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CANCER IN OFFSPRING OF PARENTS ENGAGED IN AGRICULTURAL ACTIVITIES IN NORWAY: INCIDENCE AND RISK FACTORS IN THE FARM ENVIRONMENT

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In this study of cancer in offspring we demonstrate that factors linked to horticulture and use of pesticides are associated with cancer at an early age, whereas factors in animal husbandry, in particular poultry farming, are associated with cancers in later childhood and young adulthood. Incident cancer was investigated in offspring born in 1952–1991 to parents identified as farm holders in agricultural censuses in Norway in 1969–1989. In the follow-up of 323,292 offspring for 5.7 million person-years, 1,275 incident cancers were identified in the Cancer Registry for 1965–1991. The standardized incidence for all cancers was equal to the total rural population of Noway, but cohort subjects had an excess incidence of nervous-system tumours and testicular cancers in certain regions and strata of time that could imply that specific risk factors were of importance. Classification of exposure indicators was based on information given at the agricultural censuses. Risk factors were found for brain turnours, in particular non-astrocytic neuroepithelial tumours: for all ages, pig farming tripled the risk [rate ratio (RR), 3.11; 95% confidence interval (CI), 1.89–5.13]; indicators of pesticide use had an independent effect of the same magnitude in a dose-response fashion, strongest in children aged 0 to 14 years (RR, 3.37; 95% CI, 1.63–6.94). Horticulture and pesticide indicators were associated with all cancers at ages 0 to 4 years, Wilms' tumour, non-Hodgkin's lymphoma, eye cancer and neuroblastoma. Chicken farming was associated with some common cancers of adolescence, and was strongest for osteosarcoma and mixed cellular type of Hodgkin's disease. The main problem in this large cohort study is the crude exposure indicators available; the resulting misclassification is likely to bias any true association towards unity.
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Reviews on childhood cancer (*e.g.,* Savitz and Chen, 1990) have not firmly established parental occupational exposures as causal factors. In studies of parental occupation in which all sites in childhood have been the end-points (Zack *et al.,* 1980; Sanders *et al.,* 1981; Hemminki *et al.,* 1985; Olsen *et al.,* 1991), the risk estimates for children of farmers or agricultural workers have not deviated much from the null.

Nevertheless, in several case-control studies brain turnours in childhood have been associated with parental farming (West, 1988; Wilkins and Koutras, 1988; Wilkins and Sinks, 1990; Kuijten *et al.,* 1992; Bunin *et al.,* 1994), and environmental risk factors in farming are considered to be of particular interest (Kuijten and Bunin, 1993). Both contact with animals and exposure to pesticides have been suspected as risk factors. Parental exposure to pesticides has been associated with brain tumours in several studies (West, 1988; Sinks, 1985; Davis *et al.,* 1993; Bunin *et al.,* 1994), and Leiss and Savitz (1995) found an association with the use of pest strips in the home. Gold *et al.* (1979) found increased odds ratios for contact with sick pets and use of insecticides in the home, but the results were not confirmed in a later study (Howe *et al.,* 1989). In another study, contact of either the mother (McCredie *et al.,* 1994*a*) or the child (McCredie *et al.,* 19946) with animals was not associated with brain turnours.

Apart from an increased odds ratio for acute leukaemia seen among the children of mothers in agricultural work in Shanghai (Shu *et al.,* 1988), there have been few indications that parental occupation as a farmer poses a risk for leukaemias (Van Steensel-Moll *et al.,* 1985; Lowengart *et al.,* 1987). Parental exposure to pesticides has also been associated with increased occurrence of leukaemia, mainly acute (Lowengart *et al.,* 1987; Laval and Tuyns, 1988; Shu *et al.,* 1988; Buckley *et al.,* 1989; Buckley, 1992; Leiss and Savitz, 1995). Immunologic and infectious mechanisms have been hypothesized for childhood leukaemias, and the analogy to malignancies seen in adult farmers is of interest: immunologic mechanisms triggered by pesticides or animal antigens are suspected to be important for the development of leukaemias among adult farmers, oncogenic zoonotic viruses being among the suspected agents (Blair *et al.,* 1992).

Reports concerning an association between testicular cancer and agricultural exposures are conflicting (Blair *et al.,* 1992). Testicular cancer is suspected to be related to high foetal levels of free oestrogen, and organochlorine pesticides and other oestrogenic compounds have been suggested as causative agents (Sharpe and Skakkebrek, 1993).

Pesticide use in the home has also been associated with childhood lymphoma and soft-tissue sarcoma (Leiss and Savitz, 1995). The implication of phenoxy-acid herbicides as a cause of soft-tissue sarcomas and lymphomas in adults (Blair *et al.,* 1992) is also of interest, since these malignancies are relatively common in childhood and adolescence.

To investigate cancer incidence and reproductive outcomes in the offspring, we established through linkage between several registers a national cohort of families in Norwegian agriculture. Our hypotheses comprised an excess of sarcoma, leukaemia, lymphoma, testicular cancer, and particularly nervous-system tumours.

On the basis of earlier reports, a number of hypotheses were formulated about indicators of exposure and specific groups of malignancies: exposure to animals or pesticides and brain tumours (Gold *et al.,* 1979; West, 1988; Wilkins and Koutras, 1988; Wilkins and Sinks, 1990; Kuijten *et al.,* 1992; Bunin *et al.,* 1994); exposure to animals (in particular dairy cows and chickens) or pesticides and acute leukaemia (Lowengart *et al.,* 1987; Laval and Tuyns, 1988; Shu *et al.,* 1988; Buckley *et al.,* 1989; Buckley, 1992; Leiss and Savitz, 1995); exposure to pesticides (in particular organochlorine pesticides commonly used in horticulture) and testicular cancer (Sharpe and Skakkebrek, 1993); exposure to pesticides (in particular herbicides in forestry and grain farming) and soft-tissue sarcoma and lymphomas (Blair *et al.,* 1992; Leiss and Savitz, 1995).

In general, the potential causative agents were considered to act either during the pre-conceptual period through the father's maturing germ cells, during pregnancy via the mother, or directly in early infancy. If pesticides applied seasonally

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cause cancer by acting on the father's maturing germ cells, an uneven distribution by month of birth would be anticipated for the malignancy in question. In particular, we suspected that a paternally mediated effect of pesticides applied during spring and early summer (as in grain farming and in orchards in Norway) would be strongest for children born during spring.

MATERIAL AND METHODS

Cohort

Statistics Norway have held national agricultural censuses resulting in computerized information files in 1969, 1979, and 1989, and horticultural censuses in 1974 and 1985. The criteria for participation have changed slightly over time. The 1969 census included all farms comprising an agricultural area of at least 0.5 hectare (ha); the 1979 and 1989 censuses combined agriculture and forestry and included both farm holdings with a productive forest area of 2.5 ha or more and farms smaller than 0.5 ha which met certain criteria with regard to livestock size, area of greenhouses, fields for vegetables or berries, and number of fruit trees. The inclusion criteria for the horticultural censuses covered area of greenhouses, field-grown vegetables or berries, or number of fruit trees. Participation in the agricultural and horticultural censuses was mandatory, and is considered to be complete, since governmental subsidies to farm holdings were conditional on this information.

All personal farm owners at any of the censuses who were born after 1924 were identified by the personal identity number assigned to all residents of Norway. Subtraction of duplicates (5.1 percent; owners of more than one farm at a single census) yielded 149,254 farm holders (125,873 males, 23,381 females). Individuals owning more than one farm were assigned to the place of residence.

After linkage of the file of farm owners with the Central Population Register 334,135 offspring born in 1940–1992 were identified. The Central Population Register was established in October 1964 and is based on information from all residents of Norway at the time of the 1960 population census and on continuous updating since 1964 (Brunborg and Kravdal, 1986). Linkage of parents and children is possible because each record in this register includes both personal identification numbers. Parental identification was included prospectively at birth for children born after October 1964; for children born earlier, parental identification was included in retrospect at the population census in November 1970. This was complete only for children born after 1951. Records of children born before October 1964 and who died before the 1970 census do not include the parental identification number (Brunborg and Kravdal. 1986).

The present study included all 323,359 offspring born between 1952 and 1991 who were followed up for incident cancer in the Cancer Registry of Norway. Children born between 1952 and 1964 were followed up from 1971, as earlier start of follow-up would have led to a negative bias due to lack of identification of children who died before the 1970 population census. Children born after 1964 were followed up from birth. All children were followed up through 1991, or until death or emigration. Linkage with the Cancer Registry was complete, and only 67 children who either died or emigrated before the start of follow-up in 1971 did not contribute person-time. In total, 102,055 children born between 1952 and 1964 and 221,237 children born between 1965 and 1991 were followed up for 5,696,606 person-years (Table I).

Exposure

Information about the farm holding given at one or several agricultural censuses was assigned to the records of all members of the holder's family. Since 83% of the population came

TABLE 1 – DISTRIBUTION **OF** CHARACTERISTICS AMONG OFFSPRING (n = **323,292**; **5,696,606** PERSON-YEARS) BORN IN **1952–1991** TO PARENTS **IN** AGRICULTURAL WORK ACCORDING TO THE NORWEGIAN AGRICULTURAL CENSUSES IN **1969–1989**

Descriptive **category**	Total person-time (%)
Gender	
Male	51.4
Female	48.6
Year of birth	
1952–1959	17.6
1960–1964	19.5
1965–1969	26.6
1970-1979	28.9
1980-1991	7.3
Attained age (years)	
0–4	18.4
5–9	17.8
10–14	19.1
15–19	18.1
20-29	22.0
30-39	4.7
Farm location	
East	30.6
South	15.2
West	24.6
Mid (Trøndelag)	12.5
North	17.2
Census participation	
1969	75.1
1974	3.8
1979	92.9
1985	4.9
1989	93.0
Census closest to birth date	
1969	59.7
1974	0.9
1979	33.6
1985	0.4
1989	5.5
Productive farming area (hectares)	
< 0.5	19.9
0.5–4.9	37.3
5–19.9	37.0
≥ 20	5.8
Agricultural activity'	
Animal husbandry	66.7
Cattle	46.7
Dairy cows	39.6
Pigs	25.1
Chicken/poultry	19.6
Sheep/goats	34 0
Horticulture	20.5
Field vegetables	16.0
Fruit trees	3.8
Berries	2.3
Greenhouses	1.6
Grain farming	27.2
Potatoes (20.1 hectare)	44.9
Forestry (≥ 2.5 hectares)'	63.0
No farming activity[3]	23 0
Pesticide purchase[4]	27 0
Pesticide spraying equipment'	26 8
Main income from farm holding	38.6
Either parent working ≥ 500 hr annual **on** farm	58.5
Father working outside farm holding	55 1
Mother working outside farm holding	18 6
Either parent with agricultural education	22.7

'On the farm at the census closest to the year of birth. Children from farms with several activities at the census contributed person-time in all those activities.–'Information only in 1969, 1979 and 1989 censuses (0.3% missing).–[3]Children from holdings with no animal farming, horticultural activity or grain farming at the census closest to the year of birth.–[4]Information only in 1969 census (24.9% missing).–[5]Information only in 1979 census (7.1% missing).

from family holdings, information from the same farm holding was included even in censuses held before the child's parent took over. This resulted in 1969 census information for more than 75% of the children. Information from the 1979 and 1989 censuses was available for more than 90%, while information from the horticultural censuses in 1974 and 1985 was available only for a few percent (Table I). The information included: location (municipality) of the farm holding and whether it was the residence of the holder; farming area and area used for cultivation of potatoes, different types of grain, field vegetables, greenhouses, and forestry; number and species of livestock; number and species of fruit trees and berries grown; horses, tractors, source of water (1979), use of silage, and use of fertilizers (1979, 1989); amount of money spent on pesticides in the preceding year (1969), and pesticide spraying equipment on the farm (1979): time spent on agricultural work on the farm and work outside the farm for both parents; fraction of total family income from the farm; agricultural education of holder or spouse: year of conveyance of the farm holding (1979, 1989): and whether a family farm (1979).

The exposure indicators and their distributions are given in Table I. The main types of farming in Norway are animal husbandry, horticulture, and grain farming. More than one type of farming was commoner on the holding early in the study period, and specialized production and monoculture became more prevalent in the later periods. Norwegian farms were mostly small and operated by the family members. Usually, 3 generations lived on the holding, and the children (mostly sons) took over when the parents were too old to operate the farm. The distribution of other explanatory variables in Table I indicates that a large proportion of the holdings were part-time enterprises, and part-time employment outside the holding was more commonly reported in the later censuses. The criteria for participation in the agricultural censuses are loose, and only 58% of the offspring came from holdings where either parent worked for at least 500 hr annually, which is the standard criterion for a farmer in population censuses given by Statistics Norway (Central Bureau of Statistics, 1975). This sub-set of the cohort is termed farmers' offspring.

For the majority of holdings, information was available from all 3 agricultural censuses. We considered census information for the pre-conception period, during pregnancy and in infancy most relevant in this study of early cancers and, therefore, defined the census closest in time to the child's birth as the index census, but indicators of pesticide use, water source, and fertilizers were included when available, even for non-index censuses. The index census of the oldest children took place during their adolescence or even in adulthood. For those born between 1952 and 1964, the age at the time of the index census was over 10 for 50% and over 20 for 10%. For 81% of children born between 1965 and 1991, the gap between birth and the index census was 5 years or less.

Most of the exposure indicators were quantified in categories, but they were analysed as dichotomies (present/absent), on the assumption that contact and exposures are as likely to be high for small-scale activities where work practices are more manual. Money spent on pesticides in 1968 was categorized in 4 groups: none; NOK 1–99; NOK 100–499; and NOK 500 or more. Sub-types of horticulture (except field vegetables) were uncommon, so orchards and greenhouse cultivation were combined (7% of offspring exposed).

Cancer identification

The outcome classification was based on the information on cancer site and morphology in the Cancer Registry of Norway. Case reporting to the Registry has been mandatory since 1952. Brain neoplasms and acute leukaemias were each grouped in order to ensure robust categories: neuroepithelial brain tumours were categorized according to Kleihues *et al.* (1993) as astrocytomas and non-astrocytic neuroepithelial tumours; acute leukaemias were grouped as lymphocytic, myelocytic and other types. Hodgkin's disease was divided into nodular sclerosis and the mixed cellular type.

Analysis

The analyses were performed with the "Epicure" statistical software program (Preston *et al.*, 1993). Two analytical methods were applied: indirect standardization (observed over expected cases) with an external reference population; and Poisson regression modelling with reference groups within the cohort.

Cancer morbidity was investigated by comparing the observed and expected numbers of cases. The expected numbers of cases were estimated from the person-year experience in different strata, and the 5-year age- and gender-specific rural rates in Norway for each year from 1965 through 1991. The rural population comprises residents outside towns, which was 57% of the total population in 1980. Gender-specific standardized incidence ratios (SIR) were calculated for all cancers and for cancers at specific sites for the study population; sub-set analyses were performed for offspring with a parent who fulfilled the occupational criterion for a farmer. Strata of age intervals, period of follow-up, year of birth, and geographical regions were also investigated. Ninety-five percent confidence intervals (CI) were computed under the assumption of a Poisson distribution of the observed cancers under the null hypothesis.

The associations between exposure indicators and specific cancers were-assessed in Poisson regression. The main measure of association was the ratio of incidence rates (rate ratio, RR) between subjects with the exposure indicator in question and subjects without the exposure indicator. RR estimates were adjusted for age and calendar year, or birth year and calendar year. Other exposure indicators and explanatory variables were included in the models if they altered the RR estimates by more than 15%. We calculated 95% CI, and those that did not include unity were considered statistically significant. For the pesticide purchase indicator, we performed a test of trend for the association between expenditure level and cancer whenever the number of cases were sufficient.

The relevance of the information obtained from the index census was judged on the basis of ***a priori*** criteria in order to identify offspring who were most likely to have spent the first years of their life on a farm. Information was considered "relevant" if either parent was the farm holder at the time of the index census and lived on the farm. Information was also considered "relevant" if the farm holder was closely related to the parents and was living at the farm, and either parent took over the farm at a later census. According to this definition, information was "relevant" for 70% of the study subjects. In the analyses of cancer risk at age 0 to 4 years and in analyses of infant tumours (Wilms' tumour, eye cancer, hepatic cancer, neuroblastoma), information was considered "relevant" only if the gap between birth and index census was 5 years or less, in addition to the other criteria. An increased stronger exposure-outcome association for this sub-set or the sub-set of offspring of parents who fulfilled the occupational criterion for a farmer strengthened the assumption of a true association.

RESULTS

A total of 1,275 incident cases of cancer was identified in the follow-up. The distribution for selected sites are provided in Table II. Brain tumours (ICD-7 193.0) counted 182 cases, of

TABLE II – STANDARDIZED INCIDENCE RATIOS FOR ALL CANCERS AND CANCERS AT SELECTED SITES AMONG OFFSPRING BORN 1952–1991 TO PARENTS IN AGRICULTURAL WORK, ACCORDING TO THE NORWEGIAN AGRICULTURAL CENSUSES 1969–1989, AND AMONG OFFSPRING OF A PARENT WHO FULFILLED THE STANDARD OCCUPATIONAL CRITERION FOR A FARMER (WORKING ≥ 500 HR ANNUALLY ON A HOLDING)

Cancer site (ICD 7)	Total study population[1]			Farmers' offspring[2]		
	Number of cases	SIR	95% CI	Number of cases	SIR	95% CI
All sites (140–209)	1275	98	92–103	739	101	94–109
Liver (155)	14	127	69–213	8	103	44–202
Breast (170)	35	72	50–100	16	65	37–106
Cervix uteri (171)	64	80	62–103	31	76	52–108
Ovary (175)	40	110	78–149	26	131	86–193
Testis (178)	158	111	95–130	97	124	101–152
Kidney'(180)	23	82	52–123	14	83	46–140
Melanoma (190)	133	97	82–116	65	88	68–113
Eye (192)	16	91	52–147	9	84	39–160
Nervous system (193)	232	106	92–120	141	111	94–131
Thyroid (194)	46	85	62–114	20	69	42–106
Endocrine glands (195)	22	94	59–142	17	122	71–196
Bone (196)	51	113	84–149	32	122	83–172
Connective tissue (197)	27	91	60–133	16	94	54–152
Hodgkin's disease (201)	77	110	87–138	46	117	85–156
Non-Hodgkin's lymphoma (200,202)	60	90	69–115	33	87	60–122
Leukaemia (204)	181	96	82–111	113	101	83–122
Unspecified and other sites	96	94	76–115	55	98	74–128

[1]n = 323,292; 5,696,606 person-years.–[2]n = 188,680; 3,323,876 person-years.

which 76 were classified as astrocytomas and 65 as non-astrocytic neuroepithelial tumours. Nearly all leukaemias were acute: 92 lymphocytic, 36 myelocytic, and 35 of other types. Cases of nodular sclerosis numbered 37 and of the mixed cellular type of Hodgkin's disease, 34. There were 29 cases of osteosarcomas, 27 neuroblastomas, and 17 Wilms'-tumour cases.

SIR analysis

The **SIR** for cancer at all sites was close to that expected, and no site-specific **SIR** deviated significantly from unity (Table II). Few breast cancers and cervical cancers were reported in comparison with the numbers expected. Among the major sites, non-significant elevations of the **SIR** were found for testicular cancer, bone cancer, and Hodgkin's disease. For nervous-system tumours, the **SIR** was 106 (95% **CI** 92–120).

The 188,680 offspring of farmers (either parent worked at least 500 hr annually on a farm) had 739 incident cancer cases and a **SIR** close to unity (Table II). This sub-group had **SIR** that deviated more markedly from unity for several sites: SIR were elevated for testicular cancer, nervous-system tumours, Hodgkin's disease, bone cancer and ovarian cancer, but significantly only for testicular cancer.

Table III provides results for all cancers by gender in strata relating to time and geographical location of the farm. The **SIR** was decreased for females and slightly increased for males. This gender difference was due mainly to increased **SIR** for males in the 5- to 14-year age group; the **SIR** estimates for females were decreased for all ages except 0 to 4 years, strongest during attained age of 15 to 19 years. No specific **SIR** trends were apparent in different periods of follow-up; a moderate increase of borderline significance was found for males during 1985–1991. Moderate increases in the **SIR** for both genders were found for offspring born during 1980–1991: the SIR for boys and girls combined was 119 (95% CI, 96–148).

The SIR differences for all sites in males and females in adulthood were due to some sex-specific sites (testicular cancer, breast cancer, cervical cancer). The gender difference of **SIR** in childhood was due to several sites, mainly nervous-system tumours, bone cancer and leukaemia (data not shown).

The space-time variations in SIR were investigated for specific major sites. Some of the deviations in Table III were due to clustering of nervous-system tumours and testicular cancer. Thus, during follow-up 1985–1991, 115 nervous-system tumours were diagnosed (**SIR,** 128; 95% **CI,** 106–154). In this period, 45 cases were diagnosed in the 0- to 14-year age group (**SIR,** 149; 95% **CI,** 108–199), of those, 13 cases came from **a** farm holding in the southern region (**SIR,** 256; 95% **CI,** 136–438). The testicular-cancer-incidence excess was confined to the western region, particularly at age 15 and older and for boys born between 1952 and 1969 (50 observed cases; **SIR, 167;** 95% **CI,** 125–218). Forty of those cases were observed among farmers' sons (either parent working at least 500 hr annually on the farm); the **SIR** was 216 (95% **CI,** 156–290). Similar clusters in leukaemias or lymphomas were not apparent.

Poisson regression

The incidence of cancer at all sites during the first years of life was associated with horticulture and pesticide indicators, whereas cancer later in life was related to contact with animals, in particular chickens (Table **IV).** For ages 0 to **4** years (total 201 cancer cases; 1,045,535 person-years), offspring on farms with orchards or greenhouses had a nearly doubled **RR;** the association with pesticide purchase showed a dose-response relationship for different levels of expenditure, but the test for trend was not significant (*p* = 0.12). For ages 5 to 19 years (total 403 cancer cases; 3,133,341 person-years) increased **RR** were found for exposure to chicken farming.

Brain tumours

Brain tumours were the commonest neoplasm (Table **V).** A **RR** of 1.59 for brain tumour was found in association with pig farming, while the increases were more moderate and non-significant for chicken farming, grain farming. horticulture and pesticide purchase. The increases were restricted mainly to the group of non-astrocytic neuroepithelial tumours, especially for pig farming, pesticide purchase and chicken farming; for pesticide purchase the **RR** increased for increasing expenditure levels (test for trend, $p = 0.0002$). When all exposure indicators were included simultaneously in a model, the effects of grain farming and horticulture on the risk for non-astrocytic neuroepithelial tumours were dependent on pesticide purchase, whereas pig farming (**RR,** 2.48; 95% CI, 1.37–4.50) and

TABLE III – GENDER-SPECIFIC STANDARDIZED INCIDENCE RATIOS FOR ALL CANCERS FOR SPECIFIED REGIONS AND TIME PARAMETERS AMONG OFFSPRING BORN 1952–1991 TO PARENTS IN AGRICULTURAL WORK ACCORDING TO THE NORWEGIAN AGRICULTURAL CENSUSES 1969–1989

	Males (n = 166,291; 2,924,670 person-years)			Females (n = 157,001; 2,771,936 person-years)		
	Number of cases	SIR	95% CI	Number of cases	SIR	95% CI
Total	684	104	97–112	591	91	84–99
Attained age (years)						
0–4	105	89	73–107	96	109	89–133
5–14	143	116	98–136	93	93	75–113
15–19	104	105	86–126	63	78	60–99
20–29	245	107	94–121	214	YO	79–103
30–39	87	101	81–123	125	88	74–105
Period of follow-up						
1965–1974	88	103	83–126	67	110	86–138
1975–1979	99	99	81–120	56	71	54–91
1980–1984	140	97	82–114	128	87	73–103
1985–1991	357	110	99–122	340	94	85–105
Year of birth						
1952–1959	195	104	90–120	213	89	77–101
1960–1969	301	104	92–116	227	86	76–98
1970–1979	145	104	88–122	106	97	80–117
1980–1991	43	110	80–146	45	129	95–171
Location of farm						
East	206	103	89–117	194	96	84–111
South	101	104	85–125	75	80	63–99
West	195	122	106–140	163	106	90–123
Mid	76	93	74–116	61	75	58–96
North	106	91	75–109	98	84	68–102

TABLE IV – RATE RATIOS FOR ALL CANCERS, 1965–1991,[1] BY AGE FOR EXPOSURE INDICATORS LINKED TO ANIMAL HUSBANDRY, HORTICULTURE, AND PESTICIDE USE IN OFFSPRING BORN IN 1952–1991 (n = 323,292), TO PARENTS IN AGRICULTURAL WORK ACCORDING TO THE NORWEGIAN AGRICULTURAL CENSUSES IN 1969–1989

Attained age	Exposure indicator	Number of exposed cases	Persin-years instratum	Crude RR	Adjusted RR[2]	95% CI
All ages	Horticulture	293	1,164,897	1.16	1.15	1.02–1.32
	Field vegetables	224	909,762	1.12	1.12	0.97–1.30
	Orchards or greenhouses	113	403,386	1.28	1.21	1.00–1.47
	Pesticide purchase[3]	366	1,540,541	1.10	1.16	1.00–1.34
	Horticulture and pesticide pur-	158	586,896	1.26	1.25	1.05–1.50
	Orchards or greenhouses and pesticide purchase[3,5]	78	251,042	1.44	1.38	1.09–1.76
	Animal husbandry	854	3,802,182	1.01	0.98	0.87–1.10
	Chicken farming	284	1,117,300	1.18	1.11	0.96–1.27
	Pig farming	342	1,429,804	1.09	1.04	0.91–1.18
0–4 years	Orchards or greenhouses	21	62,502	1.84	1.86	1.18–2.92
	Pesticide purchase[3]					
	Level 1	17	91,180	1.05	1.04	0.62–1.76
	Level 2	32	151,068	1.19	1.19	0.79–1.78
	Level 3	15	54,293	1.55	1.55	0.89–2.68
5–19 years	Animal husbandry	230	1,771,374	1.04	1.08	0.86–1.35
	Chicken farming	77	500,584	1.26	1.33	1.03–1.71
	Pig farming	89	630,193	1.14	1.21	0.95–1.55

[1]Subjects born 1952–1964 followed up from 1971; subjects born in 1965–1991 followed up from birth.–[2]Adjusted for year of birth and calendar year.–[3]Restricted to subjects covered in the 1969 census (total n = 243,659; 4,280,456 person-years).–[4]Reference: subjects from holdings with no horticulture or pesticide purchase.–[5]Reference: subjects from holdings with no orchards, greenhouses, or pesticide purchase.

pesticide purchase (RR, 2.11; 95% CI, 1.19–3.75) were independent risk factors. The independent effect of chicken farming was more moderate (RR, 1.77; 95% CI, 0.99–3.17).

The rates for non-astrocytic neuroepithelial tumours were high in all age groups for those exposed to pig farming or pesticide purchase. The association with pig farming was evenly distributed in all age groups, whereas the association with pesticide purchase was strongest for children under 15 years of age. For pesticide purchase, offspring aged 0 to 14 Years had 41 brain tumour cases (adjusted RR, 1.71; 95% CI, 1.11–2.63) and 22 cases of non-astrocytic neuroepithelial tumours (adjusted RR, 3.37; 95% CI, 1.63-6.94). Pesticide purchase was positively associated with non-astrocytic tumours in all categories of period of follow-up and year of birth. However, the association was slightly stronger for children born between 1980 and 1991, and during follow-up 1985–1991 (data not shown).

The risk increase for non-astrocytic neuroepithelial tumours in association with pesticide purchase was not restricted to specific types of farming, but particularly high incidence was

TABLE V – RR FOR BRAIN TUMOURS, 1965–1991[1], FOR EXPOSURE INDICATORS LINKED TO ANIMAL HUSBANDRY AND PESTICIDE USE IN OFFSPRING BORN 1952–1991 (n = 323,292) TO PARENTS IN AGRICULTURAL WORK ACCORDING TO THE NORWEGIAN AGRICULTURAL CENSUSES 1969–1989

Cancer diagnosis	Exposure indicator	Total population					"Relevant" information[2]	
		Exposed cases	Person-years in stratum	Crude RR	Adjusted RR[3]	95% CI	Exposed cases	Adjusted RR[3]
Brain tumour (ICD-7 193.0)	Pig farming	61	1,429,804	1.50	1.59	1.16–2.17	50	1.42
	Chicken farming	43	1,117,300	1.27	1.32	0.93–1.86	35	1.22
	Grain farming	59	1,551,353	1.28	1.29	0.95–1.77	49	1.28
	Horticulture	44	1,164,897	1.24	1.25	0.89–1.76	39	1.39
	Pesticide purchase[4]	60	1,540,541	1.39	1.38	0.98–1.94	55	1.46
Non-astrocytic neuroepithelial tumour[5]	Pig farming	30	1,429,805	2.56	3.11	1.89–5.13	25	3.35
	Chicken farming	22	1,117,300	2.10	2.42	1.44–4.08	17	2.32
	Grain farming	25	1,551,353	1.67	1.72	1.05–2.84	19	1.59
	Horticulture	18	1,164,897	1.49	1.54	0.89–2.65	17	2.02
	Pesticide purchase[4]							
	Level 1	7	470,523	2.04	2.00	0.85–4.74	6	2.11
	Level 2	17	780,646	2.98	2.93	1.54–5.60	16	3.29
	Level 3	7	289,373	3.31	3.28	1.39–7.76	6	3.31

[1]Subjects born 1952–1964 followed up from 1971; subjects born 1965–1991 followed up from birth.–[2]See "Material and Methods" for definition; adjusted for year of birth and calendar year.–[3]Adjusted for year of birth and calendar year.–[4]Restricted to subjects covered in the 1969 census (n = 243,659; 4,280,456 person-years).–[5]Glioma not otherwise specified, choroid plexus papilloma, ependymoma, oligodendroglioma, medulloblastoma, ganglioglioma, and neuroblastoma.

found among offspring aged 0 to 4 years on farms with pesticide purchase and grain farming combined (6 exposed *cases;* 3.8 per 100,000 person-years; RR, 8.01; 95% CI, 1.62–39.7).

The associations with pig farming and chicken farming, and pesticide indicators were also investigated for medulloblastoma which was classified in the non-astrocytic neuroepithelial group. Eight out of a total of 15 medulloblastoma cases were exposed to pigs, and the adjusted RR was even higher than for the whole non-astrocytic neuroepithelial group (RR, 4.92; 95% CI, 1.72–14.1). Chicken farming was also strongly associated with medulloblastoma (7 exposed cases; adjusted RR, 3.91; 95% CI, 1.45–10.5). For pesticide purchase, the RR estimate was doubled, *i.e.*, weaker than for the total non-astrocytic group.

Table V also includes RR estimates for the sub-set of offspring with relevant information from the index census. Compared with the total cohort, the estimates for non-astrocytic neuroepithelial tumours were slightly increased in association with both pig farming and pesticide purchase; the estimate for association with pesticide purchase was increased in this sub-set even for the age group 0 to 14 years (RR, 4.02; 95% CI, 1.78–9.08).

Offspring of a parent who worked at least 500 hr annually on the farm also showed stronger associations than the total cohort between non-astrocytic neuroepithelial tumours and exposure to pig farming (RR, 3.99; 95% CI, 2.06–7.73) or pesticide purchase (RR, 4.76; 95% CI, 1.92–11.8).

The distribution of month of birth among offspring with brain tumours in association with pesticide purchase was also investigated. Among children aged 0 to 14 years. with the pesticide purchase indicator, 50% of the non-astrocytic neuroepithelial tumours (11 out of 22) and astrocytomas (6 out of 12) were born between April and June. Using children without the pesticide purchase indicator as reference, the RR estimate of non-astrocytic tumours for exposed children born between April and June was 6.15 (95% CI, 2.66–14.2) and only 2.30 (95% CI, 1.00–5.30) for exposed children born between July and March.

Acute leukaemias

The RR estimates for an association between indicators of exposure to pesticides as well as contact with animals on the one hand and acute lymphocytic or myelocytic leukaemia on the other were close to unity (Table **VI).** For acute leukaemias there was no trend in the rates for increasing pesticide expenditure (test for trend, $p = 0.37$). ***An*** increased RR of borderline significance was found for other acute leukaemias in association with animal husbandry; the RR was close to unity for pesticide purchase. The RR for other acute leukaemias were increased in association with all animals species, but were unexpectedly strongest for pig farming. Chicken farming and dairy farming were associated only moderately with other acute leukaemias. **For** most exposures to animals, analyses of the "relevant" information sub-group produced lower RR estimates, except for pig farming. Analyses for the sub-group of offspring to a parent who worked more than 500 hr annually on the holding also produced point estimates closer to unity (for pig farming, RR, 1.78; 95% CI, 0.83–3.81).

Other associations in a priori *hypotheses*

There was no association between testicular cancer and exposure to pesticides (Table VII) or the level of pesticide expenditure (test for trend, $p = 0.49$). An increased risk was found for Hodgkin's disease in association with forestry, but after adjustment for year of birth and calendar year the estimate was not significant. The associations between grain farming and soft-tissue sarcomas or lymphomas were all close to unity. The RR for non-Hodgkin's lymphoma in association with pesticide purchase was 1.67, with a dose-response relationship for different levels of expenditure (test for trend, $p = 0.04$). This association was largely restricted to horticulture, if pesticide purchase was reported. Analysis restricted to the sub-set with "relevant" information yielded an even higher risk estimate for the latter association (10 exposed cases; adjusted RR 2.71).

TABLE VI – RR FOR ACUTE LEUKAEMIAS, 1965–1991,[1] FOR EXPOSURE INDICATORS LINKED TO ANIMAL HUSBANDRY AND PESTICIDE USE IN OFFSPRING BORN 1952–1991 (n = 323,292) TO PARENTS IN AGRICULTURAL WORK ACCORDING TO THE NORWEGIAN AGRICULTURAL CENSUSES 1969–1989

Cancer diagnosis	Exposure indicator	Total population					"Relevant" information[3]	
		Exposed cases	Person-years in stratum	Crude RR	Adjusted RR[2]	95% CI	Exposed cases	Adjusted RR[2]
Acute leukaemia	Pesticide purchase[4]	52	1,540,541	1.09	1.06	0.75–1.49	44	1.13
	Animal husbandry	112	3,802,182	1.09	1.19	0.85–1.65	92	0.95
Acute lymphocytic leukaemia	Pesticide purchase[4]	29	1,540,541	1.10	1.03	0.65–1.64	24	0.99
	Animal husbandry	57	3,802,182	0.81	0.97	0.63–1.49	48	0.92
Acute myelocytic leukaemia	Pesticide purchase[4]	12	1,540,541	1.33	1.35	0.64–2.85	11	1.38
	Animal husbandry	26	3,802,182	1.30	1.28	0.62–2.66	21	0.84
Other acute leukaemias	Pesticide purchase[4]	11	1,540,541	0.89	0.90	0.44–1.86	9	0.86
	Animal husbandry	29	3,802,182	2.41	2.28	0.95–5.51	23	1.90
	Cattle farming	21	2,661,395	1.71	1.64	0.83–3.22	17	1.21
	Dairy farming	16	2,254,687	1.29	1.22	0.63–2.37	14	1.04
	Chicken farming	10	1,117,300	1.64	1.54	0.74–3.22	7	1.08
	Pig farming	15	1,429,805	2.16	2.10	1.07–4.12	14	2.26

[1]Subjects born 1952–1964 followed up from 1971; subjects born 1965–1991 followed up from birth.–[2]Adjusted for year of birth and calendar year.–[3]See "Material and Methods" for definition, adjusted for year of birth and calendar year.–[4]Restricted to subjects covered in the 1969 census (n = 243,659; 4,280,456 person-years).

TABLE VII – *A PRIORI* SUSPECTED ASSOCIATIONS BETWEEN CANCER DIAGNOSED IN 1965–1991,[1] (EXCEPT BRAIN TUMOURS AND LEUKAEMIAS), AND EXPOSURE INDICATORS IN OFFSPRING BORN IN 1952–1991 (n = 323,292) TO PARENTS IN AGRICULTURAL WORK ACCORDING TO THE NORWEGIAN AGRICULTURAL CENSUSES IN 1969–1989: RESULTS OF POISSON REGRESSION ANALYSIS

Cancer diagnosis	Exposure indicator	Number of exposed cases	Person-years in stratum	Crude RR	Adjusted RR[2]	95% CI
Testicular cancer	Pesticide purchase[3]	36	790,254	0.84	0.89	0.60–1.32
	Horticulture	10	208,056	0.88	0.79	0.41–1.49
Soft-tissue sarcoma	Grain farming	6	1,551,352	0.76	0.76	0.31–1.88
	Forestry[4]	13	3,589,579	0.54	0.53	0.25–1.14
	Pesticide spraying equipment[5]	8	1,527,954	1.23	1.25	0.53–2.92
Hodgkin's disease	Grain farming	17	1,551,352	0.76	0.75	0.44–1.29
	Forestry[4]	56	3,589,579	1.67	1.56	0.94–2.60
	Pesticide spraying equipment[5]	22	1,527,954	1.18	1.27	0.76–2.11
Non-Hodgkin's lymphoma	Grain farming	14	1,551,352	0.81	0.81	0.45–1.47
	Forestry[4]	39	3,589,579	1.09	1.04	0.61–1.77
	Pesticide purchase[6]					
	Level 1	5	470,523	1.27	1.30	0.49–3.42
	Level 2	10	780,646	1.53	1.57	0.75–3.30
	Level 3	6	289,373	2.47	2.50	1.02-6.15
	Horticulture and pesticide purchase[6]	11	586,896	2.10	2.08	1.00–4.32

[1]Subjects born 1952–1964 followed up from 1971; subjects born 1965–1991 followed up from birth.–[2]Adjusted for year of birth and calendar year.–[3]Restricted to males covered in the 1969 census (n = 125,571; 2,202,325 person-years).–[4]Restricted to subjects covered in the 1969, 1979 or 1989 censuses (n = 322,270; 5,678,035 person-years).–[5]Restricted to subjects covered in the 1979 census (n = 300,555; 5,292,372 person-years).–[6]Restricted to subjects covered in the 1969 census (n = 243,659; 4,280,456 person-years).

Associations not included in the a priori *hypotheses*

The associations between horticulture or exposure to pesticides and cancer at an early age, and between chicken farming and cancer at later ages were also reflected in other specific groups of neoplasms (Table VIII).

Some of the associations between indicators of pesticide use in horticulture and the commoner malignancies in infancy were strong. Although there were few exposed cases, significantly increased RR were found between exposure to orchards or greenhouses and Wilms' tumour, especially when use of pesticide spraying equipment was reported. Field vegetable

TABLE VIII – POSITIVE ASSOCIATIONS NOT SUSPECTED *A PRIORI* BETWEEN CANCER AND EXPOSURE INDICATORS FOR OFFSPRING BORN 1952–1991 (n = 323,292) TO PARENTS IN AGRICULTURAL WORK ACCORDING TO THE NORWEGIAN AGRICULTURAL CENSUSES 1969–1989 RESULTS OF POISSON REGRESSION ANALYSIS

Cancer diagnosis	Exposure indicator	Total population					"Relevant" information[1]	
		Number of exposed cases	Person-years in stratum	Crude RR	Adjusted RR[2]	95% CI	Exposed cases	Adjusted RR[2]
Wilms' tumour	Orchards or greenhouses	4	403,386	4.04	4.78	1.56–14.7	2	4.42
Wilms' tumour	Pesticide spraying equipment[4]	9	1,527,954	2.77	2.54	0.98–6.58	6	4.88
Wilms' tumour	Orchards or greenhouses and pesticide spraying equipment[4,5]	4	227,982	7.95	8.87	2.67–29.5	2	12.5
Eye cancer	Field vegetables and pesticide purchase[3,6]	4	442,289	3.12	3.17	0.93–10.9	4	4.91
Neuroblastoma (age 0–4 years)	Field vegetables	7	162,642	2.38	2.51	1.03–6.13	6	3.00
Osteosarcoma	Chicken	12	1,117,300	2.89	2.90	1.38–6.11	8	2.70
Hodgkin's disease, mixed cellular type	Chicken	14	1,117,300	2.87	2.68	1.35–5.30	13	3.61

[1]See "Material and Methods" for definition, adjusted for year of birth and calendar year.–[2]Adjusted for year of birth and calendar year.–[3]Restricted to subjects covered in the 1969 census (n = 243,659; 4,280,456 person-years).–[4]Restricted to subjects covered in the 1979 census (n = 300,555; 5,292,372 person-years).–[5]Reference: subjects from holdings with no orchards, greenhouses, or pesticide purchase.–[6]Reference: subjects from holdings with no field vegetables or pesticide purchase.

farming was a risk factor both for eye cancer and for neuroblastoma at young age. However, only 2 of the 4 exposed eye-cancer cases were retinoblastomas.

A positive association was found between chicken farming and osteosarcoma, whereas an increased RR of borderline significance was seen for Hodgkin's disease; the latter association was confined to the mixed cellular type (Table VIII).

The associations reported in Table VIII were stronger when the analyses were restricted to the sub-set of children with "relevant" information from the index census. The exception was the association between chicken farming and osteosarcoma, but the slightly decreased RR was still significant. Analysis of the association for the sub-set of the cohort with a parent who worked at least 500 hr annually on the farm yielded a RR of 4.15 (95% CI, 1.61–10.7).

DISCUSSION

The total cancer experience among the offspring of farm holders was similar to that of the rural population of Norway, in accordance with case-control (Hemminki *et al.*, 1985; Olsen *et al.*, 1991) and proportionate mortality (Sanders *et al.*, 1981) studies in other countries. The incidence of cancer at specific sites did not deviate significantly from reference values in the whole study population. Offspring of a parent who worked 500 hr or more annually on a farm had moderate increases in the SIR for testicular cancer, nervous-system tumours, Hodgkin's disease and bone cancer. However, the increase was significant only for testicular cancer.

For cancer at all sites, male offspring had a SIR slightly above unity, whereas the female SIR was below unity. This difference can be explained only partially by low rates for cancers of the breast and cervix and high rates of testicular cancer. Since the difference encompasses several sites, chance is a plausible explanation. The gender difference at the ages of 5 to 19 years could also be due to environmental factors that act after birth. Children of farmers are unique in that they live at their parents' workplace and are potentially exposed to occupational agents. Most fatal accidents among farmers' children are linked to farm activities, and affect boys far more often than girls, even in the 0 to 4 year age group (Directorate of Labour Inspection, Oslo. personal communication). It is therefore probable that the risk of accidental childhood exposure is higher for boys than for girls.

The Poisson regression results indicate that pesticides poses a risk for some of the commonest malignancies of infancy and early childhood, whereas contact with animals, in particular poultry and pigs, constitutes a risk for some of the malignancies most typical of late childhood and adolescence.

Brain tumours

The most interesting confirmation of an *a priori* hypothesis was the clear relationship between brain turnours and indicators of exposure to pesticides and contact with animals. Children aged 0 to 14 years had a nearly doubled risk for brain tumours and a more than tripled risk for neuroepithelial tumours other than astrocytomas in association with pesticide purchase on the farm; RRs also increased by increasing expenditure levels. Even stronger associations were seen for sub-groups of offspring considered to have grown up on the farm or whose parents had a large work input on the farm, strengthening the evidence for a true relationship. The results are in accordance with those of several case-control studies in which indicators of parental or childhood exposure to pesticides or insecticides were associated with brain tumours (Preston-Martin *et al.*, 1982; Sinks, 1985; West, 1988; Wilkins and Koutras, 1988; Davis *et al.*, 1993; Bunin *et al.*, 1994). In those studies, the odds ratios were 1.5 to 2.0 and above, although several of the results were non-significant because of low exposure prevalence. Contrasting our results, West (1988) found that pesticides were associated more closely with astrocytoma. Use of insecticides was also reported in all case homes in a report of a cluster (Wilkins *et al.*, 1991). No increased risks were found, however, in other studies in which contact with pesticides (Howe *et al.*, 1989) or use of insecticides in the home before diagnosis (McCredie *et al.*, 1994*a*, *b*) were investigated. In a study of gliomas in adults, several groups of pesticides were found to be risk factors (Musicco et *al.*, 1988).

The credibility of a true relationship between pesticides and specific brain tumours in our study is strengthened by the space-time pattern of nervous-system tumour incidence in the cohort with an increasing SIR during the last years of follow-up and in offspring born 1980 to 1991. The same strata had a stronger association between pesticide purchase and non-astrocytic neuroepithelial tumours. Also, the highest SIR was found in the south region. where pesticides are more extensively used.

Clustering of neuroepithelial brain tumours in offspring born April to June to parents reporting pesticide use may indicate that paternal exposure 0 to 3 months before conception is crucial. Wilkins and Sinks (1990) found that the association between glioma and having a father in farming was strongest when he had held this occupation during the pre-conception period. West (1988) found that indicators of paternal exposure to pesticides constituted a risk for several histologic sub-types of brain tumours.

The association between pig farming and brain tumours was clear. RR was significantly increased by more than 50 percent for all brain tumours and 5-fold for medulloblastoma. Chicken farming also was associated with medulloblastoma. Our results are in accordance with Bunin *et al.* (1994), who reported elevated odds ratios for the tumour category including medulloblastoma in association with pigs and poultry. ***Toxoplasma gondii*** infection is a potential cause of brain tumours that is worth considering, since it infects domestic animals including chicken and pigs, and is even a suspected cause of glioma in animals (Schuman *et al.*, 1967). Pig farmers in Finland had an increased prevalence of antibodies to this micro-organism (Seuri and Koskela, 1992). In a case-control study of children and adults with tumours of the central nervous system, a significant association was found between antibodies to *Toxoplasma* and gliomas (Schuman *et al.*, 1967). In another study, a relationship was found with meningiomas but not with gliomas, but the cases included only adults (Ryan *et al.*, 1993).

Other hypotheses

The SIR analysis showed that leukaemia incidence was not increased in the study population, and the Poisson regression analysis did not indicate a relationship between animal husbandry or exposure to pesticides and acute lymphocytic or myelocytic leukaemia. The RR for other acute leukaemias were increased in association with contact with several animal species: the association was strongest for pig farming but was of borderline significance. Similar results have been reported for adult farmers (Blair *et al.*, 1992). The evidence for a true relationship is not convincing, however, since most of the associations were weaker for the sub-set of the study population for which presumably more relevant census information was available and for offspring from holdings where a parent worked at least 500 hr annually.

Interpretation of the results for leukaemia are difficult, since classification of sub-types in the Cancer Registry changed during the study period. Most of the lymphocytic and myelocytic sub-types were diagnosed later than 1975, and several other acute leukaemias would probably be classified as lymphocytic or myelocytic today. The hypothesis of an association between exposure to pesticides and acute myelocytic leukaemia at a young age (Buckley *et al.*, 1989; Buckley, 1992) is not supported by our results.

Moreover, the suspected association between soft-tissue sarcoma and lymphoma and exposure to phenoxy acids in grain farming and forestry (Blair *et al.*, 1992) was not supported by our data. An increased RR for Hodgkin's disease was found for offspring from farm holdings with forestry, but the adjusted estimate was not significant. Our data suggest that parental use of pesticides in horticulture is a risk factor for non-Hodgkin's lymphoma in childhood. The RR for pesticide purchase follow a dose-response pattern. As the increase is largely restricted to horticulture, a relationship is suggested with insecticides rather than phenoxy herbicides, which are prevalent in grain farming. Support for our result is provided by the results of several studies of non-Hodgkin's lymphoma in adults, in which insecticides (Cantor, 1982; Woods *et al.*, 1987; Zahm *et al.*, 1990, 1993; Cantor *et al.*, 1992) and orchard farming (Pearce *et al.*, 1985, 1987) constituted risk factors.

Testicular cancer was associated neither with the available indicators of exposure to pesticides nor with horticulture, where organochlorine pesticides with oestrogenic effects are used. The theory that intra-uterine exposure to such pesticides is a cause of testicular cancer (Sharpe and Skakkebæk, 1993) is therefore not supported by our results. The increased SIR for testicular cancer among farmers' sons, especially at the ages of 15 to 19 years, is at variance with the only other report on parental occupation and testicular cancer (Kardaun *et al.*, 1991). Our data suggest that testicular cancer is associated with farm practices that were common in the western part of Norway. Risk factors for testicular cancer other than exposure to pesticides in the study population are reported elsewhere (Kristensen *et al.*, 1995*a*).

Risks not included in the study hypotheses

Several positive associations not included in our study hypotheses were found, although they should be interpreted with caution, since many associations were investigated. The credibility of several of the results is strengthened, however, as they followed a specific pattern: tumours of infancy were associated with indicators of exposure to pesticides and horticulture, and malignancies that are commoner in later childhood were associated with indicators of contact with animals.

Wilms' tumour was related to living on a farm with orchards or greenhouses and pesticide spraying equipment. A significant 9-fold risk was found for offspring with both these exposure indicators, but this was based on only 4 exposed cases. This result is in agreement with those of a study from Brazil (Sharpe *et al.*, 1995), reporting paternal and maternal pesticide exposure as strong risk factors. It is also in agreement with results from the National Wilms' Tumor Study in the US, in which insecticide application during the last 3 years before diagnosis constituted a significant risk factor (Olshan *et al.*, 1990, 1993). Parental farming or rural farming residence has not been identified as risk factors of Wilms' tumour, however (Kantor *et al.*, 1979; Wilkins and Sinks, 1984; Olshan *et al.*, 1990). A relationship between paternal farming and childhood death from renal tumour has been reported (McDowall, 1985).

Growing field vegetables combined with pesticide purchase constituted risk factors of borderline significance for eye cancer and neuroblastoma. Eye cancer has been associated with the rural environment (Doll, 1991), but neuroblastoma has not been related to parental farming (Spitz and Johnson, 1985; Davis *et al.*, 1987; Wilkins and Hudley, 1990), except in one study (Bunin *et al.*, 1990). Detailed exposures were not assessed in those studies.

Chicken farming was associated with some of the common cancers of later childhood. The strongest associations were found for osteosarcoma and the mixed cellular type of Hodgkin's disease. To our knowledge, similar findings have not been reported, except for a suggestion of an association between Hodgkin's disease at young age and contact with rabbits (Dorken, 1975). It is interesting that chicken farming was a stronger risk factor than farming of other animal species. Chicken have been suspected of inducing malignancies in adult farmers through poultry viruses or chronic antigenic stimuli (Blair *et al.*, 1992). Exposure to organic dust containing micro-organisms may be very high in hen houses (Clark *et al.*, 1983).

Study validity

The study has some design features that ensure its validity. Use of the personal identification number made possible complete identification, linkage and follow-up, and cancer registration in the Cancer Registry of Norway is considered to be complete. Failure of inclusion of children born before 1965 who died before the 1970 population census would introduce a selective loss and a negative bias if a large proportion died of cancer. This bias was avoided by starting follow-up after the 1970 population census for children born between 1952 and 1964.

Agriculture in Norway occurs mainly on small and medium-sized farms that are owned and operated by the family. Only

10% of the total agricultural workforce in the 1970 population census were employees (Central Bureau of Statistics, 1975), who did not participate in the agricultural censuses. The national agricultural and horticultural censuses therefore offer an opportunity to identify most people engaged in agricultural work. We did not include offspring of farm owners born before 1925. On the basis of the age distribution of farm owners and the fertility of Norwegian farmers, we estimated that about 15% of all farmers' offspring born between 1952 and 1991 were children of farm owners born before 1925.

Inclusion criteria in the agricultural censuses were loose, and a large proportion of the parents had a low agricultural work input. The inclusion of subjects with a peripheral connection to farming may constitute a problem in the interpretation of the results of both the SIR and the Poisson regression analyses. We therefore performed separate analyses confined to offspring of farmers defined according to the standard occupational code.

Cohort subjects could also have parents who were not farmers at the time of conception or birth, since the cohort was based on information obtained at the agricultural censuses, 1969–1989, whereas the offspring under study were born between 1952 and 1991. We were unable to quantify offspring born before the first census participation, whose parents started in farming after the birth of the child. However, this problem is not likely to be substantial: less than one thousand new farms were settled in the 1950s and even fewer in the 1960s. During the same period, farms were almost entirely taken over by children (mainly sons) who lived on the farm. The main structural change in Norwegian agriculture during the study period has been a downward trend in the number of holdings and the number of people engaged in agricultural production. Therefore, farm owners whose children were born after the census year could have left the farm at the time the child was conceived or born. However, the inclusion of offspring of former farmers into the cohort would not be a major problem: less than 10,000 offspring, including only 8 cancer cases, were born after the last census participation of the parents (the majority in 1990–1991).

The main problem of our study was the use of crude proxies for true exposures and resulting exposure misclassification in the Poisson regression analysis. This may be most relevant for pesticides, as we had only information on money spent on pesticides or spraying equipment. We have assumed that associations with these indicators and with grain farming and forestry reflect exposures to phenoxy herbicides, and that the indicators of exposure to pesticides and work in orchards and greenhouses are related to exposure to organochlorine, organophosphate, and carbamate compounds. Although the approval, uses and application of pesticides were firmly regulated in the study period, our assumptions can be questioned, and inferences about types of pesticides used can hardly be made on the basis of our data. Several potential exposures to animals on individual farms are also unknown, such as the presence of zoonotic viruses or antigenic provocation by protein dust.

Equally problematic is the cross-sectional nature of our information on exposure. We have to assume that activity on a farm during the index census year reflects the activity before conception, during pregnancy or in infancy. This assumption introduces misclassification, which is most serious for cancer occurring after the first years of life, to which subjects born before the first census in 1969 make a considerable contribution. The problem affects in particular information unavailable at all censuses, such as that on pesticide use; pesticide purchase information was available at the 1969 census, but the association with brain tumours was strongest for children born 10 to 20 years later. The cross-sectional information on exposure offers little or no opportunity to make inferences about the potential mechanisms of tumourogenesis, except for the birth-month clustering of cases associated with pesticide purchase, which may be compatible with a paternal-mediated mechanism of pesticides.

The limitations of the quality of the information on exposure and its timing are not, however, related differently to the outcomes under study. The result of such non-differential misclassification for dichotomous categories will be a bias towards unity for any true association. We should therefore regard the results for the unconfirmed hypotheses as "non-positive" rather than negative.

Also the SIR estimates could be biased towards unity. This could be due to inclusion of offspring whose parents were not living or working on the farm at the time of conception or birth. *Also,* 89% of the study population lived on farms in rural municipalities, and contributed to the person-time experience of the total rural population. The study cohort had a person-time experience that was 0.20 to 0.25 that of the total rural population from 1965 to 1991 for people under 20 years. This ratio declined rapidly to 0.11 for ages 25 to 29 years and 0.01 for ages 35 to 39 years. The contribution of the study population to both the numerator and the denominator will lead to SIR estimates biased towards the null value, although the impact of this bias is limited for SIR close to unity. If the study population's person-time experience is subtracted from that of the reference population, providing a "worst-case" scenario, none of the reported SIR would change by more than a few percent.

Our results could be influenced by potential confounders. We had no information on tobacco smoking and alcohol consumption among the parents, but the cancer profile among the adult farmers strongly indicates low prevalences of both smoking and alcohol consumption compared with the total rural population (Kristensen *et al.,* 1995*b*). If parental smoking and alcohol consumption were risk factors, confounding could be the consequence, especially for the SIR results. However, parental lifestyle factors are not firmly established as risk factors for cancer in their offspring. Also, the selection of younger parents (born after 1924) could introduce confounding with regard to cancers related to parental age or parity; however, stratification on parental age in the analyses did not influence point estimates.

Although our study lacks precise exposure characterization, several results are in agreement with other reports, and farmers should consider, when handling pesticides, that even their offspring could be at risk of cancer. Further studies should address specific groups of pesticides and potential mechanisms for cancer development caused by animal contact.

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REFERENCES

BLAIR, A., ZAHM, S.H., PEARCE, N.E., HEINEMAN, E.F. and FRAUMENI, J.F. JR., Clues to cancer etiology from studies of farmers. *Scand. J. Work Environ. Health*, **18,** 209–215 (1992).

BRUNBORG, H. and KRAVDAL, O., *Fertility by birth order in Norway: a register-based analysis.* Report 86/27. Central Bureau of Statistics of Norway. Oslo-Kongsvinger (1986).

BUCKLEY, J.D., The aetiology of cancer in the very young. *Brit. J. Cancer*, **66**, Suppl. **XVIII**, S8–S12 (1992).

BUCKLEY, J.D., ROBISON, L.L., SWOTINSKI, R., GARABRANT, D.H., LEBEAU, M., MANCHESTER, P., NESBIT, M.E., ODOM, L., PETERS, J.M., WOODS, W.G. and HAMMOND, D.G., Occupational exposures of parents of children with acute non-lymphocytic leukemia: a report from the Children's Cancer Study Group. *Cancer Res.*, **49**, 4030–4037 (1989).

BUNIN, G.R., BUCKLEY, J.D., BOESEL, C.P., RORKE, L.B. and MEADOWS, A.T., Risk factors for astrocytic glioma and primitive neuroectodermal tumor of the brain in young children: a report from the Children's Cancer Group. *Cancer Epidemiol. Biomarker Prev.*, **3**, 197–204 (1994).

BUNIN, G.R., WARD, E., KRAMER, S., RHEE, C.A. and MEADOWS, A.T., Neuroblastoma and parental occupation. *Amer. J. Epidemiol.*, **131**, 776–780 (1990).

CANTOR, K.P., Farming and mortality from non-Hodgkin's lymphoma: a case-control study. *Int. J. Cancer*, **29**, 239–247 (1982).

CANTOR, K.P., BLAIR, A., EVERETT, G., GIBSON, R., BURMEISTER, L.F., BROWN, L.M., SCHUMAN, L. and DICK, F.R., Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res.*, **52**, 2447–2455 (1992).

CENTRAL BUREAU OF STATISTICS, *Population and housing census 1970. Vol. II: Industry occupation, working hours, etc.* Central Bureau of Statistics of Norway, Oslo (1975).

CLARK, S., RYLANDER, R. and LARSSON, L., Airborne bacteria, endotoxin and fungi in dust in poultry and swine confinement buildings. *Amer. ind. Hyg. Ass. J.*, **44**, 537–541 (1983).

DAVIS, J.R., BROWNSON, R.C., GARCIA, R., BENTZ, B.J. and TURNER, A., Family pesticide use and childhood brain cancer. *Arch. environ. Contam. Toxicol.*, **24**, 87–92 (1993).

DAVIS, S., ROGERS, M.A.M. and PENDERGRASS, T.W., The incidence and epidemiologic characteristics of neuroblastoma in the United States. *Amer. J. Epidemiol.*, **126**, 1063–1074 (1987).

DOLL, R., Urban and rural factors in the aetiology of cancer. *Int. J. Cancer*, **47**, 803–810 (1991).

DÖRKEN, H., Hodgkin's disease: an epidemiologic study among 140 children—urban/rural relations, parental occupation, contact with domestic animals (in German). *Arch. Geschwulstforsch.*, **45**, 283–298 (1975).

GOLD, E., GORDIS, L., TONASCIA, J. and SZKLO, M., Risk factors for brain tumors in children. *Amer. J. Epidemiol.*, **109**, 309–319 (1979).

HEMMINKI, K., SALONIEMI, I., SALONEN, T., PARTANEN, T. and VAINIO, H., Childhood cancer and parental occupation in Finland. *J. Epidemiol. Commun. Health*, **35**, 11–15 (1985).

HOWE, G.R., BURCH, J.D., CHIARELLI, A.M., RISCH, H.A. and CHOI, B.C.K., An exploratory case-control study of brain tumors in children. *Cancer Res.*, **49**, 4349–4352 (1989).

KANTOR, A.F., CURNEN, M.G.M., MEIGS, J.W. and FLANNERY, J.T., Occupations of fathers of patients with Wilms' tumour. *J. Epidemiol. Commun. Health*, **33**, 253–256 (1979).

KARDAUN, J.W.P.F., HAYES, R.B., POTTERN, L.M., BROWN, L.M. and HOOVER, R.N., Testicular cancer in young men and arental occupational exposure. *Amer. J. ind. Med.*, **20**, 219–227 (19917.

KLEIHUES, P., BURGER, P.C. and SCHEITHAUER, B.W., *Histological typing of tumours of the central nervous system. World Health Organization. International histological classification of tumours.* Springer, Berlin, Heidelberg (1993).

KRISTENSEN, P., ANDERSEN, A., IRGENS, L.M., BYE, A.S. and VAGSTAD, N., Testicular cancer and parental use of fertilizers in agriculture. *Cancer Epidemiol. Biomarkers Prev.*, (1995*a*). (In press).

KRISTENSEN, P., ANDERSEN, A., IRGENS, L.M., LAAKE, P. and BYE, A.S., Male and female cancer in Norwegian agriculture: incidence and risk factors in the farm environment. *Scand. J. Work environ. Health*, (1995*b*). (In press).

KUIJTEN, R.R. and BUNIN, G.R., Risk factors for childhood brain tumors. *Cancer Epidemiol. Biomarkers Prev.*, **2**, 277–288 (1993).

KUIJTEN, R.R., BUNIN, G.R., NASS, C.C. and MEADOWS, A.T., Parental occupation and childhood astrocytoma: results of a case-control study. *Cancer Res.*, **52**, 782–786 (1992).

LAVAL, G. and TUYNS, A.J., Environmental factors in childhood leukaemia. *Brit. J. ind. Med.*, **45**, 843–844 (1988).

LEISS, J.K. and SAVITZ, D.A., Home pesticide use and childhood cancer: a case-control study. *Amer. J. publ. Health*, **85**, 249–252 (1995).

LOWENGART, R.A., PETERS, J.M., CICIONI, C., BUCKLEY, J., BERNSTEIN, L., PRESTON-MARTIN, S. and RAPPAPORT, E., Childhood leukemia and parents' occupational and home exposures. *J. nat. Cancer Inst.*, **79**, 39–46 (1987).

MCCREDIE, M., MAISONNEUVE, P. and BOYLE, P., Antenatal risk factors for malignant brain tumours in New South Wales children. *Int. J. Cancer*, **56**, 6–10 (1994*a*).

MCCREDIE, M., MAISONNEUVE, P. and BOYLE, P., Perinatal and early postnatal risk factors for malignant brain tumours in New South Wales children. *Int. J. Cancer*, **56**, 11–15 (1994*b*).

MCDOWALL, M.E., *Occupational reproductive epidemiology. The use of routinely collected statistics in England and Wales 1980–82.* HMSO, Office of Population Censuses and Surveys, London (1985).

MUSICCO, M., SANT, M., MOLINARI, S., FILIPPINI, G., GATTA, G. and BERRINO, F., A case-control study of brain gliomas and occupational exposure to chemical carcinogens: the risk to farmers. *Amer. J. Epidemiol.*, **128**, 778–785 (1988).

OLSEN, J.H., DE NULLY BROWN, P., SCHULGEN, G. and JENSEN, O.M., Parental employment at time of conception and risk of cancer in offspring. *Europ. J. Cancer*, **27**, 958–965 (1991).

OLSHAN, A.F., BRESLOW, N.E., DALING, J.R., FALLETTA, J.M., GRUFFERMAN, S., ROBISON, L.L., WASKERWITZ, M. and HAMMOND, C.D., Wilms' tumor and paternal occupation. *Cancer Res.*, **50**, 3212–3217 (1990).

OLSHAN, A.F., BRESLOW, N.E., FALLETTA, J.M., GRUFFERMAN, S., PENDERGRASS, T., ROBISON, L.L., WASKERWITZ, M., WOODS, W.G., VIETTI, T.J. and HAMMOND, G.D., Risk factors for Wilms tumor. *Cancer*, **72**, 938–944 (1993).

PEARCE, N.E., SHEPPARD, R.A., SMITH, A.H. and TEAGUE, C.A., Non-Hodgkin's lymphoma and farming: an expanded case-control study. *Int. J. Cancer*, **39**, 155–161 (1987).

PEARCE, N.E., SMITH, A.H. and FISHER, D.O., Malignant lymphoma and multiple myeloma linked with agricultural occupations in a New Zealand cancer-registry-based study. *Amer. J. Epidemiol.*, **121**, 225–237 (1985).

PRESTON, D.L., LUBIN, J.H., PIERCE, D.A. and MCCONNEY, M.E., *Epicure.* Hirosoft International Corporation, Seattle (1993).

PRESTON-MARTIN, S., YU, M.C., BENTON, B. and HENDERSON, B.E., *N*-nitroso compounds and childhood brain tumors: a case-control study. *Cancer Res.*, **42**, 5240–5245 (1982).

RYAN, P., HURLEY, S.F., JOHNSON, A.M., SALZBERG, M., LEE, M.W., NORTH, J.B., MCNEILL, J.J. and MCMICHAEL, A.J., Tumours of the brain and presence of antibodies to *Toxoplasma gondii. Int. J. Epidemiol.*, **22**, 412–419 (1993).

SANDERS, B.M., WHITE, G.C. and DRAPER, G.J., Occupations of fathers of children dying from neoplasms. *J. Epidemiol. Commun. Health*, **35**, 245–250 (1981).

SAVITZ, D.A. and CHEN, J., Parental occupation and childhood cancer: review of epidemiologic studies. *Environ. Health Perspect.*, **88**, 325–337 (1990).

SCHUMAN, L.M., CHOI, N.W. and GULLEN, W.H., Relationship of central-nervous-system neoplasms to *Toxoplasma gondii* infection. *Amer. J. Publ. Health*, **57**, 848–856 (1967).

SEURI, M. and KOSKELA, P., Contact with pigs and cats associated with high prevalence of *Toxoplasma* antibodies among farmers. *Brit. J. ind. Med.*, **49**, 845–849 (1992).

SHARPE, C.R., FRANCO, E.L., DE CAMARGO, B., LOPES, L.F., BARRETO, J.H., JOHNSSON, R.R. and MAUAD, M.A., Parental exposures to pesticides and risk of Wilms' tumor in Brazil. *Amer. J. Epidemiol.*, **141**, 210–217 (1995).

SHARPE, R.M. and SKAKKEBÆK, N.E., Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? *Lancet*, **341**, 1392–1395 (1993).

SHU, X.O., GAO, Y.T., BRINTON, L.A., LINET, M.S., TU, J.T., ZHENG, W. and FRAUMENI, J.F. JR., A population-based case-control study of childhood leukemia in Shanghai. *Cancer*, **62**, 635–644 (1988).

SINKS, T.H. JR., *N*-nitroso compounds, pesticides, and parental exposures in the work-place as risk factors for childhood brain cancer: a case-control study. *Diss. Abstr. Int.*, **46**, 1888-B (1985).

SPITZ, M.R. and JOHNSON, C.C., Neuroblastoma and paternal occupation. *Amer. J. Epidemiol.*, **121**, 924–929 (1985).

VAN STEENSEL-MOLL, H.A., VALKENBURG, H.A. and VAN ZANEN, G.E., Childhood leukemia and parental occupation. *Amer. J. Epidemiol.,* **121,** 216–224 (1985).

WEST, C.G., *Parental occupation and occurrence of brain tumors in children.* Doctoral thesis, Harvard School of Public Health, Boston (1988).

WILKINS, J.R. III and HUDLEY, V.D., Paternal occupational exposure to electromagnetic fields and neuroblastoma in offspring. *Amer. J. Epidemiol.,* **131,** 995–1008 (1990).

WILKINS, J.R. and KOUTRAS, R.A., Paternal occupation and brain cancer in offspring: a mortality-based case-control study. *Amer. J. ind. Med.,* 14, 299–318 (1988).

WILKINS, J.R. III, MCLAUGHLIN, J.A., SINKS, T.H. and KOSNIK, E.J., Parental occupation and intracranial neoplasms of childhood: anecdotal evidence from a unique occupational cancer cluster. *Amer. J. ind. Med.,* 19, 643–653 (1991).

WILKINS, J.R. III and SINKS, T.H. JR., Paternal occupation and Wilms' tumour in offspring. *J. Epidemiol. Commun. Health,* **38,** 7–11 (1984).

WILKINS, J.R. III and SINKS, T., Parental occupation and intracranial neoplasms of childhood: results of a case-control interview study. *Amer. J. Epidemiol.,* **132,** 275–292 (1990).

WOODS, J.S., POLISSAR, L., SEVERSON, R.K., HEUSER, L.S. and KULANDER, B.G., Soft-tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxyherbicide and chlorinated phenol exposure in western Washington. *J. nat. Cancer Inst.,* **78,** 899–910 (1987).

ZACK, M., CANNON, S., LOYD, D., HEATH, C.W. JR., FALLETTA, J.M., JONES, B., HOUSWORTH, J. and CROWLEY, S., Cancer in children of parents exposed to hydrocarbon-related industries and occupations. *Amer. J. Epidemiol.,* **111,** 329–336 (1980).

ZAHM, S.H., WEISENBURGER, D.D., BABBITT, P.A., SAAL, R.C., VAUGHT, J.B., CANTOR, K.P. and BLAIR, A., A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. *Epidemiology,* 1, 349–356 (1990).

ZAHM, S.H., WEISENBURGER, D.D., SAAL, R.C., VAUGHT, J.B., BABBITT, P.A. and BLAIR, A., The role of agricultural pesticide use in the development of non-Hodgkin's lymphoma in women. *Arch. environ. Health,* **48,** 353–358 (1993).