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Occupational and other environmental factors and multiple myeloma: a population based case-control study

Mikael Eriksson, Maria Karlsson

Abstract

Epidemiological studies on the aetiology of multiple myeloma are reviewed as a background to this population based case-control study performed in an area with a high incidence of multiple myeloma. The purpose was to identify and evaluate several suspected environmental factors in relation to this disease. A total of 275 confirmed cases diagnosed in four counties in northern Sweden during four years were compared with the same number of control subjects drawn from population registries. The controls were matched for age, sex, county, and vital status. Occupations and work associated exposures to chemicals and other potential carcinogens were assessed by an extensive questionnaire that also included questions on smoking habits, residential building materials, vicinity to electrical power lines, and leisure time contact with animals, electrical equipment, and chemicals. Information obtained from the questionnaires was completed by telephone interviews when necessary. Univariate analysis and multivariate logistic regression were performed. The study confirmed an association found earlier between farming and multiple myeloma. Some domestic animals (cattle, horses, and goats) and two types of pesticides (phenoxyacetic acids and DDT) were indicated as risk factors within farming. Exposure to electromagnetic fields, asbestos, and organic solvents were negatively associated with myeloma in this study.

Multiple myeloma is an incurable malignant lymphoproliferative disease with an increasing incidence and mortality in several countries. The causes of the disease are poorly understood. Some reports on familial multiple myeloma indicate a possible hereditary influence.[1-4]

Exposure to high doses of ionising radiation is now generally accepted as a factor increasing the risk of developing multiple myeloma. Atomic bomb survivors in Hiroshima and Nagasaki have been clearly shown to have a dose related increase in the risk for multiple myeloma, with rather long latency periods.[5-7] Workers at the Hanford atomic plant in Washington State have been followed up regarding different causes of death, and a statistically significant dose-response trend for degree of radiation exposure has been obtained for multiple myeloma, although this was based on few exposed cases.[8-11] A survey of all cohorts of persons exposed to radiation for which data on cancer related mortality were available showed an excess of multiple myeloma in most cohorts.[12]

An association between farming and multiple myeloma was first found in a case-control study from Washington State." Several studies with different methodologies and from different countries have confirmed this finding,[14-26] but some other recent epidemiological studies do not support the association.[27 28] In a case-control study from the middle of Sweden a statistically significant increased crude rate ratio (RR) of 1.9 for farming was obtained, but in further analysis with multiple regression the RR decreased to 1.4, which was not significant.''

Some studies have investigated further the possible connection between farming and multiple myeloma by trying to identify specific risk factors. Thus some American studies with different methodologies indicate an association between exposure to pesticides and multiple myeloma[i6 23 30 31] but no firm conclusions could be drawn concerning any particular class of pesticides responsible for the increase in risk. A study from New Zealand did not find any significant differences between cases and controls regarding potential exposure to phenoxy herbicides, chlorophenols, or any other agricultural chemicals, whereas significantly raised RRs were found for sheep farming and exposure to beef cattle."

Exposure to asbestos has been connected with

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multiple myeloma in two recent case-control **studies,**[21,27] but by contrast a recent American study did not find any such **association.**[23] Furthermore, an American multicentre population based case-control study did not find any correlation between jobs with probable exposure to asbestos 7nd multiple myeloma.=

Benzene is an established risk factor for acute leukaemia, and multiple myeloma and other haematological malignancies have been associated with exposure to benzene or other organic **solvents.**[22,31,33,34] Occupational exposure to petroleum products gave an increased **risk** for myeloma in a case-control study[27] as **well** as in a cohort study,'' both from the United States. Other chemical exposures associated with observed increases in incidence or mortality in multiple myeloma in single studies encompass **arsenic,**[36,37] lead,'' carbon monoxide,'' and engine exhausts and creosote.'' Some specific occupations with potential exposure for different chemicals have **also** been identified as entailing an increased **risk** of myeloma—for example, hairdressers and **cosmetologists,**[14,39,40] machinists,'' and leather **workers.**''[43]

Some studies have connected multiple myeloma with the furniture **industry**[44,45] or carpentry.'' Furthermore, a Swedish case-control study found woodworkers in contact with fresh wood to be at risk for myeloma.''

The possible carcinogenic effect of electromagnetic fields **has** been much debated in recent years as a result of some epidemiological studies. A cohort study from the western United States investigating mortality in amateur radio operators exposed to electromagnetic fields showed a statistically significant increased mortality from malignancies of lymphatic tissues, including multiple myeloma and non-Hodgkin's lymphoma.''

The present study investigated those suspected risk factors for multiple myeloma, in a **high** incidence area of Sweden. **Special** emphasis was placed upon possible hazards in farming, such as contact with pesticides and different domestic animals.

Materials and methods

CASES

Ail persons living in the four most northern counties of Sweden who were diagnosed as having multiple myeloma and were reported to the Swedish Cancer Registry between **1** July **1982** and **30** June **1986** were eligible for inclusion in **this** study. In Sweden all physicians are obliged to report all incident cases of malignant tumours to the Cancer Registry.

In this way **293** patients with a diagnosis of myeloma were identified. The medical records of these patients were scrutinised to confirm the diagnosis, and all cases who could not fulfil widely accepted diagnostic criteria proposed for use in therapeutic trials[47] were excluded. A total of **18** patients did not meet these criteria. The remaining **275** patients constituted the cases; **156** (57%) of these were alive and **119 (43%)** were deceased. No restrictions regarding age or sex were used. Of all cases **141** were men and **134** were women.

CONTROLS

For every living case two eligible control persons were extracted from the Swedish National Population Registry. **This** was done through a matching procedure taking into consideration age, sex, and county. In Sweden everybody has a unique personal identity number composed of date of birth and four additional figures. The two persons with same sex, living in the same county and being closest in personal identity number—that is, in age—to the respective case were selected, and from these two, one was randomly chosen as the control person.

For each deceased case, one deceased control was selected in an equivalent way from the National Registry for Causes of Death. The same matching criteria as for the living cases were used, and, furthermore, the deceased controls were matched on year of death. For reasons of humanity, persons who committed suicide were not used as controls. The study thus involved **275** cases and **275** controls, in all 550 persons.

ASSESSMENT OF EXPOSURE

An extensive questionnaire was mailed to all living subjects in the study. To obtain data concerning deceased persons the questionnaire was sent to the next of kin defined in the order of husband or wife, child, parent, sibling, or other. The specific nature of the investigation was not disclosed, and there was no reference to the special disease under study. Instead, the general information given was that different factors of potential importance for health were studied. The questionnaires contained several questions regarding the persons' various jobs over the years, as well as time and place for employment, and work associated exposure to chemicals and other potential carcinogens. It also included questions about smoking habits, residential building materials, vicinity to electrical power lines, and leisure time contact with animals, electrical equipment, and **chemicals.**

At the end of the questionnaire were some pages with questions concerning diseases, medications, and other treannents, as well as an inquiry about hereditary circumstances. These pages were detached and filed by a secretary for later analysis when the questionnaires were returned from the subjects, **so** as not to disclose whether the subject was a case or a control. That particular information is not considered further in this presentation.

After this all questionnaires were handed over to a

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specially trained interviewer who did not know whether the persons were cases or controls. The interviewer scrutinised all answers and supplemented them by telephone according to written instructions if any data were unclear or incomplete. Some subjects, or next of kin, were unable or unwilling to answer the questionnaire, but accepted a telephone interview, which did not then include the questions about diseases, treatments, and heredity. This avoided interviewer bias by not disclosing whether the subject was a case or control.

All persons who had been working in agriculture were carefully questioned if any answers about livestock or use of pesticides were missing. Furthermore, regardless of the answers in that respect all persons who had been working within farming, forestry, or horticulture during the period when pesticides have been used in Sweden (since 1945) were phoned to ensure a good and uniform assessment of exposure to such chemicals. In the same way all persons who, during this period, had been employed in saw mills, where different biocides have been used to protect against blue stain and as impregnates, or employed as roadworkers, or railroad embankment workers were phoned to verify and specify any exposure to pesticides.

After the questionnaires had been completed by the interviewer, the front page, including name, personal identification number, and address, was removed, thus enabling a blinded coding of the answers by one of us (ME).

Some special considerations were taken into account when assessing different exposures. Thus as in earlier epidemiological studies in the same geographical area a minimum exposure of one whole working day was used for exposure to phenoxyacetic herbicides and the related chlorophenols.

If the information about type or trade names of biocides was lacking or unsure, even if there was a strong suspicion, the subject was only regarded as exposed to pesticides in general and not to any specific type of substance.

Exposure to organic solvents is common in some occupations, and also occurs in some leisure time work and hobby activities. Separate analyses were done for these two types of exposure.

Enquiries about the building material of all dwellings inhabited by the subjects were made. In the analysis, the subjects were regarded as exposed if they had ever lived in a house built of the material in question. Wood, stone, concrete, light concrete, plaster and brick were thereby analysed separately. According to estimations of γ-radiation from different building materials in Swedish dwellings[48] stone, concrete, and light concrete houses were also analysed by aggregation, and the same was done for plaster and brick houses.

Only subjects who reported that they had been living less than 1 km from electric power lines were regarded as exposed to an electromagnetic field.

The above mentioned criteria for different exposures were all decided before the coding of exposure.

STATISTICAL METHODS

For calculation of the RR the maximum likelihood estimate was used, both in univariate and multivariate models. The procedures "match" and "logreg" in the statistical computer program "Epilog" was used for the univariate matched analysis and the multivariate logistic regression respectively. The 90% confidence intervals (90% CIs) were obtained with the approximative procedure described by Miettinen[49] in the "match" procedure, and with the Newton-Raphson interactive technique in the "logreg". In all analyses the matched pairs were kept together.

All occupations as well as specific exposures were analysed in univariate analyses. Multivariate logistic regression was then used to evaluate the importance of different exposure factors. Occupations were not included in the multivariate model, as these were strongly connected with the specific exposure variables—for example, farmers with domestic animals. The following criteria were used to choose the exposure variables to be included in the multivariate model:

The RR in the univariate analysis had to be either (a) statistically significant with a 90% CI not including unity, or (b) $\geqslant 1{\cdot}5$ or $\leqslant 0{\cdot}67$ (1/1·5), and representing at least 10 exposed subjects.

The variables should not cover other specific exposure variables. Thus the variable "all pesticides", which covers different specific pesticides, as well as the variaoles with combined types of building materials mentioned above, were excluded.

All variables that could meet these criteria were thus analysed in a multivariate model, in which all factors with a risk estimate between 0·9 and 1·1 were gradually excluded. Also, to check any potential confounding from variables not primarily included in the model, the Pearson-correlation coefficient among the referents was used.[50] Thus factors with an absolute value of the correlation coefficient $\geqslant 0{\cdot}25$ and with at least 10 subjects exposed were considered as relevant, and they were included in the model after the initial exclusion steps (table 5).

Results

Of the 312 living subjects, 12 refused to participate in the study, and of the 238 deceased, no answers were obtained from the relatives of seven persons. The refusal rate was consequently 3·45%. Six of the refusers were cases and 13 were controls. Thus 19 subjects and their 19 matched counterparts could not

Table I Occupations and exposures with a staristically significant increased or decreased RR in univariate analysis

Occupation/ exposure factor	No of exposed cases	No of exposed controls	RR (90% CI)
Occupation:			
Fanner	151	121	1·68 (1.23-2.33)
Electrician	3	9	0.33 (0·11–0·81)
Exposure factor:			
Power saw	40	27	1.57 (1·01–2·48)
Asbestos	19	33	0.50(0·29–0·82)
Organic solvents (occupational)	21	37	0·50 (0·30–0·80)
Pesticides, all	81	59	1.55 (1·15–2·26)
Phenoxy acids	20	9	2.22 (1·15–4·66)
DDT	53	32	1·75 (1·19–2·64)
Copy machines	6	14	043 (0·19–0·87)
Electromagnetic fields (occupational)	6	15	0.31 (0·12–0·66)
Cattle	152	118	1.72 (1·27–2·36)
Horses	137	101	1·78 (1·32–2·45)
Hogs	124	99	1.49 (1·11–2·03)
Sheep	60	41	1·66 (1·12–2·49)
Goats	24	11	2.18 (1·20–4·24)

be used in the analysis, which deals with the remaining 512 subjects or 256 matched pairs.

UNIVARIATE ANALYSIS

Table 1 shows the result of the univariate analysis for occupations and exposures with a statistically significant increased or decreased risk. In tables 2 and 3 other occupations and exposure factors with at least 10 exposed subjects or of a special interest because of

Table 2 Occupations without any sraristically significant differences between cases and controls in univariare analysis. Only variables with at least 10 exposed subjecrs or of special interest due to findings in earlier studies are included

Occupation	No of exposed cases	No of exposed controls	RR (90% CI)
Railroad worker	7	11	0·50 (0·18– 1.22)
Road worker	19	17	1.14 (0.63– 2.12)
Motor vehicle driver	17	17	1·00 (0.51– 1.97)
Building metal worker/mechanic*	7	11	0·64 (0.29– 1·34)
Other metal work†	4	8	0·50 (0·18– 1·22)
Miner	8	8	1·00 (0·44– 2.31)
Surface	6	4	1·50 (0.52– 4·83)
Underground	8	7	1.14 (0·49– 2.77)
Gardener/garden worker	4	7	0·57 (0.20– 1·46)
Lumberjack	82	69	1·48 (0.98– 2.27)
Afforestation worker	34	25	1.41 (0·89– 2.27)
Sawmill worker	21	18	1.19 (0·68– 2.11)
Building worker	20	22	0·90 (0.53– 1.53)
Furniture industry worker	2	4	0.50 (0.12– 1.72)
Pulp industry worker	10	10	1·00 (0·44– 2.31)
Laundry worker/ laundress	6	5	1·20 (0·44– 3·44)
Hairdresser/ cosmetologist	2	3	0·67 (0·15– 2·71)
Petrol station/ garage worker	6	7	0.86 (0.34– 2.12)
Refinery worker	1	1	1·00 (0·10–10·06)
Other chemical work	8	7	1.14 (0.4% 2.77)

*Machine-repairman, welder, and plumber included.
†Blacksmith, turner, and founder included.

results in earlier studies on multiple myeloma are presented.

Among occupations only farmers showed an increased risk for myeloma, whereas electricians seemed to be negatively associated with the disease.

Exposure to any pesticides resulted in a significantly increased risk, which was further augmented when only phenoxyacetic herbicides were considered. Exposure to dichlorodiphenyltrichloroethane (DDT) also gave an increased risk for myeloma. On the other hand, no increased risks were noted for exposure to chlorophenols, creosote, arsenic, or mercurial seed dressing. Each and every other type of pesticide was just mentioned sporadically, and none gave a significant RR.

Increased risks were also noted for exposure to different domestic animals—namely, cattle, horses, hogs, sheep, and goats—but not for poultry or any other animals.

Exposure to asbestos gave, contrary to the results of some other studies, a decreased risk for myeloma. Occupational exposure to organic solvents also

Table 3 Exposure factors without any statistically significant differences between cases and controls in univariare analysis. Only variables wirh at leasr 10 exposed subjects or of a special interest due to findings in earlier studies are included

Exposure factor	No of exposed cases	No of exposed controls	RR (90% CI)
Welding	3	7	0.43 (014-1.12)
Tractor driving	19	15	1·40 (0·71–2·89)
Sulphite pulp	6	8	0·67 (0·23–1·81)
Chlorophenols	20	19	1.06 (0·60–1·90)
Organic solvents (leisure time use)	43	37	122 (0·80–1·89)
Man made mineral fibres	14	13	1·08 (0·56–2·13)
Arsenic	4	3	1·33 (0·38–5·21)
Creosote	4	5	0.75 (0·21–2·51)
Mercurial seed dressing	5	3	1·67 (0·50–6·44)
Electromagnetic fields:			
Leisure time exposure	6	5	1.20 (0·44–3·44)
Amateur radio operator	2	2	1·00 (0·19–5·37)
Power line near home	40	42	0·94 (0·64–1·40)
Display monitor unit	3	5	0·60 (0·18–1·80)
Poultry	86	74	1·24 (0·91–1·71)
Dogs	137	140	0.96 (0·72–1·27)
Cats	112	106	1·11 (0·82–1·51)
Birds	9	15	0.50 (0·22–1·05)
Building material (home):			
Wood	249	248	1.14 (0.49-2.77)
Light concrete	20	17	1·20 (0·68–2·17)
Concrete	48	60	0.76 (0·53–1·07)
Brick	45	56	0.77 (0·53–1·09)
Plaster	12	14	0·86 (0·45–1·63)
Stone	17	19	0·89 (0·52–1·54)
Light concrete, concrete, stone	72	88	0.74 (0·53–1·01)
Plaster, brick	51	63	0.77 (0·55–1·08)
Radioactivity in work	2	3	0.67 (0·15–2·71)
Smoking	106	117	0·80 (057-1.11)
Fresh wood*	92	81	1·48 (0·95–2·35)
Engine exhausts†	61	50	1·38 (0·92–2·09)

*Working with power saws, at a sawmill, or at a pulp industry.
†Working with tractor, power saws, or as drivers

Table 4 Dose-resp… significant deviated … done) refer to days o…

Exposure factor
Phenoxyacetic acids
Organic solvents (wor…
Asbestos
DDT
Cattle
Horses
Hogs
Sheep
Goats

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Table 5 Multivaria… METHODS. Univariat… as well as 90% CIs o… excluded. The Pearso… model (see text)

Exposure factor
Cattle
Horses
Hogs
Sheep
Goats
Poultry
Cats
Dogs
Birds
Phenoxyacetic acids
Chlorophenols
DDT
Organic solvents (work
Asbestos
Sulphite pulp
Power saw
Copy machine
Electromagnetic fields (…
Fresh wood*
Engine exhausts*
Man made mineral fibre…
Brick†

*Defined as in table 3
'Building material in dw…

Table 4 Dose-response calculation on exposure facrors with reliable information abour duration of exposure and statistically significant deviated risks in univariate analysts as presented in table 1. The categories of exposure (decided before analysis was done) refer to days of work with phenoxyacetic acids and D D T and years of exposure for the rest of rhe factors

Exposure factor	Duration of exposure ≤5 (RR (90% CI))	6–20 (RR (90% CI))	≥21 (RR (90% CI))
Phenoxyacetic acids	3·00 (0·78–1 1.49)	2.00 (0·63–6·40)	2·00 (0·73–5·48)
Organic solvents (work)	0.37 (0·09– 1·48)	0·59 (0·28–1·25)	0.37 (0·18–0·74)
Asbestos	0.10 (0.02– 0·66)	0.21 (0·06–0·66)	0·58 (0·26–1·31)
DDT	1·08 (0.41– 2·81)	1.54 (0·86–2·77)	1.61 (0·63–4·12)
cattle	1·69 (0·68– 4.20)	1.30 (0·83–2·05)	1·85 (1·33–2·57)
Horses	1·87 (0.63– 5.53)	1.17 (0·73–1·86)	1·86 (1·33–2·59)
Hogs	2·10 (0·65– 6.75)	097 (0·60–1·54)	1·56 (1·12–2·19)
Sheep	1·39 (0·55– 3.54)	1.22 (0·63–2·38)	2-13 (1·30–3·94)
Goats	—	1·00 (0.34–2.59)	3.20 (1·38–7·43)

seemed to be negatively associated with myeloma, but leisure-time use gave a slightly increased risk.

Exposure to electromagnetic fields during work, which is the case for electricians and for linemen, and some other occupations, also gave a decreased RR, whereas residential exposure from power lines produced a risk around unity.

No statistically significant increased risk resulted from any type of residential building material, or from occupational exposure to radioactivity, activity as an amateur radio operator, work as hairdresser, or cosmetologist, or smoking.

For some exposure factors such as chemicals, animals, and residential building materials, where information on duration of exposure was good, a dose-response analysis was performed. Table 4 presents the results of this calculation for exposure factors with a statistically significant increased or decreased risk in the univariate analysis (table 1).

Exposures to several domestic animals showed statistically significant increased RR only at the highest dose. This indicates a dose-response pattern and further supports an association between these animals and multiple myeloma.

MULTIVARIATE ANALYSIS

In the multivariate analysis several exposure factors were included according to the criteria described. Table 5 presents the stepwise reduction with the resulting values of RRs. The 90% CIs of the RRs in the last step are also given.

Exposure to hogs and sheep were eliminated as risk

Table 5 Multivariate analysis of different exposure facrors chosen according to the criteria described in STATISTICAL METHODS. Univariate risk rarios (URRs) are given, and a stepwise reduction with resulting values of risk ratios is presented as well as 90% CIs of the values in the reduced model. All variables with a risk estimate between 0.9 and 1·1 were gradually excluded. The Pearson-correlation coefficient was used to include potential confounding factors not primarily included in the model (see text)

Exposure factor	URR	Step No 1	2	3	4	(90% CI)
Cattle	1.72	1.52	1.51	1.54	1·48	(0·76–2·91)
Horses	1·78	1.45	1.45	1.66	1·64	(0·93–2·91)
Hogs	1.49	0.71	0.70	0·84	0·85	(0·42–1·69)
Sheep	1.66	0.95				
Goats	2.18	1.37	1.33	1.50	1·51	(0·75–3·03)
Poultry	1·24			0·68	0·68	(0·40–1·15)
Cats	1.11			0.91		
Dogs	0.96			0·80	0.79	(0.56–1·10)
Birds	0.50	0.73	0.73	0.69	0.69	(0·27–1·77)
Phcnoxyacetic acids	2.22	1·60	1·60	1·87	1.92	(0·84–4·36)
Chlorophenols	1.06			0·86	0·85	(0·40–1·80)
DDT	1.75	1·29	1.29	1.42	1·40	(0·88–2·25)
Organic solvents (work)	0.50	0.61	0.61	0·68	0.67	(0·38–1·21)
Asbestos	0.50	0.66	0.67	0.52	0·54	(0·27–1·08)
Sulphire pulp	0·67	0·87	0·88	0.91		
Power saw	1·57	0·88	0·87	0.78	0.75	(0.36–1.58)
Copy machine	0.43	0.55	0·54	0.59	0.55	(0·23–1·33)
Electromagnetic fields (work)	0.31	0 32	0.32	0·37	0.36	(0·13–0·99)
Fresh wood*	1.48			0.90		
Engine exhausts'	1.38			1.11	1.11	(0·60–2·05)
Man made mineral fibres	1·08			2·00	2·00	(0·83–4·82)
Brick†	0·77			0.91		

*Defined as in table 3.
†Building material in dwelling

Table 6 Some exposure factors within farming and forestry. Only matched pairs with both subjects being occupied in those industries (n = 94) were included in the analysis

Exposure *factor*	*RR (90% CI)*
Cattle	2·00 (0·93–4·70)
Hones	1·64 (0·94–2·99)
Hogs	1·00 (0·59–1·71)
Sheep	1.26 (0.76–2.13)
Goats	1.71 (0·78–4·06)
Poultry	1.04 (0·65–1·68)
Phcnoxyacetic acids	2·00 (0·88–5·07)
Chlorophenols	1.14 (0·49–2·77)
DDT	1.86 (1·08–3·35)
Mercurial seed dressing	1·00 (0·19–5·37)
Pesticides, other	0.71 (0·27–1·79)
Tractor driving (fanning)	2.25 (0·84–7·11)

factors for myeloma in the multivariate setting, whereas exposure to cattle, horses, and goats seemed to remain important although RRs were weakened. Phenoxyacetic herbicides and DDT also remained as risk factors, but with slightly decreased RRs.

The significantly decreased risk Connected with exposure to electromagnetic fields during work remained. Exposure to organic solvents and asbestos was still negatively associated with myeloma but with less pronounced decreased RRs.

Some exposure variables were introduced in the model as they were fulfilling the correlation criterion described above, but of these only man made mineral fibres gave an increased risk.

For further details on this multivariate analysis see table **5**.

In another approach to study the importance of different specific factors within farming and related work, a separate analysis was done including only the pairs with both subjects affirming work in farming or forestry. A total of **94** pairs were used in this analysis. It confirmed the mentioned domestic animals and pesticides as possible risk factors for multiple myeloma (table *6).*

Discussion

This study was performed to further evaluate risk factors for multiple myeloma described in other studies. The Swedish compulsory reporting system for malignant diseases makes it likely that almost all incident cases in the study area during the four years of inclusion were utilised. **A** matched study design controlling for age, sex, county, and vital status was used, thereby increasing efficacy in the analysis.

To reduce the possible influence of recall bias—for example, a supposed tendency for the cases to remember more hazardous exposures than controls—the aim of the study was unexpressed. Thus no allusion to the disease under study was made in the information to the subjects. Furthermore, the questionnaire asked for information on many different occupations and exposures not specially focussing on any debated risk factors.

To minimise theoretical observational bias during telephone interviews, any data disclosing whether the subject was a case or a control were removed from the questionnaires before they were completed over the phone. The final coding of the answers was also done blinded in this respect.

In the analyses univariate as well as multivariate methods were used. To our knowledge this is the first study using multivariate analysis to dissolve different specific risk factors for myeloma among farmers, although some studies have used this method to evaluate farming *v* other risk factors outside farming“‘ or *v* pesticides specifically.”

The study confirmed the earlier finding of farmers being at an increased risk of developing multiple myeloma. Contact with different domestic animals, and exposure to some pesticides (phenoxyacetic herbicides and DDT), were associated with multiple myeloma, thus giving support to some theories regarding the specific risk factors at hand in farming.

Oncogenic zoonotic viruses have been suggested as possible aetiological agents in haematopoetic and lymphatic malignancies in human subjects, as RNA viruses have been connected with such tumours in several mammalian species.[51 52] It is also interesting to consider a viral disease in mink, Aleutian mink disease, characterised by systemic proliferation of plasma cells associated with marked hyper-γ-globulinaemia, with some of the affected minks also developing a myeloma-like γ-globulin spike. This disease has been found in all of the mink raising areas of Scandinavia and North America. Furthermore, a case of Aleutian mink disease in man has been described,[53] as well as a case of multiple myeloma in a *mink* handler who, during many years, had been bitten repeatedly on the hands and arms by mink in a farm where the presence of the viral disease was well documented.[54] In the present study, one case and one control were working with mink raising, and another case worked on a fox farm.

In our study the univariate analysis supported cattle, horses, hogs, sheep, and goats as risk factors for myeloma. This was further supported by dose-response calculations. The multivariate analysis, however, eliminated hogs and sheep, and decreased the RR somewhat for horses, goats, and cattle. For cattle these results are in accordance with the findings in a study from New Zealand,” whereas horses and goats have not been reported as risk factors for myeloma in any earlier study. The mechanism responsible for this connection between certain domestic animals and multiple myeloma may well be some unknown viral transmission. Interestingly, a virus has been found to be an important aetiological agent in a bovine type of lymphosarcoma prevalent in cattle.[55 56]

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On the other hand, this investigation gave no support for any association between poultry and myeloma, an association that has been suggested in some univariate correlation studies from the United States.[16,18,30,57]

The increased RR for exposure to pesticides supported results of an American case-control study in which no particular class of pesticides could be found responsible, however." In our present study both phenoxyacetic herbicides and DDT gave statistically significant increased RRs for multiple myeloma in the univariate analysis, and although the risks decreased somewhat, and were non-significant in the multivariate analysis, they both remained increased. No earlier studies exist indicating these pesticides as risk factors for multiple myeloma. Some studies have, however, disclosed phenoxyacetic herbicides as risk factors for non-Hodgkin's lymphoma.[58,59] Myeloma and lymphoma are related lymphoproliferative diseases with Occurrence of both diseases in some families' and a possible common viral aetiology as already discussed. Thus it was an a priori hypothesis in this study that exposure to phenoxyacetic herbicides might be a risk factor for multiple myeloma. Consequently, it is less probable that the risk increase found was due to chance alone. Some of the phenoxy herbicides are contaminated with dioxins and furans, which can be highly toxic substances. The dioxin isomer 2,3,7,8-TCDD is a recognised carcinogen in animals[60–62] and other isomers also seem to have this property.[63,64] A recent epidemiological study indicated that dioxins in phenoxyacetic herbicides and chlorophenols might be a risk factor for soft tissue sarcoma in human subjects.[65] A carcinogenic effect by the phenoxyacetic herbicides themselves cannot be excluded, however.

DDT is a potent insecticide, the use of which was cancelled in the United States in 1972, and in Sweden in 1975, because of its harmful ecological effects, particularly on predatory birds and on marine life. It is a stable substance and may accumulate in human tissue where it is a potent inducer of the microsomal enzyme system of the liver. Carcinogenicity of DDT is also established in mice, causing liver and lung neoplasms as well as malignant lymphoma.[66] Liver tumours have also been found in DDT treated rats.[67,68] Some epidemiological studies indicate a possible association between exposure to DDT and malignant lymphoma or chronic lymphatic leukaemia in human subjects.[58,69,70] This may lend support to the indication of DDT as a risk factor for myeloma in our study, a finding not described earlier. Other pesticides such as creosote and arsenic have been connected to myeloma in some studies, but these findings were not verified in our present study.

Occupational exposure to asbestos as well as organic solvents, which in some, but not all, earlier studies have been identified as possible risk factors for multiple myeloma, were both negatively associated with myeloma in this study, thereby opposing any idea of association between these substances and multiple myeloma.

In the univariate, but not in the multivariate analysis, work with power saws gave a statistically significant increased risk for myeloma. A non-significant risk was also seen for tractor driving. These risks are reflected by the slightly increased risk for occupational exposure to engine exhausts found by univariate analysis. An association between engine exhausts and multiple myeloma was first suggested in an earlier Swedish study," in which the possible role of the known mutagenic agents in both diesel and gasoline exhausts was emphasised.

In the same study" woodworkers in contact with fresh wood were found to be at increased risk for myeloma, which prompted us to evaluate the risk for people occupied in forestry, at a sawmill, or at a pulp industry combined. The moderately increased risk found in the univariate analysis was eliminated when logistic regression was performed.

A protective effect of being an electrician, or being exposed to electromagnetic fields in any occupation, was a constant finding with statistical significance even in the multivariate analysis. Display monitor units may generate weak electromagnetic fields, and their influence was studied separately. In this case also, exposure seemed to lower the risk for multiple myeloma, but the exposed subjects were few. On the other hand, the RR was close to unity regarding exposure to electromagnetic fields from power lines near the subjects' homes, with exposure defined as living less than 1000 m from the power line. The risk was not substantially influenced by the distance between home and power line (100 m and 500 m as criteria). No physical or biological explanation is forthcoming for the decreased risk seen in relation to occupational exposure to electromagnetic fields. Ongoing studies—for example, in Sweden—will hopefully shed more light upon the possible association between electromagnetic fields and different types of malignant tumours.

In conclusion, this case-control study confirmed the association between farming and multiple myeloma. Within this occupation the domestic animals, cattle, goats, and horses, and two types of pesticides, phenoxyacetic acids and DDT, were indicated as risk factors. Occupational exposures to electromagnetic fields, asbestos, and organic solvents should be further considered with regard to whether or not some mechanism could explain the decreased risk for myeloma for those exposures, which appeared in this study.

This study was supported by grants from the Swedish Cancer Fund (project 2683-B90-02X).

We thank Anna-Lena Zakari for performing excellent telephone interviews. We are also grateful to Monica Sandstrom and Ingemar Majholm for professional assistance in the data collection, and to Professor Olav Axelson for valuable viewpoints and constructive criticism.

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Accepted 3 June 1991

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