ORIGINAL ARTICLE

Mortality and cancer incidence among alachlor manufacturing workers 1968–99

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Background: Alachlor is the active ingredient in pre-emergent herbicide formulations that have been used widely on corn, soybeans, and other crops. It has been found to cause nasal, stomach, and thyroid tumours in rodent feeding studies at levels that are much higher than likely human exposures.
Aims: To evaluate mortality rates from 1968 to 1999 and cancer incidence rates from 1969 to 1999 for alachlor manufacturing workers at a plant in Muscatine, Iowa.
Methods: Worker mortality and cancer incidence rates were compared to corresponding rates for the Iowa state general population. Analyses addressed potential intensity and duration of exposure.
Results: For workers with any period of high alachlor exposure, mortality from all causes combined was lower than expected (42 observed deaths, SMR 64, 95% CI 46 to 86) and cancer mortality was slightly lower than expected (13 observed deaths, SMR 79, 95% CI 42 to 136). Cancer incidence for workers with potential high exposure was similar to that for Iowa residents, both overall (29 observed cases, SIR 123, 95% CI 82 to 177) and for workers exposed for five or more years and with at least 15 years since first exposure (eight observed cases, SIR 113, 95% CI 49 to 224). There were no cases of nasal, stomach, or thyroid cancer.
Conclusions: There were no cancers of the types found in toxicology studies and no discernible relation between cancer incidence for any site and years of alachlor exposure or time since first exposure. Despite the small size of this population, the findings are important because these workers had chronic exposure potential during extended manufacturing campaigns, while use in agriculture is typically limited to a few days or weeks each year.

There has been significant interest in recent years about the health experience of farmers and other pesticide exposed populations. In general, farmers have lower mortality and cancer rates than the general population,[1 2] largely due to a low prevalence of cigarette smoking.[3 4] There is some disagreement about whether, on balance, farmers have increased rates of certain types of cancer,[1 2] other than lip cancer, and research is ongoing to assess the site specific cancer experience of large agricultural populations of pesticide users.[5]

Alachlor (2-chloro-2′,6′-diethyl-N-[methoxymethyl] acetanilide) is the active ingredient in herbicidal formulations that have been used extensively for pre-emergent weed control for corn, soybeans, and other crops. Monsanto Company has manufactured alachlor since March 1968 in Muscatine, Iowa. From 1969 to 1987, alachlor was second only to atrazine in pounds applied in United States agriculture.[6 7] It is no longer widely used in the United States, having been replaced by a closely related acetanilide molecule, acetochlor, which has similar herbicidal efficacy at a much lower application rate.

Toxicological research

Chronic feeding studies with high doses of alachlor have been found to cause nasal, thyroid, and stomach tumours in rats, but not in mice.[8 9] Mechanistic research suggests that these tumours result from non-genotoxic, threshold based modes of action to which the rat is especially sensitive.[10] The rat nasal tumour mode of action involves a diethyliminoquinone metabolite of alachlor and related local cytotoxicity and cell proliferation. The stomach tumours appear to develop through a combination of regenerative cell proliferation and a gastrin induced tropic effect on the gastric mucosal epithelium. Lastly, the thyroid tumours are believed to be a secondary effect of liver enzyme induction, resulting in increased elimination of thyroid hormone and a compensatory stimulation of the thyroid gland leading to hyperplasia and eventually neoplasia. The effective doses in these studies are much higher than the range of anticipated human exposures.[10]

Previous epidemiological research

Previously, we reported mortality and cancer incidence findings for alachlor manufacturing workers for the period 1968 to 1993.[11 12] The cohort of workers was relatively young as of 1993 (that is, 74% of person years under observation were less than 40 years of age), and the maximum follow up period was less than 25 years. Nonetheless, the results were important because the chronic exposure potential in manufacturing is unique. In contrast, use in agriculture is limited to a few weeks each year early in the planting season, and most agricultural users work with alachlor only a few days each year. Periodic follow ups of this cohort, therefore, have a relatively high importance in any comprehensive assessment of potential health risks of alachlor exposure. In this article, we update mortality and cancer incidence findings for alachlor manufacturing workers to the end of 1999.

METHODS

Eligibility for mortality analyses and vital status follow up

The Muscatine plant population was enumerated from hard copy records at the plant, computerised personnel files, and

Abbreviations: 95% CI, 95% confidence interval; CML, chronic myeloid leukaemia; NDI, National Death Index; OEC, occupational exposure categories; SHRI, State Health Registry of Iowa; SIR, standardised incidence ratio; SMR, standardised mortality ratio; SSA, Social Security Administration; USEPA, United States Environmental Protection Agency

Main messages

- Mortality and cancer incidence were similar to expected for alachlor manufacturing workers.
- There were no cancers for workers of the types found in excess in toxicology studies.

Policy implications

- The lack of a discernible relation between exposure and cancer rates for alachlor manufacturing workers, though based on a relatively small and young cohort, is important information for any comprehensive risk assessment for this chemical.

Social Security Administration (SSA) Quarterly Reports on Earnings (form 941A). The cohort was restricted to workers with at least one year of documented employment from plant start up as an ammonia facility in 1961 to 31 December 1999. We excluded 31 workers who were included in our previous studies. These exclusions resulted from a check of personnel records for workers with temporary job titles in which we found 31 instances with gaps in individuals' employment histories and documented employment of less than one year.

The Institutional Review Board (IRB) at the University of Alabama at Birmingham approved the procedures for vital status follow up. Vital status was determined for the cohort until the end of 1999 using a variety of sources including: company payroll, pension and mortality data, SSA, the National Death Index (NDI), and the Iowa state motor vehicle bureau. Death certificates were obtained for all known decedents. We used the underlying cause of death code from the NDI retrieval report when available. Otherwise, trained nosologists coded underlying cause of death from death certificates according to the eighth revision of the International Classification of Diseases (ICD) for deaths that occurred before 1979 and the ninth ICD revision thereafter.[13 14]

Eligibility for cancer incidence analyses and case identification

The cancer incidence cohort was a subset of the mortality cohort, including those subjects who were white and who lived in Iowa for some time during the period 1969–99. The criterion of Iowa residence during the period 1969–99 reflects the catchment area for the State Health Registry of Iowa (SHRI), which was the source for identifying incident cancers in this study. The SHRI is a statewide population based cancer registry that has been operating since 1969 and has been a participant since 1973 in the National Cancer Institute's Surveillance Epidemiology and End Results Program.[15]

The IRBs at the University of Iowa and at the University of Alabama at Birmingham approved procedures for cancer incidence determination and subject tracing. Subjects were matched against the SHRI master database to identify workers diagnosed with invasive cancer after their first alachlor exposure and during the period 1969–99. Cancer cases were identified based on the correspondence between workers' identifying information (social security numbers, full names, and birth dates) in Monsanto's records and in SHRI's database. SHRI was also the source for Iowa general population cancer incidence rates that were used as a basis of comparison for workers' cancer incidence rates.

We used a number of data linkage and tracing procedures to enumerate workers' person-years in the Iowa catchment area for the cancer incidence analysis. We had previously determined residence histories for 98.4% of workers for the period 1969–93,[12] so we focused on updating residence histories for the period 1994–99 and ascertaining residence histories for workers hired after 1993. Current addresses were obtained from company records for active plant workers. Current Iowa residents who lived in Iowa or moved to Iowa when hired at the Muscatine plant were assumed to have lived in Iowa since their plant hire date. Former employees who had a current or forwarding address outside of Iowa—mainly transferees within Monsanto—were assumed to have been Iowa residents from their start date at the Muscatine plant until their transfer or employment termination date. We also matched workers with the Iowa Department of Motor Vehicles and LexisNexis to establish possible Iowa residency after employment termination. Finally, we traced workers whose residence histories remained incomplete through mail and phone surveys to complete as many residence histories as possible. As a result of these tracing procedures, residence history was determined for 97.1% of workers with potential alachlor exposure as of 31 December 1999 (see table 1). The other 2.9% of workers were assumed to have an Iowa exit date equivalent to the latest of their employment termination date, their Iowa motor vehicle license issue date, or their contact date from our previous tracing activities.

Exposure assessment

Plant workers had potential alachlor exposure through occupational contact and, during the period 1968–75, through contamination of plant drinking water. The primary route of occupational exposure was judged to be dermal contact because alachlor has a low vapour pressure (1.6×10^{-5} mm Hg at 25℃),[16] and airborne monitoring at the plant, instituted in 1981, averaged less than 100 ppb from February 1981 to June 1982, less than 20 ppb from July 1982 to February 1983, which were the limits of detection of the monitoring method during those periods, and less than 10 ppb thereafter.[17] There was insufficient information to estimate quantitatively the amount of dermal exposure during the study period. Therefore, our exposure estimation was qualitative, based on work history information, industrial hygiene judgement, and, to a lesser extent, recent exposure monitoring data.

We updated, through 1999, an existing department/job title dictionary and exposure matrix that covered all work locations and job assignments found in workers' personnel records through 1993.[18] New job titles during the period 1994–99 were identified, consolidated based on similar exposure potential, and organised into occupational exposure categories (OEC). Each job for each worker, therefore, corresponded to an OEC and was assigned a high, medium, low, or negligible qualitative exposure ranking for alachlor as well as for other specific chemicals. We classified workers for analysis based on having any alachlor exposure, any high alachlor exposure, and according to the length of time they held jobs with potential exposure. The qualitative exposure rankings for the entire period 1968–99 did not discriminate between daily and intermittent exposures for workers with different jobs in the same department/location. Thus, production and maintenance workers had the same exposure ranking, though exposure opportunities for maintenance workers were intermittent.

A source of potential exposure of uncertain magnitude and duration was inadvertent contamination of the plant drinking water. In 1975, while developing a method for measuring

Table 1 Distribution of workers by sex, alachlor exposure status, and follow up status

Group	Men	Women	Total
Mortality study			
Total workforce	1091	300	1391
No alachlor exposure (excluded)	125	60	185
Alachlor exposed	966	240	1206
Alive	920	227	1147
Dead	42	6	48
Lost to follow up	4	7	11
Incidence study			
Mortality cohort	966	240	1206
Non-whites (excluded)	32	12	44
Left Iowa before 1969 (excluded)	4	1	5
Never lived in Iowa (excluded)	4	0	4
Incidence sub-cohort	926	227	1153
In Iowa through study end or death date	629	157	786
Left Iowa, date known	274	60	334
Incomplete residence history	23	10	33
Incident cancers	29	7	36

alachlor concentrations in water, a ''control'' sample from the plant's drinking water was found to have an alachlor concentration of 2 mg/l (that is, 2 parts per million). Plant management immediately brought in bottled drinking water for workers and, soon thereafter, switched the plant's water supply to other wells at the plant. Alachlor measurements from the new wells averaged 8 µg/l (that is, 8 parts per billion) throughout 1980. At that time, a carbon filtration system was completed that reduced alachlor in the water supply to below the detection level of 0.03 µg/l (that is, 30 parts per trillion).

Workers' exposure to alachlor from plant drinking water would have depended on the duration of the water contamination and the amount of water consumed on a daily basis. Both aspects of exposure are unknown. We estimate that exposure from drinking a litre of water at 2 ppm would be approximately equivalent to the exposure potential for a job classified as having high exposure. Therefore, we classified all workers employed from 1968 to 1975 in the high exposure category—to allow for the maximum possible period of drinking water contamination—even if their jobs entailed no occupational exposure. We had found previously that there was little effect on results from assuming more restrictive periods of drinking water contamination.[12]

Epidemiological analysis

We calculated standardised mortality ratios (SMR) and standardised incidence ratios (SIR) to compare disease rates for alachlor workers with rates for the Iowa general population. These measures were expressed as 100 times the ratio of observed to expected events and are equivalent to the ratio, on a percentage basis, of disease rates for workers and the general population adjusted for age, sex, race, and calendar period. The numbers of expected deaths or incident cases were calculated by summing the product of the number of employee person-years, stratified by five year age groups, five year calendar periods, and sex, and rates for the corresponding groups in the Iowa general population. We obtained Iowa mortality rates for males and females from the Mortality and Population Data System (MPDS) of the University of Pittsburgh. The mortality rates were based on deaths coded according to the 8th ICD revision before 1979 and the 9th ICD revision thereafter. MPDS rates for Iowa were available for the period 1962–98 for all causes and for non-cancer causes of death and for the period 1950–98 for cancer deaths. We applied Iowa rates for the period 1995–98 to employee person-years accumulated between 1995 and 1999 to obtain the expected number of deaths for the latter calendar period category. The Occupational Cohort Mortality Analysis Plus Program was used to conduct the SMR and SIR analyses.[19] The 95% confidence interval (CI) was calculated as a measure of the statistical variability of the SMR or SIR.

Enumeration of person-years for the mortality and cancer incidence analyses began one year after first employment or on the date of first alachlor exposure, if later. For the mortality analysis, person-years were accumulated through the end of study date for employees found to be alive, until date lost to follow up for workers whose vital status was unknown, or until death date for deceased employees.

For the cancer incidence analyses, for workers who did not have a SHRI cancer diagnosis, person-years were accumulated until the end of the study period for employees who were alive and residing in Iowa at the end of study date, until the date of death for employees who died in Iowa during the study period, until the Iowa exit date for employees who were known to have left the state before the end of 1999, or until the date of last known Iowa residence for employees with incomplete residence histories. Workers with an SHRI cancer diagnosis were withdrawn from analyses of specific cancers on the date when that specific cancer was diagnosed. They remained at risk, however, for other cancers as long as they were Iowa residents.

SMRs and SIRs were evaluated for workers by the number of years of alachlor exposure and by the time since first exposure. The latter is most informative for analyses of chronic conditions that take years to develop after sufficient occupational exposure.

We excluded employees who did not work in alachlor departments and who were not employed at the plant during the 1968–75 and 1976–80 drinking water contamination periods. The major non-alachlor departments included ammonia production and storage before 1968, and acrylonitrile-butadiene-styrene plastics production during the period 1975–99. For the cancer incidence analysis, we excluded non-whites and plant employees who never lived in Iowa.

RESULTS

Mortality

A total of 1206 workers met the criteria for inclusion in the mortality analysis and had potential alachlor exposure in manufacturing jobs or via the plant drinking water (table 1). As of the end of our study period, 95% were alive, 4% were dead, and 1% were lost to follow up. The median ages at the

end of follow up were 46 for workers with any alachlor exposure and 49 for workers with potential high exposure.

For the period 1968–99, mortality from all causes combined was lower for alachlor workers than for the Iowa population (table 2). Mortality from cancer was similar to Iowa rates and there were no deaths from cancers of the stomach, thyroid, or nose. Cardiovascular and respiratory disease rates were lower than rates for Iowa residents. There were too few observed and expected deaths for more detailed analyses.

Cancer incidence

The cancer incidence sub-cohort had 1153 workers with potential alachlor exposure (table 1). Of these, 68% lived in Iowa for the entire study period; the Iowa exit date was known for all but 33 of the remaining workers. Linkage with SHRI identified 36 invasive cancers during the study period. Cancer incidence was slightly, but not statistically significantly, higher for all alachlor workers than for the Iowa general population (table 3). Among workers judged to have had high alachlor exposure, including occupational exposures and presumed drinking water exposures during the 1968–75 period, there were 29 observed cancers versus 24 expected. Cancer incidence was similar to expected values for workers with five or more years of high exposure and 15 or more years since first exposure.

There were no nasal, stomach, or thyroid cancers for workers with alachlor exposure. The expected numbers of cases for these sites were small: 0.1, 0.5, and 0.8, respectively. The only cancer found to be statistically significantly increased among workers with high exposure was chronic myeloid leukaemia (CML), based on two observed cases (table 4). There was, however, no case of CML among workers with at least five years' exposure and 15 years from first high exposure. One of the CML cases was diagnosed three years after first exposure, which, given the usual course of CML, suggests aetiological factors that preceded the period of alachlor exposure. Among other cancers, malignant melanoma was somewhat more frequent than expected among all alachlor exposed workers. There was no case of melanoma among workers with five or more years of high alachlor exposure and 15 years since first exposure. Findings for other cancers were in line with expectations given the small number of observed and expected cancers.

DISCUSSION

Patterns of mortality and cancer incidence for alachlor workers to the end of 1999 are very similar to those reported previously.[12] Overall, mortality rates for workers were lower than general population rates and there was an appreciable deficit of deaths from ischaemic heart disease. Cancer mortality was somewhat less frequent than expected among workers. The small number of deaths for individual cancers precludes further evaluation. Overall, the mortality profile for these workers was typical of that for a healthy employed population.

Cancer incidence rates of workers were slightly higher, though not significantly different, than rates for the Iowa general population. There were no cases of the types of cancers found in excess in toxicology studies and no discernible relation between cancer incidence for any site and years of alachlor exposure or time since first exposure. Workers with more than five years in high exposure jobs and 15 years since first exposure had approximately as many observed as expected cancers. Incidence rates were significantly increased for all workers for malignant melanoma and chronic myeloid leukaemia, but the pattern of incident cases does not support a causal interpretation.

It is noteworthy that while cancer mortality was slightly lower than general population rates, cancer incidence was slightly higher. This was due largely to the excess incidence of malignant melanoma and the lack of any deaths related to these cancers. Incidence results for testicular and colorectal cancer, though not significant, also contributed to the small disparity between mortality and incidence findings. Since melanoma, testicular cancer, and colorectal cancer were not associated with estimated alachlor exposure, the disparity between cancer incidence and mortality could be due to greater medical surveillance or more effective therapy among this employed population, to chance, or to confounding factors.

There are a number of limitations to this study. First, the numbers of deaths and incident cancers are small as reflected in SMRs and SIRs that are relatively imprecise. Compared

Table 2 Standardised mortality ratios* (SMRs) 1968–99 for various causes of death for employees with potential alachlor exposure (work place and drinking water)

	Any exposure			High exposure		
Cause of death	O/E†	SMR	95% CI	O/E†	SMR	95% CI
All causes	48/79.1	61	45 to 80	42/65.8	64	46 to 86
All cancers	16/19.4	82	47 to 134	13/16.4	79	42 to 136
Digestive	6/4.5	133	49 to 288	4/3.9	104	28 to 265
Oesophagus	1/0.5			1/0.4		
Stomach	0/0.5			0/0.4		
Colon	2/1.8	111	13 to 400	0/1.5	0	0 to 240
Rectum	0/0.4			0/0.3		
Liver	1/0.3			1/0.3		
Pancreas	1/0.9			1/0.8		
Lung	2/6.0	34	4 to 121	2/5.2	39	5 to 139
Melanoma	0/0.5			0/0.4		
Breast	0/0.8			0/0.6		
Prostate	0/0.6			0/0.5		
Kidney	0/0.5			0/0.5		
Non-Hodgkin's lymphoma	2/0.9	215	26 to 776	2/0.8	260	31 to 937
Leukaemia	2/0.9	223	27 to 804	2/0.7	275	33 to 994
Ischaemic heart disease	10/18.9	53	25 to 97	9/16.6	54	25 to 103
Non-malignant respiratory disease	1/3.5	28	1 to 157	1/3.1	33	1 to 181
External causes	15/18.3	82	46 to 135	14/13.9	100	55 to 169
Accidents	8/12.9	62	27 to 122	7/9.9	70	28 to 145

*SMRs and 95% CIs were not calculated unless observed or expected cases exceeded 1.
†Observed number of cases/expected number of cases.

Table 3 Standardised incidence ratios (SIRs) for all cancer for employees with potential alachlor exposure (workplace or drinking water)

Years of exposure/years since first exposure	Subjects*	Person-years	O/E† cases	SIR	95% CI
All alachlor exposed workers					
<5 years/<15 years	1152	7081	9/5.8	156	71 to 297
<5 years/15+ years	260	2010	6/4.9	124	45 to 269
5+ years/<15 years	519	4350	5/4.9	102	33 to 237
5+ years/15+ years	433	4441	16/12.8	125	72 to 203
Total‡	1153	17882	36/28.3	127	89 to 176
Workers with high alachlor exposure					
<5 years/<15 years§	699	6697	6/5.8	104	38 to 226
<5 years/15+ years	387	3747	12/9.1	132	68 to 230
5+ years/<15 years	158	1454	3/1.6	183	38 to 534
5+ years/15+ years	142	1994	8/7.1	113	49 to 224
Total[c]	700	13891	29/23.6	123	82 to 177

*Numbers of workers not mutually exclusive across groups, though person-years are.
†Observed number of cases/expected number of cases.
‡One worker moved into the Iowa study area after achieving either five years' exposure or 15 years since first exposure.
§Refers to years of high exposure and years since first high exposure.

with our previous publication,[12] however, the findings of the present study reflect an 80% increase in the number of deaths and a 50% increase in the number of cancers. As the cohort ages and background mortality and cancer incidence accelerates, future updates of this cohort will become increasingly informative.

A second limitation is the potential for exposure misclassification due to the difficulty in estimating dermal occupational exposures and exposures from plant drinking water. Nonetheless, exposure estimation is more straightforward for these manufacturing workers than for agricultural populations because the plant manufacturing history is well documented, there is a long standing industrial hygiene programme, and work history records documenting departmental assignments and workers' jobs were fairly complete.

Lastly, we were not able to control for cigarette smoking or other potential confounding factors (for example, sunlight exposure, obesity). We based our analysis on mortality and cancer incidence rates for Iowa residents, controlling for sex, age, race, and calendar period, to minimise the potential for confounding by these factors. However, there are likely to be some differences in the distribution of confounding factors between workers and the general population. There was some information on smoking available to us from worker medical examinations from the period 1982 to 1990. In 1989, for example, smoking prevalence at the plant, based on medical examinations for almost every active worker, was 32%. Smoking prevalence for the Iowa general population based on the 1989 Behavioral Risk Factor Survey was 21% for men and 24% for women.[20] Nonetheless, mortality rates for major smoking related causes of death and smoking related cancers were lower for workers than for the general population.

Despite the limitations of this study, the findings are important for assessing potential alachlor related health risks. The exposure circumstances for this manufacturing cohort are unique in terms of exposure duration and intensity compared with those who use alachlor in agricultural applications. Periodic follow up of this cohort, therefore, in

Table 4 Standardised incidence ratios* (SIRs) for various cancers for employees with potential alachlor exposure (workplace or drinking water)

	Any alachlor exposure			High alachlor exposure			5+ years high exposure 15+ years since first exposure		
Type of cancer	O/E†	SIR	95% CI	O/E†	SIR	95% CI	O/E†	SIR	95% CI
All cancers	36/28.3	127	89 to 176	29/23.4	123	82 to 177	8/7.1	113	49 to 224
Buccal cavity	2/1.4	144	17 to 520	2/1.2	163	20 to 590	0/0.5		
Digestive	8/5.6	142	61 to 279	6/4.9	122	45 to 265	2/1.9	108	13 to 389
Colon	4/2.4	169	46 to 434	4/2.1	194	53 to 497	2/0.8	256	31 to 925
Rectum	2/1.3	160	19 to 580	0/1.1	0	0 to 224	0/0.4		
Liver, gall bladder	1/0.4			1/0.3			0/0.1		
Pancreas	1/0.6			1/0.6			0/0.2		
Lung	2/4.5	45	5 to 162	2/4.0	50	6 to 181	1/1.7	59	2 to 327
Melanoma	6/2.2	278	102 to 606	4/1.8	229	62 to 587	0/0.4		
Breast	2/2.8	71	9 to 255	2/2.0	101	12 to 363	0/0.3		
Female genital	2/1.5	136	17 to 492	1/1.0			0/0.2		
Prostate	4/3.5	115	31 to 295	4/3.2	125	34 to 319	2/1.7	120	15 to 434
Testis	3/1.3	235	49 to 686	1/1.0			0/0.1		
Kidney	1/1.1	94	2 to 526	1/0.9			1/0.4		
Non-Hodgkin's lymphoma	3/1.7	173	36 to 504	3/1.5	207	43 to 604	1/0.5		
Hodgkin's disease	1/0.7			1/0.5			0/0.1		
Leukaemia	2/1.1	176	21 to 636	2/1.0	206	25 to 744	0/0.3		
Chronic myeloid leukaemia	2/0.2	955	116 to 3448	2/0.17	1165	141 to 4210	0/0.04		

*SIRs and 95% CIs were not calculated unless observed or expected cases exceeded 1.
†Observed number of cases/expected number of cases.

conjunction with ongoing studies of farmers and applicators should provide the most comprehensive assessment of potential health risks for workers with various levels of alachlor exposure. At present, the available data for this relatively young cohort of manufacturing workers does not indicate a discernible hazard from alachlor exposure during the period 1969–99.

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