Scand J Work Environ Health 1982;8(1):37-42

<https://doi.org/10.5271/sjweh.2498>

Issue date: Mar 1982

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Key terms: [2,4-dichlorophenoxyacetic acid](#); [2,4,5-trichlorophenoxyacetic acid](#); [chlorinated phenoxy acid](#); [Finland](#); [herbicide](#); [herbicide applicator](#); [mortality](#); [prospective cohort study](#)

This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/7134921

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Mortality of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid herbicide applicators in Finland

First report of an ongoing prospective cohort study

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RIIHIMÄKI V, ASP S, HERNBERG S. Mortality of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid herbicide applicators in Finland: First report of an ongoing prospective cohort study. *Scand j work environ health* 8 (1982) 37—42. Some recent epidemiologic studies have suggested that chlorinated phenoxy acid herbicides are human carcinogens. The mortality experience in a cohort of 1,926 men who had sprayed 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) during 1955—1971 has been followed prospectively from 1972 to 1980. The total phenoxy acid exposure was generally rather low because the duration of work had mostly been less than two months. In 1972—1976 mortality from all natural causes in the cohort was only 54 % of the expected value (based on age-specific rates for the general population), and in the succeeding 4-a period 81 % of the expected value. In the assessment of cancer, mortality allowance was made for 10- and 15-a periods of latency between the first exposure and the start of the recording of vital status during the follow-up. No increase in cancer mortality was detected, and the distribution of cancer types was unremarkable. No cases of death from lymphomas or soft tissue sarcomas were found. The study results must, however, be viewed with great caution owing to the small size of the cohort, the low past exposure, and the brief follow-up period.

Key terms: chlorinated phenoxy acids.

The herbicides 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) have been used in Finland since about 1955 to destroy brushwood vegetation. Their peak consumption occurred during the latter part of the 1960s when 50—70 t of active ingredients of both compounds were sprayed per year. Since 1972 the use of these chemicals has declined. Four governmental organizations or state-owned companies (the Finnish State Railways, the Highway Authority, the Forestry Authority and an electric power company) have been responsible for the majority of herbicidal use to control brushwood, and during the years of intensive appli-

cation about 500 workers, almost exclusively males, were employed annually in this work (20).

The chemical control of brushwood mainly involved the spraying of foliage in rights-of-way (railroads, highways, electric transmission lines) and in forests. The spraying season was restricted to about two to eight weeks during the summer. Spraying was, for the most part, performed with portable, manually operated or motor-driven knapsack rigs, with the exception of that done by the Highway Authority which mainly used moving vehicles. Throughout the 1950s and 1960s the methods of application and the work habits did not change appreciably. Because the workers were not informed of any hazards connected with the spraying, no special precautions were taken to avoid inhalation of the aerosols or skin contact.

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The most extensively used commercial herbicide preparations were 2:1 mixtures of emulsified esters of 2,4-D and 2,4,5-T dissolved in water. Even pure 2,4,5-T preparations were used. It is now well appreciated that the eventual hazards from the use of 2,4,5-T may be associated with a toxic dioxin impurity, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). It is not known with certainty how extensive the exposure to TCDD may have been in the early years of 2,4,5-T application. Analysis of some old herbicide preparations used in Finland in 1962–1967 suggested that the TCDD content ranged between 0.1 and 0.9 mg/kg; in one of the samples it was below the detection limit (18).

Public concern about alleged adverse health effects from brushwood-control herbicides precipitated an extensive survey of the situation in 1972 by an ad hoc working group (20), which, however, did not find material evidence to support such claims with regard to morbidity. However in a nationwide search for suspected phenoxy acid-related symptoms and signs, several reports of skin disorders were received. These mostly pointed to obvious toxic reactions, and, in at least one case, the skin disease, which was also later seen by a dermatologist, suggested a mild form of chloracne. A mortality study incorporated into the survey did not allow any conclusions to be drawn regarding mortality rates in general and cancer mortality rates in particular owing to the doubtful validity of the cohort and the short period of latency. It was intended to follow this cohort of herbicide sprayers in the years to come.

New suspicions of a possible carcinogenic effect of exposures to chlorinated phenoxy acids were raised in Sweden (1, 8), and they prompted us to begin a 5-a prospective mortality study in 1977. An interim report was prepared at the request of the International Agency for Research on Cancer (19), but it was not refined into a scientific report because we had reservations as to its power to provide significant evidence with respect to the problem of the cancer risks associated with phenoxy acid exposures.

More recently further epidemiologic studies (2, 5, 11, 12) and a case report (9) have shown or suggested an association

between exposure to chlorinated phenoxy acids and increased cancer risk. In response to the renewed public concern, Finnish health authorities established a new working group in 1979 to evaluate risks associated with the use of chlorinated phenoxy acids (and some other herbicides). The working group supplemented earlier mortality studies by assessing the cancer morbidity in the cohort in 1967–1974 through the files of the Finnish Cancer Register. The observed numbers of different types of cancer did not significantly differ from those expected on the basis of the cancer incidence in the general population, and no cases of soft tissue sarcoma were found (15).

Subsequently, a further 4-a prospective follow-up of mortality in the original cohort was instituted.

The debate on the hazards of chlorinated phenoxy acids still continues, and only a limited number of studies have been made available for the assessment of risks. Our observations, while not formally published, have been referenced in this context. We therefore felt it was important to present the results of this 9-a prospective follow-up on the mortality experience of the Finnish 2,4-D and 2,4,5-T herbicide applicators in detail although we acknowledge the preliminary nature of these results.

Material and methods

The cohort of herbicide applicators was collected in 1972 from the personnel records of the four main Finnish employers involved in chemical brushwood control. The cohort included 1,971 male workers who had been exposed for at least two weeks during 1955–1971 to 2,4-D and 2,4,5-T. The data were collected by office personnel in the respective companies from different sources including old payrolls, because the files did not always provide information on specific assignments. Therefore, in some cases the files of exposed workers were based on the memory of the foremen and clerks, and the reported exposure characteristics, eg, the duration of exposure, were likely to be imprecise. Special instructions were given to guarantee that pensioners and those

who had changed jobs would not be omitted.

The duration of exposure to the herbicides had been quite brief. Three-fourths of the study population had a summed exposure duration of two to seven workweeks, and only one-fourth of eight weeks or more, as of 1971, divided over one or more summer seasons. For many persons in the cohort further exposure may have taken place after 1971. About two-thirds of the study population had had their first exposure rather recently, in 1966—1971.

At the onset of exposure one-third of the individuals in the cohort had been less than 25 a of age, and the study population is still relatively young. In the beginning of 1972 the median age of the Forestry Authority employees was 33.5 a, and the corresponding figures for the Highway Authority employees, power company employees and State Railways employees were 38.0, 38.3 and 47.8 a, respectively.

During 1955—1971, 45 individuals in the cohort of 1,971 persons died. Thus in the beginning of 1972 there were 1,926 persons alive who were followed through 1972—1980. The lists of names and identification numbers were checked against the population data register at the Social Insurance Institution, where every citizen is registered. In all, 15 individuals could not be traced, and they were removed from the cohort. For those who had died, the underlying causes of death were obtained from death certificates registered at the Central Statistical Office. The expected numbers of deaths from different causes were calculated by multiplying the age-

specific person-years of observation by the cause and age-specific national death rates for 1975. The fractional age group values were summed to yield corresponding figures for the whole cohort. The person-years and expected numbers of deaths were assessed in a conventional way, as well as by making allowance for the minimum of 10- and 15-a periods (of latency) between the first exposure and the start of the recording of vital status during the follow-up.

Results

During the 9-a prospective follow-up period the cohort accumulated 16,694 person-years of observation, and 105 persons had died from natural causes versus 155 expected. The follow-up was divided into two time periods, 1972—1976 and 1977—1980, and the observed, as well as expected, deaths are presented in table 1. In 1972—1976 the number of deaths from all natural causes was only 54 % of the expected value, whereas, during the succeeding 4-a period, the observed deficit in deaths was less than 20 % (observed/expected = 0.81). At variance to the previously published mortality data over 1972—1976 (19) the present investigation found one more death from cancer and six additional deaths from other natural causes. One case had been omitted due to a technical error. The loss of three cases may be attributed to a delay in reporting since the deaths had occurred at the end of 1976, whereas the inability to find the three others is unexplained. In the present investigation an error of this kind is un-

Table 1. Observed (O) and expected ^a (E) deaths among 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) applicators during the prospective follow-up period of 1972—1980. In the calculations no allowance was made for latency period.

Follow-up period	Number of person-years	All deaths		All cancers		All natural causes of death	
		O	E	O	E	O	E
1972—1976	9,442	62	92.9	9	18.1	41	76.7
1977—1980	7,252	82	91.1	17	18.4	64	78.6
1972—1980	16,694	144	184.0	26	36.5	105	155.3

^a Based on age-specific national death rates for males in 1975.

Table 2. Observed (O) and expected^a (E) deaths among 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) applicators during the prospective follow-up period of 1972–1980. Allowance was made for 10- and 15-a latency periods in the calculations.

Cause of death	10-a period of latency		15-a period of latency	
	O	E	O	E
All causes	88	118.6	35	53.6
All cancers	20	24.3	5	11.3
Lung cancer	12	11.1	4	4.7
All natural causes	71	103.6	33	48.1

^a Based on age-specific national death rates for males in 1975.

Table 3. Localization of malignant tumors found among 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) applicators, and expected values,^a during the prospective follow-up period 1972–1980. Allowance was made for a 10-a latency period in the calculations.

Site or type of tumor	Observed number of cases	Expected number of cases
Lung	12	11.1
Stomach + esophagus	4	3.7
Prostate	2	1.1
Multiple myeloma	1	0.2
Metastatic, unknown origin	1	0.3
Other sites and types	—	7.9
Total	20	24.3

^a Based on age-specific national death rates for males in 1975.

likely since the search for individuals in the cohort was performed by the register officials themselves.

When allowance was made for 10- and 15-a latency periods, the numbers of person-years were restricted to 8,445 and 2,888, respectively, and the numbers of deaths from natural causes were 71 and 33, respectively. Even in these populations there were considerably fewer natural deaths than expected (mortality rates 69 % of the expected values) (table 2). The total number of cancer deaths was also lower than that expected, while the occurrence of certain cancer types approximated the expected values. The distribution of different types of malignant tumor in the population with a 10-a latency period was rather unremarkable, and no cases of death from lymphomas [International Classification of Diseases (ICD) 200–202, 8th revision] or soft tissue sarcomas (ICD

171) were found (table 3). Follow-up for mortality in the four employer groups with the 10-a latency period included (table 4) showed a marked and unexplained undermortality among the Highway Authority employees.

Although there were uncertainties with regard to data on the actual duration of exposure, mortality figures were assessed separately for the reportedly more heavily exposed populations. Mortality figures (all natural causes and all cancers) for those exposed for six weeks or more or during 5 a and for those exposed for eight weeks or more or during 5 a (table 5) did not uncover any indications of an increased mortality in these subgroups.

Discussion

We have followed the mortality of a cohort of 1,971 men exposed over a period of at least two weeks to 2,4-D and 2,4,5-T herbicides during 1955–1971. Because of the methods used in collecting individuals for the cohort in 1972, selection bias could not be totally excluded, and thus the validity of the retrospective follow-up is questionable. For the prospective follow-up of all those alive in 1972 (totaling 1,926 men) similar problems do not exist.

The results of this investigation show that the general population was not an appropriate comparison group for the herbicide applicators, probably because of work requirements which selected able-bodied and healthy individuals. This undermortality seems to decrease with time, a phenomenon typical of the “healthy worker effect” (16), although even 10–15 a after the first exposure, at a relatively

young age, natural mortality was still slightly less than 70 % of that for the general population. With regard to cancer mortality the healthy worker effect is known to play a less significant role (16), and the present observations show the same tendency.

Chemically-induced cancer has a long induction-latency period, and therefore it was necessary to assess the mortality experience of the herbicide applicators after a relatively long time, at least 10 a, had elapsed since the first exposure. This was even more important because the estimated total exposure had been quite low and of short duration. When allowance was made for 10- and 15-a periods of latency, which of course restricted the small material even more, no increase of cancer mortality was uncovered. Furthermore, the distribution of the cancer types was unremarkable. No cases of death from lymphomas or from soft tissue sarcomas were found in the population with the 10-a latency period, the expected values being 0.8 for lymphomas and 0.1 for soft tissue

sarcomas. No information was available on the smoking habits of the individuals in the cohort.

The question arises of whether the present findings can be used in support of arguments that exposures to 2,4-D and 2,4,5-T, and to impurities in their commercial preparations, do not cause increased long-term risks of fatal diseases, particularly cancer. This investigation cannot be regarded as a conclusive negative study for a number of reasons: (i) the cohort was relatively small, (ii) the exposures to herbicides were low, particularly in terms of duration, and (iii) the follow-up period was still too brief to demonstrate in full the possible cancer risks from herbicide exposures. Obviously, further observations on the mortality of this cohort with the passage of time will permit the drawing of more valid conclusions.

Yet, it needs to be pointed out that the present results do not confirm the previously shown association between mixed herbicide exposures and increased overall cancer risks (2) as far as specific exposures

Table 4. Observed (O) and expected^a (E) deaths among 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) applicators of different employers during 1972–1980. Allowance was made for a 10-a latency period in the calculations.

Cause of death	State Railways (2,209 person-years)		Highway Authority (2,302 person-years)		Forestry Authority (3,343 person-years)		Power company (591 person-years)	
	O	E	O	E	O	E	O	E
All causes	39	49.0	12	27.4	31	35.1	6	7.1
All cancers	10	10.6	3	5.4	6	6.9	1	1.4
All natural causes	34	44.7	10	23.3	22	29.5	5	6.1

^a Based on age-specific national death rates for males in 1975.

Table 5. Observed (O) and expected^a (E) deaths among the more heavily exposed 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) applicators.

Cause of death	No latency period			10-a period of latency			15-a period of latency		
	Person-years	O	E	Person-years	O	E	Person-years	O	E
<i>Exposure for six weeks or more during 5 a</i>									
All natural causes	6,300	34	66.0	3,588	29	48.0	1,378	15	23.9
All cancers	6,300	8	15.4	3,588	8	11.3	1,378	1	5.7
<i>Exposure for eight weeks or more or during 5 a</i>									
All natural causes	4,338	23	50.9	2,717	21	40.1	1,151	13	21.5
All cancers	4,338	5	12.0	2,717	5	9.5	1,151	1	5.1

^a Based on age-specific national death rates for males in 1975.

to 2,4-D and 2,4,5-T are concerned. Neither did our observations support the finding that a markedly increased risk of lymphoma is associated with exposures to chlorinated phenoxy acids (11). The association between an increased risk of soft tissue sarcoma and exposures to chlorinated phenoxy acids, chlorinated phenols, and their chlorinated dibenzodioxin (TCDD in particular) and dibenzofuran impurities has been strengthened by recent epidemiologic (6, 10) and clinical (3, 13, 17) observations. Unfortunately, no certain conclusions on the risk of soft tissue sarcoma can be drawn in the present study because the material is small. TCDD is a recognized animal carcinogen, whereas the chlorinated phenoxy acids, including 2,4,5-T, are not (4, 7, 14). How great a potential risk of cancer for man is associated with exposures to 2,4,5-T containing small amounts of TCDD is not known. The results of this investigation can only suggest that minor exposures to 2,4,5-T do not pose great risks of cancer.

Acknowledgment

The authors wish to thank Dr L Teppo for his valuable comments on the manuscript.

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Received for publication: 16 December 1981