

Indicators of mancozeb exposure in relation to thyroid cancer and neural tube defects in farmers' families

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Objectives The fungicide mancozeb has been suspected of causing thyroid cancer and neural tube defects. The aim of the study was to investigate associations of indicators of mancozeb exposure with thyroid cancer and neural tube defects in farmers' families.

Methods National registers in Norway, identifying 105 403 female and 131 243 male farmers, born in 1925–1971, and their 300 805 children available for analyses, born in 1952–1991, were cross-linked with national agricultural censuses, 1969–1989, and the population register. Neural tube defects (ICD-8 740–742) at birth among the 102 703 children conceived between May 1973 and April 1991 were identified in the medical birth register. Likewise thyroid cancer (ICD-7 194) was identified in the cancer register through 2000. Data on farm production and fungal forecasts (humid and temperate weather conditions) in 1973–1990, obtained from agricultural censuses and meteorological measurement stations, respectively, served as the mancozeb exposure indicators. The adjusted rate ratio or prevalence ratio (PR) estimates with 95% confidence intervals (95% CI) were computed in a Poisson regression analysis.

Results Neural tube defects (131 cases, prevalence 12.8/10 000 births) was moderately associated with potato cultivation (PR 1.6, 95% CI 1.1–2.3) and paternal work of >500 hours/year (PR 1.6, 95% CI 1.1–2.5). Altogether 319 thyroid cancer cases were identified: 141 in female farmers (incidence 10.2/100 000 person-years), 79 in male farmers (incidence 3.2/100 000 person-years), and 99 in offspring (female and male incidence 3.4 and 0.6/100 000 person-years, respectively). Mancozeb exposure was not associated with thyroid cancer.

Conclusions A moderate association seems to exist between mancozeb exposure and neural tube defects, but not between mancozeb exposure and thyroid cancer.

Key terms central nervous system malformation; cohort study; epidemiology; pesticide; zinc manganese ethylene bisdithiocarbamate.

Mancozeb has been the most frequently used fungicide in agriculture in Norway [The Norwegian Food Safety Authority. Plantevernmiddele-statistikk (Pesticide statistics). Web-site: <http://www.mattilsynet.no/>. The Norwegian Food Safety Authority. Oslo, Norway], as well as in the United States (1). In Norway, it has been used mainly in potato cultivation against potato late blight (dry rot). Mancozeb degrades (2) and is metabolized (3) to ethylenethiourea (ETU), also identified in commercial mancozeb preparations (4, 5). ETU is a thyroid peroxidase inhibitor in rats and primates (6). It induces malformations of the neural tube in rats (7, 8) and frogs (9) and also thyroid cancers in rats and mice (10). ETU

was earlier classified by the International Agency for Research on Cancer as possibly carcinogenic to humans (group 2B), but, in 2001, it was reclassified into group 3 (not classifiable as to its carcinogenicity in humans) (11). This reclassification has been disputed (12), and published studies indicate that occupational exposure to ETU resulting from mancozeb use may perturb thyroid homeostasis (3, 13–15).

Closure of the human neural tube is normally completed at 27 days after fertilization, and the failure of this closure leads to neural tube defects (16). The prevalence of neural tube defects at birth shows remarkable geographic and temporal variation that indicates that

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environmental factors are important for the pathogenesis of neural tube defects (17, 18). Folic acid depletion induces neural tube defects, and its supplement during early pregnancy was found to be associated with a 72% reduction in the number of cases of a neural tube defect (19), but the prevention of such defects by folic acid supplements has not been effective so far (20). Other factors reported to affect the risk of neural tube defects are genetic predispositions (21), fever during early pregnancy (22), socioeconomic deprivation (23), parity (24), and maternal agricultural activity (25). Associations between potato consumption and spina bifida, as well as anencephaly, has been hypothesized (26), but substances inducing neural tube defects have not been isolated from potatoes (27, 28). In Norway, the prevalence at birth in 1967–1991 was 34, 51, and 38 per 10 000 births for anencephaly, spina bifida, and congenital hydrocephalus, respectively (29).

Thyroid cancer is mainly explained by ionizing radiation early in life (30), but it has also been linked to the consumption of seafood (31), differences in iodine uptake, overstimulation by thyroid-stimulating hormone (TSH) (30), and high parity (32). In an early Norwegian study, Pedersen (33) noted a higher proportion of thyroid cancer in eastern counties typical of potato, animal, and grain farming, and, in northern counties, of fishing industries. In Norway, the rates of thyroid cancer show increasing gradients from east to west, as well as from south to north, and also the female-to-male ratio varies substantially between Norwegian counties, the national rates in 1982–1986 being 5.1 and 1.6 per 100 000 person-years for females and males, respectively, adjusted to the world standard population (34).

A correlation between thyroid cancer incidence in 1953–1961 and mortality from anencephaly in 1951–1965 in Norway has been noted (35). Recently, several cancers and developmental perturbations have been hypothesized to stem from common exposures that occur early in life (36), and Nakagawara (37) suggested that the tyrosine kinase receptor might constitute a bridge between disturbances of neural development and papillary thyroid cancers. The hypothesis of our study was that exposure to mancozeb or its degradation product ETU causes neural tube defects and thyroid cancer. The aim of the study was to assess associations between indicators of mancozeb exposure and the outcomes. The study was performed in an earlier established cohort of farmers' families (38).

Study population and methods

A study cohort of farmers' families was established through register linkage with the Central Population

Register of the participants of agricultural censuses performed by Statistics Norway in 1969 and 1979. Farmers' children conceived between May 1973 and April 1990 were identified in the Medical Birth Registry of Norway. Follow-up of incident thyroid cancer in the Cancer Registry of Norway was performed from the first agricultural census of participation in 1969–1989 through the year of 2000 for the farm holders, while spouses' person-time before 1986 was excluded due to the uncertainty of the historical marriage records before that year (38). The follow-up of children started from the age of 13 years. Data on agricultural production were obtained from the agricultural censuses in 1969, 1974, 1979, 1985, and 1989. Meteorological data obtained from 46 measurement stations of the Norwegian Meteorological Institute for 1973–1990 were allocated to the nearest farm. The establishment of the cohort has been explained in more detail elsewhere (39).

Exposure

Mancozeb exposure was reflected by the combination of potato farming, pesticide use, and meteorologically based fungal forecasts. Potato farming was defined as potato cultivation in any census in 1969–1989. For neural tube defects, we also analyzed the 49 369 births (giving rise to 65 cases) that occurred after conceptions within 3 years of a census of participation for the respective farm, using information on potato production from this census exclusively. Pesticide use was defined as pesticide purchase in 1968 or pesticide application equipment on the farm in 1978. Fungal (late blight) forecasts have been broadcasted in Norway since the 1950s to help potato farmers decide when to apply fungicides against potato dry rot. A fungal forecast is issued when the following criteria are met during two consecutive 24-hour periods: $T_{\max} > 17^{\circ}\text{C}$, $T_{\min} > 10^{\circ}\text{C}$, relative humidity at noon $> 75\%$, and rainfall > 1 mm (40). The number of fungal forecasts for each year between 1973 and 1990 from the nearest station was allocated to each farm in order to calculate the number of forecasts in the conception season applied in the analyses for neural tube defects. The number of seasons with more than one fungal forecast in 1973–1990 was computed and applied (in quartiles) in the analyses for thyroid cancer. The farms were further categorized according to work input of more than 500 hours yearly by either parent (yes, no), agricultural education of the farm holder (yes, no), agricultural acreage (4 categories), and geographic location (5 regions, as well as within 50 km of Norwegian western coastal line or not) of the farm (table 1). Mancozeb sales in Norway [The Norwegian Food Safety Authority: Plantevernmiddel-statistikk (Pesticide statistics); web-site: <http://www.mattilsynet.no/>] in

Table 1. Thyroid cancer (N=319) according to the parental generation born in 1925–1971 (N=236 646), the filial generation born in 1952–1991 (N=286 475), and the exposure indicators and the prevalence of neural tube defects (N=131) at birth, according to the children (N=102 703) (filial generation) born to farmers in 1973–1991 and the exposure indicators. (95% CI=95% confidence interval)

Observational categories	Thyroid cancer				Neural tube defects			
	Persons at risk	Cases	Incidence ^a	95% CI	Number of births	Cases	Rate ^b	95% CI
Parental generation								
Female	105 403	141	10.2	8.66–12.1	.	.	.	.
Male	131 243	79	3.23	2.59–4.03	.	.	.	.
Filial generation								
Female	139 541	83	3.42	2.76–4.24	49 881	75	15.0	12.0–18.9
Male	146 934	16	0.62	0.38–1.02	52 822	56	10.6	8.16–13.8
Potato farming								
No	199 938	136	4.27	3.61–5.06	50 167	48	9.57	7.21–12.7
Yes	323 183	183	3.25	2.82–3.76	52 536	83	15.8	12.7–19.6
Pesticide use ^c								
No	315 214	201	3.78	3.29–4.34	57 280	73	12.7	10.1–16.0
Yes	207 907	118	3.38	2.82–2.05	45 423	58	12.8	12.8–16.5
Work input on the farm by any family member								
0–500 hours/year	213 451	141	3.91	3.31–4.61	40 618	40	9.84	7.22–13.4
>500 hours/year	309 670	178	3.43	2.96–3.97	62 085	91	14.7	11.9–18.0
Farm holder educated in agriculture								
No	378 445	232	3.62	3.19–4.12	72 378	84	11.6	9.37–14.4
Yes	144 676	87	3.62	2.93–4.47	30 325	47	15.5	11.6–20.6
Farm acreage								
0–0.4 hectares	79 747	38	3.10	2.25–4.26	25 172	24	9.53	6.39–14.2
0.5–2.4 hectares	101 818	72	3.97	3.15–5.00	11 959	13	10.9	6.31–18.7
2.5–9.9 hectares	243 542	151	3.61	3.08–4.24	36 695	56	15.3	11.7–19.8
≥10 hectares	98 014	58	3.66	2.83–4.74	28 877	38	13.2	9.58–18.1
Region								
East	179 066	95	3.17	2.59–3.88	36 111	46	12.7	9.54–17.0
South	69 786	23	2.00	1.33–3.00	6 094	16	26.3	16.1–42.9
West	127 438	94	4.41	3.60–5.40	36 641	38	11.0	7.98–15.1
Middle	66 022	41	3.68	2.71–5.00	12 989	14	10.8	6.38–18.2
North	80 809	66	4.68	3.68–5.95	12 868	17	13.2	8.21–21.3
Fungal forecasts 1973–1990 ^d								
0	114 285	75	3.82	3.05–4.79	27 957	36	12.9	9.29–17.9
1–2	151 651	83	3.26	2.63–4.05	20 977	64	15.7	11.2–22.1
3–5	115 282	69	3.55	2.81–4.50	23 274	20	9.88	5.57–14.9
6–13	141 903	92	3.90	3.18–4.78	30 495	11	12.8	9.24–17.5
Fungal forecasts made in conception season ^e								
0	.	.	.	.	57 440	74	12.9	10.3–16.2
1	.	.	.	.	27 553	39	14.2	10.4–19.4
2	.	.	.	.	9 670	7	7.24	3.45–15.2
>2	.	.	.	.	8 121	12	13.7	7.58–24.7
Along Atlantic or North sea coast								
No	223 173	114	3.06	2.54–3.67	43 818	48	11.0	8.26–14.5
Yes	299 948	205	4.04	3.52–4.63	58 885	83	14.1	11.4–17.5
Year of birth								
1925–1939	99 631	106	5.72	4.72–6.91	.	.	.	.
1940–1949	75 081	67	5.71	4.49–7.26	.	.	.	.
1950–1959	94 654	78	3.93	3.14–4.90	.	.	.	.
1960–1969	124 709	54	2.13	1.63–2.79	.	.	.	.
1970–1979	90 105	13	1.17	0.68–2.01	45 944	62	13.5	10.5–17.3
1980–1991 ^f	38 941	1	0.70	0.10–4.94	56 759	69	12.2	9.60–15.4

^a Crude incidence rate per 100 000 person-years.^b Neural tube defects (anencephaly, spina bifida, or hydrocephalus), prevalence rate per 10 000 births diagnosed at birth.^c Pesticide purchase in 1969 census or spraying equipment in 1979 census.^d Categories of years with more than one fungal forecast events in meteorological station nearest the farm. A fungal forecast is issued when the following criteria are met during two consecutive 24-hour periods: $T_{\max} \geq 17^{\circ}\text{C}$, $T_{\min} \geq 10^{\circ}\text{C}$, relative humidity at noon $\geq 75\%$, rainfall ≥ 1 mm.^e Number of fungal forecast events in station nearest the farm in the conception season.^f Observation of thyroid cancer starts at the age of 13 years.

1967–1990 (figure 1) were sufficient to cover the total potato acreage on an average of 1.5 times a year (from 0.5 times in 1979 to 2.7 times in 1990), given a recommended dosage of 1.5 kg/hectare. Reportedly, the potato crop loss due to dry rot was especially low during 1973–1978 and high during 1979–1981, 1983, 1985, and 1988 (41). Conceptions were categorized according to the level of mancozeb sales in the year of conception (analyzed in tertiles) and according to high potato crop loss due to dry rot in that year (yes, no). Finally, we also investigated the effect of summer conception in May–September versus conception in October–April for the outcome of neural tube defects, because mancozeb application is performed during the summer months. The conception month was calculated using the month of birth and reported gestational age in 95% of the births in which gestational age was considered valid; otherwise 40 weeks of gestation was assumed. We considered the first month after conception as the relevant window of exposure for neural tube defects, while lifetime exposure was considered relevant for thyroid cancer.

For each conception from May until April the next year we defined the number of fungal forecasts in the conception season as the number of forecasts in the same period.

Outcomes

By means of the national identification number, cases of neural tube defects [740–742 in the International Classification of Diseases, eighth revision (ICD-8)] in the Medical Birth Registry of Norway were identified in the study group, which included 102 703 children (52 822 males and 49 881 females) of known gestation age conceived between May 1973 and April 1990. Data on subgroups of neural tube defect—*anencephaly*, *spina bifida*, and *hydrocephaly* (ICD 8740, 741, and 742,

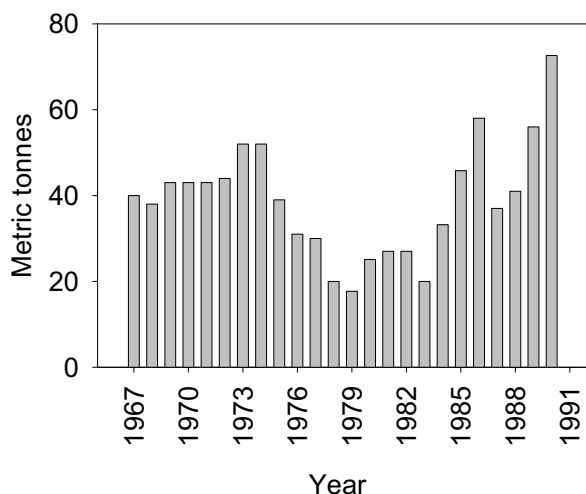


Figure 1. Annual mancozeb sales per year in 1967–1990.

respectively)—and parity were obtained from the Medical Birth Registry of Norway. Likewise, we updated the cohort in the Cancer Registry of Norway from 1969 through the year 2000 or until death, emigration, or a diagnosis of thyroid cancer, identifying cases of incident thyroid cancer (ICD-7 194) in the study group, which included 141 389 farm holders born in 1925–1971, 95 257 spouses to farm holders, and their 286 475 children born in 1952–1987, for a total of 278 177 males and 244 944 females. Thyroid cancers were also categorized as papillary or nonpapillary according to histology.

Statistical methods

The prevalence rates of neural tube defects at birth (cases/10 000 births) and incidence rates of thyroid cancer (cases/100 000 person-years of observation) were observed in categories of the exposure variables, reference categories were chosen, and comparisons were made between the strata of exposure. Using a Poisson regression, we built models to estimate adjusted rate ratios and their 95% confidence intervals (95% CI) in strata of the exposure variables. The model building started with covariates defined by the a priori hypothesis, and other covariates were included if their inclusion in the model changed the main determinants in the model by more than 15%. The statistical analyses were carried out with a personal computer using SPSS 11.0 software (SPSS Inc, Chicago, IL, USA) for file preparation and Epicure 2.0 (Hirosoft International Corporation, Seattle, WA, USA) for the tabulations and regression analysis.

Results

We identified 131 cases of a neural tube defect among a total of 102 703 births (crude rate 12.8/10 000 births) and 319 cases of thyroid cancer among a total of 8.81 million person-years (crude rate 3.6/100 000 person-years) (table 1). Of the thyroid cancer cases, 141 occurred in female farmers (incidence 10.2/100 000 person-years), 79 in male farmers (incidence 3.2/100 000 person-years), and 99 in offspring (female and male incidence 3.4 and 0.6/100 000 person-years, respectively).

Neural tube defects (table 2) were associated with potato production and with the input of more than 500 hours on the farm by the father, but not by the mother. In the analyses of neural tube defects, the subgroups *anencephaly* and *hydrocephalus* were associated with potato production. Increasing categories of fungal forecasts in the conception season were not associated with the outcome. Summer conceptions, years of high mancozeb sales, and years of reportedly high crop damage

Table 2. Final Poisson regression model of the associations between the indicators of mancozeb exposure and neural tube defects in 102 703 children born to Norwegian farmers in 1973–1991. ^a (PRR = prevalence rate ratio, 95% CI = 95% confidence interval)

Exposure indicator	All neural tube defects (N=131)		Anencephaly (N=46)		Spina bifida (N=45)		Hydrocephalus (N=42)		Neural tube defects within 3 years of census ^c (N=69)	
	PRR ^b	95% CI	PRR ^b	95% CI	PRR ^b	95% CI	PRR ^b	95% CI	PRR ^b	95% CI
Potato farming										
No ^d	1	.	1	.	1	.	1	.	1	.
Yes	1.55	1.07–2.25	1.66	0.88–3.12	1.10	0.59–2.05	1.98	1.00–3.93	1.64	0.98–2.78
Mother's work ^e										
<500 hours ^d	1	.	1	.	1	.	1	.	1	.
≥500 hours	0.85	0.57–1.27	1.37	0.70–2.70	0.78	0.39–1.53	0.58	0.28–1.21	0.78	0.45–1.35
Father's work ^e										
<500 hours ^d	1	.	1	.	1	.	1	.	1	.
≥500 hours	1.62	1.06–2.47	1.16	0.58–2.27	1.67	0.79–3.51	2.37	1.11–5.04	1.58	0.88–2.86
Fungal forecasts ^f										
0 ^d	1	.	1	.	1	.	1	.	1	.
1	1.09	0.74–1.62	1.10	0.57–2.13	1.12	0.56–2.23	1.11	0.56–2.19	1.42	0.83–2.42
2	0.61	0.28–1.34	^g	^g	1.02	0.35–3.00	0.44	0.13–1.48	0.49	0.15–1.61
>2	1.12	0.59–2.13	0.81	0.33–2.03	1.42	0.53–3.71	^g	^g	1.06	0.44–2.56
Region										
East ^d	1	.	1	.	1	.	1	.	1	.
South	2.04	1.14–3.65	2.85	1.17–6.94	1.76	0.58–5.36	1.41	0.46–4.32	1.43	0.58–3.55
West	0.81	0.52–1.26	1.02	0.48–2.14	0.94	0.47–1.90	0.51	0.22–1.20	0.82	0.46–1.48
Middle	0.81	0.44–1.49	0.73	0.24–2.26	0.62	0.21–1.87	1.02	0.39–2.64	0.96	0.44–2.06
North	0.99	0.56–1.77	0.74	0.26–2.10	0.93	0.30–2.90	1.22	0.50–2.98	0.88	0.37–2.12
LRT test ^h	P=0.49		P=0.54		P=0.92		P=0.28		P=0.23	

^a The same model was applied to each subcategory of neural tube defects; the model included gender, potato farming, yearly farm work input by mother and father (>500 hours), pesticide use, fungal forecasts in conception season, and region. Two cases of anencephaly were also diagnosed with spina bifida.

^b Adjusted for the other covariates in the model.

^c In this column is the resulting fit of the model applied to the 52 360 births that occurred within 3 years of an agricultural census to which the farm contributed, using data on potato production from this census exclusively.

^d Reference category.

^e Farm work input by mother or father.

^f Number of fungal forecasts in the conception season from May until April next year.

^g Categories 2 and >2 were collapsed into one category due to the absence of cases in the indicated category.

^h Likelihood ratio test for the significance of the forecast covariate.

due to potato dry rot in the conception season were not associated with the outcome. Southern Norway showed the highest adjusted rates of anencephaly and neural tube defects, and 8 of 16 cases in this region were found along the southernmost coastal line.

Thyroid cancer (table 3) was not associated with any farm production or meteorological covariate, but the rates were higher in western and northern Norway. Papillary thyroid cancer showed an even stronger association with the same districts.

Discussion

We found that neural tube defects were associated with potato production, whereas thyroid cancer was not associated with indicators of mancozeb exposure.

The major weakness of the study was the use of exposure indicators as proxies for real exposure, leading to potential misclassification of the true exposure and difficulties when inferences are drawn from the results. Although it is not feasible to obtain precise data on the

Table 3. Final Poisson regression model of the associations between the indicators of mancozeb exposure and the thyroid cancer incidence of Norwegian farmers (N=247 232) and their children (N=286 475). (RR = rate ratio, 95% CI = 95% confidence interval)

Exposure indicator	Thyroid cancer (319 cases)		Papillary subgroup of thyroid cancer (228 cases)	
	RR ^a	95% CI	RR ^a	95% CI
Potato farming				
No ^b	1	.	1	.
Yes	0.87	0.69–1.19	0.89	0.67–1.18
Fungal forecasts ^c				
0 seasons ^b	1	.	1	.
1–2 seasons	1.01	0.71–1.43	1.06	0.70–1.62
3–5 seasons	1.16	0.76–1.77	1.28	0.77–2.14
6–13 seasons	1.27	0.83–1.93	1.48	0.89–2.45
Region				
East ^b	1	.	1	.
South	0.67	0.41–1.07	0.68	0.38–1.21
West	1.36	0.98–1.87	1.49	1.02–2.19
Middle	1.15	0.78–1.71	1.28	0.81–2.05
North	1.66	1.16–2.38	2.08	1.35–3.22

^a Adjusted for gender, age, birth year (6 intervals), potato farming, fungal forecasts, and region.

^b Reference category.

^c Number of seasons in 1973–1990 with more than one fungal forecast (events of temperate and humid weather conditions).

historical use of pesticides at the farm level, the use of more blunt data on production, district level, and meteorology at the farm level may be useful in the identification of possible risk factors of the outcomes, as data on exposure are collected independently of the outcome status. The resulting misclassification of exposure is therefore likely to be nondifferential, leading to a bias towards the null of any true associations between the exposure and outcome (42). Thus the associations that were identified should be taken seriously, while nonassociations could have depended on the misclassification of exposure in a situation in which a true association exists.

The major strengths of this study were the absence of selection bias of the participants, as all economically active farmers report to the agricultural censuses, and the high reporting rate and quality of data of the Cancer Registry of Norway and Medical Birth Registry of Norway. Another strength is that the observation period for the prevalence of neural tube defects occurred before the major campaign to increase folic acid intake started, accordingly differential compliance to this recommendation between subgroups of the study base did not affect our estimates. The Cancer Registry of Norway is considered to be more than 99% complete for solid cancers (43). The reporting to the Medical Birth Registry of Norway in the period of interest was compulsory for all pregnancies beyond 16 weeks. In a study using double registration systems, 90% of malformations of the central nervous system were found to be reported to the Medical Birth Registry of Norway (44). Failure to report prenatally diagnosed cases of birth defects that resulted in termination of pregnancy may have affected the rates for neural tube defects (45), but the impact of this underreporting on Norwegian rates of neural tube defects may be smaller than earlier anticipated (29). As the hypothesis of an association between potato cultivation and neural tube defects is not generally known, there is no reason to believe that such underreporting would be dependent on the study outcome and thus lead to a reporting bias in our study.

Mancozeb treatments of potato fields vary within and between seasons, districts, and farms. In 2001, 87% of the Norwegian potato acreage was treated with fungicides, and the main fungicides used were fluazinam (introduced in 1995) and mancozeb, the months of treatment were June (8% of treated area), July (89% of treated area), August (93% of treated area), and September (29% of treated area) (46). Fungicide spraying was somewhat more abundant on larger farms than on smaller ones. Since mancozeb sales in 1973–1990 (figure 1) indicated mancozeb application to a substantial part of the potato acreage (1), potato production itself is probably the best single parameter reflecting mancozeb application to the crop. In our study, both potato farming

and work input above 500 hours yearly by the father were associated with neural tube defects, but none of the factors under study were associated with thyroid cancer. The finding of a stronger association between potato production and neural tube defects when the analysis was restricted to the births within 3 years of a census of participation could indicate less misclassification and, accordingly, less attenuation of the association measure for these births. A lack of association between increasing categories of fungal forecasts and neural tube defects could indicate that a true association is not present. Alternatively, a true relationship could be explained by the farmers' choice of crop and fungicide application regimen on the basis of the normally expected climate at the site of the farm. Thus only pregnancies in areas normally at low risk of fungal forecasts could be susceptible to the effect of fungal forecasts in the conception season. Mancozeb sales and dry rot damage level reported in the conception season years on a national level did not contribute to the explanation for the risk of neural tube defects, neither for all conceptions nor for potato farmers exclusively. A geographic variation of neural tube defects, as was shown in this study, has been reported in several studies (47, 48).

In our study, we found no associations between the indicators of mancozeb exposure and thyroid cancer. The incidence of thyroid cancer varied by region in this study according to the same pattern that was demonstrated in the total Norwegian population (34) with the highest incidence rates in the coastal areas to the west and north. Contrary to this pattern was the finding of a high prevalence of neural tube defects in the southernmost district of Norway, the west and north districts showing the lowest rates. Thus the pattern of thyroid cancer differed from that of neural tube defects both with respect to mancozeb exposure indicators and geographic farm location. This finding does not support the suggestion of a common agriculture-related etiologic factor for thyroid cancer and neural tube defects.

This study offers limited support for the hypothesis that mancozeb applications common in potato farming could affect the risk of neural tube defects. We found no support in this study for the hypothesis that mancozeb affects thyroid cancer risk in the Norwegian agricultural population. Inferences from this study should be drawn with the crude nature of the exposure indicators used born in mind, along with the resulting opportunity for the misclassification and attenuation of true associations.

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