spraying. A further 1 676 subjects were considered to have had only background exposure.

Table 2. Observed and expected deaths in the major disease categories. (SMR = standardized mortality ratio, 95 % CI = 95 % confidence interval.)

Disease category ^a	Observed deaths	From national rates			From national rates with rural correction factor		
		Expected deaths	SMR	95 % CI	Expected deaths	SMR	95 % CI
All causes of death (0—999)	1 039	1 232.9	84	79— 89	1 134.3	92	86— 97
All neoplasms (140—239)	297	314.0	95	84—106	276.3	107	96—120
Hypertensive and ischemic heart disease (401—414, 428—429)	337	414.9	81	73— 90	390.0 ^b	86	77— 96
Respiratory disease (460—519)	93	152.8	61	49— 75	126.8	73	59— 90
Digestive disease (520—579)	35	33.1	106	74—147	.. ^c	.	.
Injury and poisoning (800—999)	77	71.6	108	85—134	.. ^c	.	.

^a Code of the International Classification of Diseases (ICD), ninth revision, in parentheses.

^b The rural correction factor for hypertensive and ischemic heart disease was from data for hypertensive, ischemic, and other nonrheumatic heart disease (ICD 401—416, 420—429).

^c Rural correction factors for digestive disease and injury and poisoning were not available.

Table 3. Observed and expected deaths from cancer. (SMR = standardized mortality ratio, 95 % CI = 95 % confidence interval.)

Cancer ^a	Observed deaths	From national rates			From national rates with rural correction factor		
		Expected deaths	SMR	95 % CI	Expected deaths	SMR	95 % CI
Tongue (141)	1	1.04	96	2— 534	0.89	112	3— 623
Pharynx (146—149)	1	2.19	46	1— 255	1.84	54	1— 303
Esophagus (150)	8	8.87	90	39— 178	8.52	94	41— 185
Stomach (151)	26	33.34	78	51— 114	28.67	91	59— 133
Small intestine (152)	1	0.65	154	4— 859	0.63	159	4— 884
Large intestine (153)	19	18.97	100	60— 156	18.59	102	62— 160
Rectum (154)	8	14.30	56	24— 110	13.58	59	25— 116
Gall bladder and bile ducts (156)	2	1.86	107	13— 388	1.67	119	14— 432
Pancreas (157)	9	13.27	68	31— 129	12.47	72	33— 137
Peritoneum and retroperitoneal tissue (158)	2	0.78	256	31— 925	0.73	273	33— 985
Nose (160)	3	0.70	429	88—1 253	0.61	493	102—1 440
Larynx (161)	4	2.98	134	37— 343	2.29	174	48— 446
Lung, pleura and mediastinum (162—164)	117	126.81	92	76— 111	101.45	115	95— 138
Bone (170)	1	1.22	82	2— 455	1.12	89	2— 496
Soft tissue sarcoma (171)	1	0.94	106	3— 593	0.96	104	3— 581
Melanoma of skin (172)	1	1.96	51	1— 285	2.02	50	1— 276
Other skin cancer (173)	3	0.97	309	64— 904	0.98	306	63— 895
Prostate (185)	18	13.51	133	79— 211	13.65	132	78— 208
Testis (186)	4	1.69	236	64— 605	1.79	223	61— 572
Other male genital organs (187)	1	0.50	201	5—1 118	0.44	227	6—1 266
Bladder (188)	8	11.13	72	31— 142	9.46	85	37— 167
Kidney (189)	5	5.63	89	29— 207	5.07	99	32— 230
Brain and nervous system (191—192)	11	8.69	127	63— 227	8.86	124	62— 222
Thyroid (193)	1	0.57	177	4— 984	0.59	170	4— 949
Non-Hodgkin's lymphoma (200, 202)	2	5.53	36	4— 131	5.36	37	5— 135
Hodgkin's disease (201)	1	3.51	28	1— 159	3.44	29	1— 162
Multiple myeloma (203)	5	3.09	162	53— 377	3.09	162	53— 378
Leukemia (204—208)	14	8.00	175	96— 294	7.92	177	97— 297

^a Code of the International Classification of Diseases (ICD), ninth revision, in parentheses. In addition to the cancers shown, three deaths were ascribed to brain tumors of unspecified malignancy (ICD 239.6); two to carcinoma of the suprarenal gland (ICD 194); one each to carcinoma of the parotid (ICD 142), bleeding cerebral angioma (ICD 228) and multiple renal tract papillomas (ICD 223); and 12 to carcinomatosis of unknown origin (ICD 199).

on his death certificate as having worked more recently as a carpenter.

Mortality ratios tended to be somewhat higher when rural correction factors were applied, but in essence the findings were similar.

Analyses by grade and duration of potential exposure to phenoxy acids (tables 4 and 5), and allowing for a latency of 5 or 10 years from the time of first exposure (table 6), did not suggest any further disease associations.

Table 4. Mortality from selected cancers by grade of potential exposure to phenoxy acids.^a

Cancer	Grade of potential exposure ^b								
	Background			Low			High		
	O	SMR _N	SMR _R	O	SMR _N	SMR _R	O	SMR _N	SMR _R
Esophagus	4	122	127	3	113	118	1	34	35
Stomach	13	99	115	6	59	69	7	69	81
Large intestine	11	151	155	4	70	71	4	67	68
Rectum	2	36	38	4	93	98	2	45	47
Gall bladder and bile ducts	1	141	156	—	0	0	1	168	188
Pancreas	2	40	43	1	25	27	6	139	147
Nose	—	0	0	—	0	0	3	1 249	1 437
Larynx	—	0	0	1	111	144	3	318	414
Lung, pleura and mediastinum	39	83	103	35	90	113	43	105	132
Soft tissue sarcoma	—	0	0	—	0	0	1	280	272
Skin (other than melanoma)	2	507	508	1	346	341	—	0	0
Prostate	7	117	116	6	142	140	5	151	150
Testis	1	209	197	2	427	401	1	134	126
Bladder	3	67	79	1	29	34	4	123	145
Kidney	3	151	168	—	0	0	2	101	112
Brain and nervous system	5	182	179	2	80	79	4	116	113
Non-Hodgkin's lymphoma	—	0	0	2	124	127	—	0	0
Hodgkin's disease	—	0	0	1	100	102	—	0	0
Multiple myeloma	1	90	90	2	215	215	2	191	190
Leukemia	5	180	182	3	127	128	6	210	213

^a Where a subject worked in several jobs, he was classified according to that with the highest grade of exposure.

^b O = observed number of deaths, SMR_N = standardized mortality ratio based on national rates, SMR_R = standardized mortality ratio based on national rates with rural correction factor.

Table 5. Mortality from selected cancers by duration of potential exposure to phenoxy acids. (Subjects with background exposure only have been excluded.)

Cancer	Duration of potential exposure ^a								
	< 1 month			1–6 months			> 6 months		
	O	SMR _N	SMR _R	O	SMR _N	SMR _R	O	SMR _N	SMR _R
Esophagus	1	198	204	2	103	107	1	32	33
Stomach	1	55	64	2	28	33	10	88	102
Large intestine	—	0	0	6	147	150	2	31	31
Rectum	1	126	133	2	66	69	3	61	64
Gall bladder and bile ducts	—	0	0	1	248	278	—	0	0
Pancreas	—	0	0	3	104	110	4	86	91
Nose	—	0	0	3	1 914	2 155	—	0	0
Larynx	—	0	0	2	314	406	2	194	252
Lung, pleura and mediastinum	7	97	122	25	91	113	46	103	128
Soft tissue sarcoma	—	0	0	1	442	426	—	0	0
Skin (other than melanoma)	—	0	0	1	494	495	—	0	0
Prostate	—	0	0	5	191	189	6	141	139
Testis	—	0	0	—	0	0	3	495	464
Bladder	—	0	0	3	129	152	2	53	63
Kidney	—	0	0	1	78	87	1	49	55
Brain and nervous system	—	0	0	1	47	46	5	155	152
Non-Hodgkin's lymphoma	1	283	295	—	0	0	1	50	52
Hodgkin's disease	—	0	0	—	0	0	1	79	80
Multiple myeloma	—	0	0	1	145	145	3	271	270
Leukemia	3	592	594	2	107	108	4	142	143

^a O = observed number of deaths, SMR_N = standardized mortality ratio based on national rates, SMR_R = standardized mortality ratio based on national rates with rural correction factor.

Only one death from soft tissue sarcoma (ICD 171) was recorded during the period of follow-up. The man in question had worked as a spray operative for six months 18 years before his death. The cause of death, certified as a spindle cell neurilemmal sarcoma, has been confirmed by independent expert review of the tumor histology. We also obtained histological material

from the tumors of two patients whose deaths were ascribed to retroperitoneal cancer (ICD 158), but neither of these tumors turned out to be a soft tissue sarcoma. One was a carcinoma, and the other a myeloid sarcoma.

Three subjects died from malignant lymphomas (ICD 200–202) as compared with approximately nine

Table 6. Mortality from selected cancers allowing for latencies of 0, 5, and 10 years from first exposure. (Subjects with background exposure only have been excluded.)

Cancer	Latency ^a								
	0 years			5 years			10 years		
	O	SMR _N	SMR _R	O	SMR _N	SMR _R	O	SMR _N	SMR _R
Esophagus	4	72	75	4	74	77	4	79	82
Stomach	13	64	75	12	63	74	12	70	82
Large intestine	8	68	70	8	72	74	7	69	70
Rectum	6	69	72	6	72	76	6	79	83
Gall bladder and bile ducts	1	86	96	1	91	101	1	99	110
Pancreas	7	84	89	6	75	80	5	68	72
Nose	3	670	766	3	716	821	3	799	907
Larynx	4	217	282	4	229	297	3	187	244
Lung, pleura and mediastinum	78	98	122	72	95	118	63	90	113
Soft tissue sarcoma	1	159	156	1	177	175	1	204	200
Skin (other than melanoma)	1	174	171	1	183	180	1	202	198
Prostate	11	146	144	11	149	147	10	141	140
Testis	3	247	232	2	218	205	2	326	309
Bladder	5	75	88	4	62	73	4	67	78
Kidney	2	55	61	2	58	64	2	63	70
Brain and nervous system	6	101	99	6	111	109	5	108	106
Non-Hodgkin's lymphoma	2	55	56	2	59	61	2	67	69
Hodgkin's disease	1	41	42	—	0	0	—	0	0
Multiple myeloma	4	202	202	4	209	209	4	225	225
Leukemia	9	173	174	7	150	151	6	149	151

^a O = observed number of deaths, SMR_N = standardized mortality ratio based on national rates, SMR_R = standardized mortality ratio based on national rates with rural correction factor.

deaths expected in the total cohort. Among workers with likely exposure to phenoxy acids six deaths from lymphoma would have been expected.

Discussion

Suspicion that phenoxy acids or their contaminants cause cancer first arose from the observation in northern Sweden of seven cases of soft tissue sarcoma among men who had been occupationally exposed to phenoxy herbicides (5). Subsequently the association was supported by two Swedish case-referent studies (2, 8) and by follow-up of employees at plants in the United States where 2,4,5-T or 2,4,5-trichlorophenol had been manufactured (10). However, doubts have been raised about the possible effects of recall bias in the Swedish investigations (1) and about the accuracy of certified causes of death in the American cohort studies (3). More recent research has been less conclusive. A case-referent study of soft tissue sarcoma in New Zealand has shown only a weak and statistically nonsignificant association with reported exposure to phenoxy acids (16), and studies in the United States have failed to demonstrate an increased risk of soft tissue tumors among Vietnam veterans exposed to Agent Orange (a 1:1 mixture of 2,4,5-T and 2,4-D) (4, 13). In Victoria, Australia, follow-up of 2 181 state employees who sprayed 2,4-D and 2,4,5-T during the years 1951 to 1970 has shown one death from soft tissue sarcoma with 0.7 expected (15).

To date, most investigations have concentrated on subjects with exposure to 2,4,5-T or 2,4,5-trichloro-

phenol, and few have examined separately the effects of exposure to phenoxy acids uncontaminated by 2,3,7,8-TCDD. This is an important question since, in Britain, 2,4-D and MCPA have been used on a much larger scale than 2,4,5-T and are a major factor in the current high levels of agricultural output. A separate analysis for phenoxy herbicides uncontaminated by 2,3,7,8-TCDD was possible in one of the early Swedish case-referent studies (2), and it revealed an association with soft tissue sarcoma, although the relative risk of 4.2 was less than that for all phenoxy acids combined. Otherwise, the only relevant epidemiologic data come from a recent study of MCPA manufacturers in Denmark (14). Five cases of soft tissue sarcoma were observed in male employees at two factories followed between 1947 and 1982. When compared with the 1.84 cases expected, these five cases gave a relative risk of 2.72 with a 95 % confidence interval of 0.88–6.34. A confounding effect of 2,3,7,8-TCDD could not be entirely ruled out because, for part of the period of study, 2,4,5-T was processed at the factory where the five cases occurred. However, it was only handled on a very limited scale.

A similar limitation applies to our study also, but any such confounding would only be relevant in the context of positive findings. Coincident exposure to 2,4,5-T could not obscure a carcinogenic effect of other phenoxy acids.

Overall mortality in our cohort was less than that expected from national rates. This occurrence may be due in part to a healthy worker effect, but the low death rates from causes such as respiratory disease may also reflect the rural residence of the workforce. When adjustment was made for urban/rural differences in

disease frequency, most of the SMR values increased, and the deficit of deaths from neoplastic disease became a small excess.

Only one death from soft tissue sarcoma was recorded, the expected number of fatalities being 0.9 in the complete cohort and 0.6 among workers potentially exposed to phenoxy acids. Independent expert review confirmed that the tumor was a neurilemmal sarcoma. No further cases were found on detailed scrutiny of the death certificates, and none were registered among living members of the cohort. However, given the incompleteness of cancer registration in Britain, especially during the early years of the follow-up period, it is possible that a nonfatal case could have gone unrecorded. There is also a possibility that one or more soft tissue tumors have been missed because they were incorrectly diagnosed — the differentiation of sarcomas from anaplastic carcinomas is often far from easy — or because a death was assigned simply to cancer without specification of the histology. Unfortunately, it would not have been practical to review the histopathology of all cancers diagnosed in the study cohort, but we were able to obtain histological material from the two patients whose deaths were ascribed to retroperitoneal tumors. Neither of these cancers was a soft tissue sarcoma.

The other cancer which has previously been linked with exposure to phenoxy acids is malignant lymphoma (6). In our study, however, Hodgkin's disease and non-Hodgkin's lymphoma both caused fewer deaths than expected.

Several tumors occurred more frequently than in the general population, but the excesses were small and may well have arisen by chance. The highest SMR was for cancer of the nose and nasal sinuses, from which there were three deaths, all in subjects with potential exposure to MCPA. We are unaware of any cases of nasal cancer in other cohort studies of phenoxy herbicide workers, and, although an association between phenoxy acids and tumors of the nose and nasopharynx has been reported in a case-referent study, the relative risk was only 2.1 and not statistically significant (7). It is also relevant that one of the subjects who died from nasal cancer was stated on his death certificate to have worked most recently as a carpenter, an occupation known to carry a risk of nasal carcinoma (9). In view of this finding, and the small number of cases underlying the association, interpretation should be cautious.

The excess of deaths from multiple myeloma and leukemia is also of interest, but again has not been a consistent finding in other studies.

The importance which can be attached to the negative findings of this investigation hinges on the extent to which the workforce under examination was exposed to phenoxy acids. Unfortunately, no measurements of exposure were available for the period of study. In contrast to the processes used by some companies, production of MCPA was carried out entirely

in the liquid phase and did not entail a flaking or drying operation where high levels of dust may be produced. On the other hand, in the early years of production and herbicide application, hygiene was not a major priority, and cumulative exposure to MCPA is likely to have been higher in this group of workers than in any industrial cohort of comparable size in the United Kingdom.

The results do not exclude the possibility that MCPA is a human carcinogen. In particular, the small cluster of nasal cancers will require further evaluation in the light of other investigations currently in progress. However, the findings suggest that, if there is a hazard of soft tissue sarcoma due to MCPA, then the risk is less than that suggested by earlier studies of 2,4,5-T and 2,4,5-trichlorophenol, and it is small in absolute terms.

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