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Herbicide exposure and tumor mortality

An updated epidemiologic investigation on Swedish railroad workers

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AXELSON O, SUNDELL L, ANDERSSON K, EDLING C, HOGSTEDT C, KLING H. Herbicide exposure and tumor mortality: An updated epidemiologic investigation on Swedish railroad workers. *Scand j work environ health* 6 (1980) 73—79. An earlier cohort study of Swedish railroad workers indicated a possible relationship between exposure to herbicides and an increased overall tumor morbidity and mortality. The cohort of 348 individuals has now been followed through October 1978. In this updated analysis of the causes of death among railroad workers, the observed number of tumor deaths was higher than expected, especially among individuals exposed in the earlier years of the study to both amitrol and phenoxy acids. However, the excess tumor mortality among persons exposed to amitrol became more moderate, and the earlier, slightly increased tumor mortality among people exposed to phenoxy acids more pronounced. No specific type of tumor predominated although there were three stomach cancers and three lung cancers. The result of the previous analysis of deaths among these railroad workers has been confirmed as to an excess of tumors, but the aspects of causal relationships to specific agents remain rather unclear, especially since workers exposed to a combination of amitrol and phenoxy acids seem to be the most seriously affected. However, the result, being in agreement with animal data and other epidemiologic studies, suggests a need for the careful handling of amitrol and phenoxy acids as increasingly suspicious carcinogens.

Key terms: amitrol, cancers, 2,4-dichlorophenoxy acetic acid, diurone, herbicides, monurone, phenoxy acids, railroad workers, tumors, 2,4,5-trichlorophenoxy acetic acid.

In 1974 increased overall tumor morbidity and mortality were reported among railroad workers with exposure to various herbicides, mainly amitrol (3-amino-1,2,4-triazol) and phenoxy acids such as 2,4-D (2,4-dichlorophenoxy acetic acid) and 2,4,5-T (2,4,5-trichlorophenoxy acetic acid) (2). Many other organic preparations had been used however, eg, monurone and diurone, but also inorganic preparations like potassium chlorate. There is no detailed knowledge about railroad workers' exposure with regard to these less commonly used herbicides, nor is there any information about the vehicles used and the occurrence of contaminants in the commercial preparations. Henceforth, these preparations are referred to by the name of the active substances.

In the previous study, increased morbidity and mortality from different tumor diseases were mainly referable to persons exposed to amitrol. This association to amitrol exposure was consistent with animal experiments (10, 12). In the group exposed to phenoxy acids a slight excess morbidity was noted, but it was interpret-

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ed as due to the fact that persons exposed to phenoxy acids were also somewhat exposed to amitrol. However, a reanalysis of the data, initiated through a theoretical interest in the problem of confounding (1), showed, somewhat surprisingly, that an increased frequency of tumors could also be associated with exposure to phenoxy acids (1, 3). Moreover, a contemporary case-report (7) had suggested a carcinogenic hazard to man from phenoxy acids with regard to soft tissue sarcomas. Additional investigation on this possible relationship was initiated, and in 1979 two case-referent studies were reported that showed a fivefold increase in risk for these types of tumors among persons exposed to phenoxy acids, mainly in agriculture and forestry work (6, 9). Also people who had worked with chlorophenols, mainly used for wood preservation in saw mills, showed an increased morbidity with regard to soft tissue sarcomas.

Quite recently, an additional case report appeared showing a possible connection also between malignant lymphomas and exposure to phenoxy acids (8).

Material and methods

The earlier studied cohort of 348 persons, defined by a total exposure to herbicides of more than 45 d during the period 1957—1972, has now been followed through October 1978. In the earlier analysis, through December 1972, partly overlapping cohorts were used, but, because of the aforementioned difficulties in interpreting the data, the material has now been subdivided into cohorts with exposure to amitrol, phenoxy acids and combinations of the two. However, overlapping cohorts, as used in the previous study, can easily be derived from the presented tables. It should also be made clear that the recognized exposures have been mixed with other unknown exposures; unfortunately there was no possibility of subdividing the material in this respect, eg, according to concomitant or consecutive exposure to monurone and diurone. Two persons only, both healthy, were exclusively exposed to these "other herbicides;" they have been included in the subcohort with combined exposure to amitrol and phenoxy acids [cf original study on "other herbicides and combinations" (2)].

None of the 348 individuals in the total cohort were lost during the follow-up. For those having died, the underlying causes of death were recorded as classified by the National Central Bureau of Statistics and based on the death certificates.

We calculated the expected numbers of total deaths and deaths from different tumors by multiplying the person-years of observation by the cause and age-specific national death rates for males during the respective calendar years of the study period and then summarized the fractional contributions of the cohorts. In these calculations, the official mortality statistics of Sweden were used for the respective calendar years until 1975, but for the period 1975—1978 the mortality rates of 1975 were applied since no later national death rates were available.

A ten-year lapse from the first day of exposure was required for the induction-latency time as shown in tables 2, 3 and 5. In the previous study the latency time requirement had been added to the time when 45 d of exposure had been achieved, which sometimes took several years.

The material has also been analyzed with regard to the time-course of exposure ie, with regard to the exposure taking place during the first 5-a period 1957—1961 and later. The outcome during the period 1972 to October 1978 has also been specifically considered. The calculations of one-tailed p-values were based on the Poisson distribution (5).

Results

The follow-up of the total cohort, disregarding induction-latency time for the disease to develop, resulted in 5,541 person-years of observation for the 348 persons under study. A total of 45 deaths were observed versus 49 expected, ie, the usually occurring deficit in the number of deaths was present as a manifestation of the so-called healthy worker effect (11); 17 tumors were found versus 11.85 expected. The excess mortality from tumors occurred particularly among persons with

combined exposure to amitrol and phenoxy acids (table 1).

With the requirement of 10 a for the induction-latency time from the first day of exposure (table 2), the excess mortality from tumors appears as almost fourfold in the subcohort with combined exposure to amitrol and phenoxy acids: 6 cases versus 1.78 expected.

For the subcohorts with exposure to amitrol or phenoxy acids the rate ratios were 1.5 and 1.9, respectively, based on 3 and 6 observed cases. The total number of deaths in the combined exposure cohort, as well as in the cohort with exposure to phenoxy acids, was higher than expected, whereas the amitrol cohort showed a lower than expected number of deaths — however, three out of four deaths were due to tumors. Among persons with exposure to phenoxy acids, there were 2 cases of stomach cancer observed versus 0.33 expected; another case of stomach cancer oc-

Table 1. Observed and expected number of deaths among 348 herbicide sprayers during 1957—1978, no induction-latency time required.

Cohort/Exposure	Cause of death	Person-years of observation	Expected	Observed	Rate ratio
Amitrol (A)	All deaths	1,545	13.77	7 *	0.5
	Tumors		3.34	5	1.5
	Stomach		0.37	0	0
	Lung		0.62	2	3.2
Phenoxy acids (P)	All deaths	2,265	23.03	20	0.9
	Tumors		5.62	6	1.1
	Stomach		0.65	2	3.1
	Lung		1.05	0	0
Amitrol + phenoxy acids (A + P)	All deaths	1,731	12.22	18	1.5
	Tumors		2.89	6	2.1
	Stomach		0.32	1	3.1
	Lung		0.52	1	1.9
Total [A + P + (A + P)]	All deaths	5,541	49.02	45	0.9
	Tumors		11.85	17	1.4
	Stomach		1.34	3	2.2
	Lung		2.19	3	1.4

* $p < 0.05$.

Table 2. Observed and expected number of deaths in different subcohorts of herbicide sprayers, 10 a of induction-latency time required.

Cohort/Exposure	Cause of death	Person-years of observation	Expected	Observed	Rate ratio
Subcohort Amitrol	All deaths	613.0	7.83	4	0.5
	Tumors		1.95	3	1.5
	Stomach		0.20	0	0
	Lung		0.38	1	2.6
Subcohort Phenoxy acids	All deaths	816.5	12.53	17	1.4
	Tumors		3.14	6	1.9
	Stomach		0.33	2 *	6.1
	Lung		0.61	0	0
Subcohort Amitrol + phenoxy acids	All deaths	702.5	7.25	15 **	2.1
	Tumors		1.78	6 ***	3.4
	Stomach		0.18	1	5.6
	Lung		0.35	1	2.9

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.005$.

curred in the combined exposure cohort versus 0.18 expected. There was one case of lung cancer in each of the subcohorts with exposure to amitrol and combined exposure to amitrol and phenoxy acids (table 2). A third case of lung cancer had occurred since the previous analysis; however, only two of the three cases met the requirement

Table 3. Observed and expected number of deaths among herbicide sprayers in the total cohort and subdivisions with regard to the time-course of exposure, 10 a of induction-latency time required.

Cohort	Cause of death	Person-years of observation	Expected	Observed	Rate ratio
Total	All deaths	2,132	27.61	36	1.3
	Tumors		6.87	15 ***	2.2
	Stomach		0.71	3 *	4.2
	Lung		1.34	2	1.5
Exposure 1957—1961	All deaths	1,749	22.00	31 *	1.4
	Tumors		5.44	13 ***	2.4
	Stomach		0.57	3 *	5.3
	Lung		1.06	1	0.9
Exposure 1962 and later	All deaths	383	5.61	5	0.9
	Tumors		1.43	2	1.4
	Stomach		0.14	0	0
	Lung		0.28	1	3.6

* $p < 0.05$, *** $p < 0.005$.

Table 4. Cancer sites among railroad workers exposed to herbicides.[a]

Subcohort	Case number	Diagnosis	Year of diagnosis	Latency time (a)	Year of death	Latency time (a)
Amitrol	163	Ca maxillaris	1970	12	1972	14
	354	Reticular cell sarcoma (retroperitoneal)	1972	14	1973	15
	138	Mb Hodgkin	1974	13	—	—
	014	Ca pancreatis	1965	7	1965	7
	256	Ca pulm. (oat cell ca)	1967	9	1967	9
	257	Ca pulm. (acinous adenoca)	1970	13	1972	15
	135	Ca vesicae urinariae	1969	12	—	—
Phenoxy acids	127	Ca ventriculi	1972	15	1972	15
	172	Hypernephroma	1972	14	1976	18
	173	Ca ventriculi	1975	17	1975	17
	268	Ca recti	1967	7	1978	—
	317	Mb Hodgkin	1970	12	1978	20
	328	Ca prostatae	1977	10	1978	11
	388	Leukaemia	1973	12	—	—
	113	Tumor cerebri	1978	18	1978	18
Amitrol + phenoxy acids	009	Leukaemia	1969	12	1975	18
	010	Ca ventriculi	1976	19	1976	19
	079	Ca coli	1970	10	1973	13
	309	Ca epipharyngis	1968	9	1973	14
	334	Ca prostatae	1971	12	1972	—
	098	Ca labii	1962	2	—	—
	266	Tumor cerebri	1970	13	1970	13
	290	Ca pulm	1976	10	1977	11

[a] Two cases, numbers 268 and 334, registered as cancers by the Cancer Registry and included in the previous study seem to be uncertain in view of the cause of death; the cancer diagnosis was not confirmed by the National Central Bureau of Statistics.

of a 10-a induction-latency period (table 4).

In view of the time course of exposure (table 3), the increased mortality due to tumors was mainly observable among the workers exposed in 1957—1961. However, the individuals in this group tended to be older, and no age standardization was made between them and those exposed in 1962 or later. Moreover, the number of person-years only amounted to 383 for those with the later exposure.

As indicated in table 4, no specific type of tumor can be considered to predominate, although there were three stomach cancers and three lung cancers. Instead, an increase in overall tumor mortality seems to be the trend among these railroad workers.

Discussion

In a retrospective study, exposure evaluation and the assessment of different cohorts could be influenced by knowledge of diseases and deaths among the workers. To determine whether such a bias existed in this study, we studied the mortality rate of different subcohorts for the period 1972—1978, ie, for the prospective period of this study. With the requirement of 10 a for induction-latency time there was still an overmortality due to tumors in the subcohorts with exposure to phenoxy acids, 6 observed versus 2.60 expected, and for the combination of phenoxy acids and amitrol, 5 observed versus 1.34 expected (table 5).

Moreover, the group of railroad workers consisted of people from all over the country, and therefore the use of national death rates in the estimation of expected numbers of deaths was reasonable. Neither was there a deviating pattern in smoking habits in a comparison to the national average, as shown already in the original study (2).

In this updated analysis of the causes of death among railroad workers with exposure to different herbicides, particularly amitrol and phenoxy acids, the observed number of tumor deaths was higher than expected, especially among those with an early exposure to both amitrol and phenoxy acids. However, the tumor mortality among persons exposed to amitrol was rather moderate, and the earlier slight excess of tumor deaths among people exposed to phenoxy acids had become more pronounced. In particular there was an excess of stomach cancer, 3 observed cases versus 0.41 expected, among those with exposure to phenoxy acids in 1957—1961, including those with a combined exposure. For the workers exposed to amitrol during 1957—1961, including those with combined exposure to phenoxy acids, the expected number of tumor deaths was 3.14 and the observed number was 9. When the amitrol workers with exposure in 1962 or later

Table 5. Observed and expected number of deaths in 1972—1978 in different subcohorts of the herbicide sprayers, 10 a of induction-latency time required.

Subcohort	Caused of death	Person-years of observation	Expected	Observed	Rate ratio
Amitrol	All deaths	451.5	6.39	4	0.6
	Tumors		1.61	3	1.9
	Stomach		0.15	0	—
	Lung		0.32	1	3.1
Phenoxy acids	All deaths	624.5	10.29	15	1.5
	Tumors		2.60	6	2.3 *
	Stomach		0.26	2	7.7 *
	Lung		0.50	0	—
Amitrol + phenoxy acids	All deaths	479.5	5.39	13	2.4 ***
	Tumors		1.34	5	3.7 *
	Stomach		0.12	1	8.3
	Lung		0.27	1	3.7

* $p < 0.05$, *** $p < 0.005$.

were also included, the expected number of deaths rose to 3.73, and the observed number to 10. Of the 10 there were 2 cases of lung cancer versus 0.73 expected, but otherwise there was no particular overrepresentation of different types of tumors.

The tumor incidence was also updated but provided little additional information. The incidence data have therefore been omitted from this presentation.

Although the result of the previous analysis of deaths among railroad workers was confirmed with respect to an excess of tumors, the aspects of the causal relationships remain rather unclear, especially since the workers exposed to a combination of amitrol and phenoxy acids seem to have been the most seriously affected. The overrepresentation of stomach cancer, even though the number of cases was small, agrees to some extent with another observation of a tendency towards a gastrointestinal location of mesenchymal tumors in relation to exposure to phenoxy acids (Hardell, personal communication).

The excess of tumors among the workers with early exposure was quite obvious, while those exposed in 1962 or later did not show a clear excess mortality. This finding might be interpreted in different ways, eg, the variety of herbicides during the early period could be of importance and/or the work conditions may have been much more primitive and the herbicide handling more careless, resulting in a higher degree of exposure. There is also the possibility that 2,4,5-T preparations at that time contained higher concentrations of impurities such as chlorinated dibenzodioxines. It should be remembered, however, that today there is also some evidence of a carcinogenic effect of not only 2,4,5-T but also other phenoxy acids (6, 14).

Epidemiologic experiences of an increased mortality from lung cancer among pesticide workers have also been reported in the German Democratic Republic (4). The German workers were exposed both to the phenoxy acids 2,4-D and 4-chloro-2-methyl-phenoxy acetic acid (MCPA) and to a number of other pesticides, ie, organic phosphorous compounds, lindane and organic nitro compounds. In the future, therefore, it seems necessary to try to identify and follow more purely exposed groups so that a more definite evaluation of the effects of the different pesticides can be obtained, especially the effects of those pesticides used in large quantities like the phenoxy acids. However, enough evidence seems to have been accumulated from both animal data and human studies to suggest the need for the careful handling of amitrol and phenoxy acids, perhaps particularly the 2,4,5-T preparations, as increasingly suspicious carcinogens, although other epidemiologic data do not show any excess of tumors among workers with exposure to 2,4-D and 2,4,5-T (13).

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