Risk of cancer in pesticide applicators in Swedish agriculture

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ABSTRACT The risk of cancer was analysed in a cohort of 20 245 licensed pesticide applicators in agriculture who had licences issued between 1965 and 1976. Most were men (99%) and about 50% had been born in 1935 or later. The cohort was followed up in the Swedish Cancer Register from date of licence until death or 31 December 1982. The mean follow up time was 12·2 years. Average time since first exposure was longer, however, since one fifth of the cohort was exposed in the 1950s. A total of 558 malignant tumours was found compared with 649·8 expected, which resulted in a statistically significantly decreased standardised incidence ratio (SIR) of 0·86 (95% confidence interval (CI): 0·79–0·93). Significantly decreased risks of cancer were also found for liver (SIR = 0·45, 95% CI: 0·18–0·93), pancreas (SIR = 0·50, 95% CI: 0·26–0·87), lung (SIR = 0·50, 95% CI: 0·35–0·68), and kidney (SIR = 0·53, 95% CI: 0·32–0·84). No statistically significantly increased risks or any time trends were observed. SIR for testicular cancer was increased (SIR = 1·55, 95% CI: 0·92–2·45) and increased with period since licence. Eighteen cases with testicular cancer were found. For those born in 1935 or later a non-significant increased overall risk of cancer was observed (SIR = 1·07, 95% CI: 0·82–1·37). Comparisons were made with agricultural workers in general since pesticide applicators are mainly farmers that use or have used pesticides to a greater extent. Higher risks for pesticide applicators were found for testicular cancer, tumours of the nervous system and endocrine glands, and Hodgkin’s disease.

Major changes have taken place in Swedish agriculture over the past five decades. The development may be characterised by increased mechanisation and specialisation of production. The number of large farms has increased and many small farms have disappeared. The use of agricultural chemicals, especially pesticides, has increased rapidly since the 1940s; some of these are suspected of being carcinogenic on the basis of animal studies and epidemiological studies of human populations. The carcinogen may be the active ingredient, another ingredient, or a contaminant in the formulation. Most of these pesticides are now withdrawn from the Swedish market (including Dieldrin, Aldrin, and DDT). A review of the delayed health hazards of exposure to pesticides concluded that neither phenoxy herbicides nor dioxins could unequivocally be stated to cause cancer in man. Another review has suggested, however, that exposure to phenoxy acid herbicides may be associated with an increased incidence of cancer.

Agricultural workers in Australia, Canada, the United States, and several European countries have a lower overall risk for cancer. Reduced risks were also found for cancers of the colon, liver, lung, and urinary bladder. For cancer of the lip, stomach, prostate, skin, and for leukaemia and multiple myeloma the risks were shown to be increased. Swedish agricultural workers also have a decreased overall risk of cancer. For many individual sites, and especially for cancers of the respiratory tract the risks were found to be low. The risks for lip cancer, malignant melanoma, and skin carcinoma in the head and neck region, multiple myeloma, and stomach cancer were increased.

Studies of risks of cancer among workers who handle agricultural chemicals can assess the overall public hazards of cancer since they are probably exposed to higher levels than the general population. Since 1965 only licensed pesticide applicators have by law been allowed to handle the most acutely toxic pesticides in Swedish agriculture. They are, therefore,
an appropriate group for studying the health effects of pesticides.

The aim of this study was to generate new hypotheses about the associations between pesticides and cancer by studying risks of cancer and their trends over time and by comparing risks in different years of birth and year of license groups among Swedish licensed pesticide applicators. The study also included comparisons with agricultural workers, since most of the pesticide applicators are farmers. The difference compared with farmers is that applicators use and have used pesticides to a much greater extent.

**Material and methods**

**COHORT**

The study cohort consisted of 20,245 subjects (99% men, 1% women) who had a licence for pesticide application issued between 1965 and 1976 and who had a complete personal identification number. Only 18% of those with a licence were excluded owing to incomplete identification. About half the cohort were born in 1935 or later (table 1). One third of the applicators lived in the southernmost part of Sweden where the use of pesticides has been and still is the highest in the country. Only 7% lived in northern Sweden. Half the licences were issued in the first two years after they became compulsory in 1965–6.

A random sample of 268 applicators in the cohort was studied with reference to the use of pesticides with information of trade name, number of application days a year and number of years, application method, the use of protective clothing, tobacco habits, and occupational history during the 1950s, 1960s, and 1970s. The response rate was 85%. The answers were coded and registered in computer files. The results of that survey have been reported in detail elsewhere and are briefly summarised here (J Dich et al, unpublished data).

The survey showed that only a few of the applicators in the cohort worked full time with pesticides. The most common occupations were in agriculture or forestry, or both (70%), and in horticulture (10%). The remainder were workers at grain stores, silos or seedshops, teachers at agricultural schools, millers, building workers, welders, carpenters, truckdrivers, bakers, brick workers, plumbers, metal workers, or turners.

Pesticides had been used one day or more in 1950–79 by 92%. About 20% had used herbicides during the 1950s. The corresponding figure was 51% for the 1960s and 68% for the 1970s. The most commonly used herbicide in all three decades was MCPA (4-chloro-2-methyl phenoxy acetic acid; CAS: 94-74-6), a phenoxy acid which has been used against weeds. In the 1950s and 1960s Dinoseb (2-sec-butyl-4,6-dinitrophenol; CAS: 88-85-7) and mixtures of 2,4-D(2,4-dichlorophenoxy acetic acid; CAS: 94-75-7) and 2,4,5-T(2,4,5-trichlorophenoxy acetic acid; CAS: 93-76-5) were also commonly used. In the 1970s Ioxynil (4-hydroxy-3,5-diiodobenzoitrile; CAS: 1689-83-4) and Dichlorprop ((-±)-2-(2,4-dichlorophenoxy) propionic acid; CAS: 120-36-5) were the second and the third most used herbicides.

Insecticides have been used to a lesser extent; 15% in the 1950s, 34% in the 1960s, and 46% in the 1970s. During the 1950s and 1960s DDT (p,p’ DDT = 1,1,1-trichloro-2,2-bis (p-chlorophenyl)ethane; CAS: 50-29-3) was the most used insecticide and in the 1970s Fenitrothion (O,O-dimethyl-O-(3-methyl-4-nitrophenoxy)phosphor thiioate; CAS: 122-14-5).

Fungicides have been used to a lesser extent than either herbicides or insecticides, 7%, 16%, and 31% respectively in the three decades. Maneb (ethylenedibis (dithiocarbamate)manganese; CAS: 12427-38-2) was the most commonly used fungicide in the 1950s and 1960s. During the 1970s Triadimefon (1-(4-chlorophenoxy)-3,3-dimethyl-1-(1H-1,2,4-triazol-1-yl)-2-butaneone; CAS: 43121-43-3) was in the first place.

The use of mercury as a seed disinfectant was most common in the cohort during the 1950s and 1960s.

The use of protective clothing has, despite special education, been only slightly more frequent than among farmers in general and as late as in the 1970s about 50% never or seldom wore mask, glasses, or dress when applying pesticides.

**FOLLOW UP**

The cohort was followed up in the Swedish Cancer Register (SCR) from date of licence until 31 December 1982 or until death if before that date. The unique personal identification number was used as the matching concept in the computerised record linkage. Notification of all malignant and some benign tumours has been compulsory for almost all physicians and pathologists since the SCR was established in 1958. Each case is thus in general reported from two different sources. The study included all registered
cases of malignant tumours according to the modified version of the seventh revision of the Classification of Diseases (ICD7) that is used in the SCR.1

STATISTICAL ANALYSIS
Expected numbers of cases (E) in the cohort were based on the annual incidence of cancer in five year age and sex groups in the whole Swedish population. Tumour sites (on a three digit level) with more than five expected cases were analysed separately, otherwise in "other sites." The standardised incidence ratio (SIR) was thereafter calculated as the ratio between the observed number (O) and E. The 95% confidence intervals (CI) for SIR were derived from a Poisson distribution table. Test of trends (time since licence, year of birth, licence year group) were performed according to the method of Breslow and Day." These analyses were made for the numerically largest cancer sites. Testicular cancer was analysed from interesting results in other studies.9,10

Only a few in the cohort were full time pesticide applicators and the most common occupation was farmer or other occupations in agriculture (J Dich, unpublished data). Swedish farmers have a lower overall risk of cancer and for many cancer sites the risk was statistically significantly decreased.6 Pesticide applicators have used pesticides to a greater extent than farmers in general. The risks of cancer among pesticide applicators were, therefore, also compared with those observed for farmers. For the purpose of this study only risks of cancer during 1966–79 were used in the analyses.

The risks for applicators and farmers were plotted in a coordinate system with the risk for farmers on the x axis and for applicators on the y axis. The hypothesis of equal risks were tested by \( \chi^2 \) test with 26 degrees of freedom:

\[
\chi^2 = \sum_{i=1}^{26} \frac{(O_i - RR_i E_i)^2}{RR_i E_i}
\]

where, \( O_i \) = observed number of cases among applicators for diagnosis i; \( E_i \) = expected number of cases among applicators for diagnosis i; \( RR_i \) = relative risk among farmers for diagnosis i.

Results

There was a significantly decreased overall risk of cancer in the cohort, with a total of 558 malignant tumours versus 649.8 expected, SIR = 0.86 (95% CI: 0.79–0.93). Statistically significantly decreased risks were also observed for cancers of the liver (primary), pancreas, lung, and kidney (table 2).

Increased risks, although not statistically significant, were found for cancers of the lip, testis, and skin (including malignant melanomas), for tumours in the nervous system and in endocrine glands, and for Hodgkin's disease (table 2).

No statistically significant trends by time since licence were found. For all sites together SIR was decreased in all intervals (table 3). For testicular cancer SIR increased from 0.94 (0.26–2.41) in the first period to 2.54 (1.10–5.00) in the last.

SIR was decreased for all cancer sites among applicators born in 1934 or earlier (table 4). SIR was

### Table 2  Observed number of cases (Obs), SIR, and 95% CI for SIR in the cohort of licensed pesticide applicators for different cancer diagnoses

<table>
<thead>
<tr>
<th>Tumour site</th>
<th>ICD ?</th>
<th>Obs</th>
<th>SIR with 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>140–205</td>
<td>558</td>
<td>0.86 (0.79–0.93)</td>
</tr>
<tr>
<td>Lip</td>
<td>141–144</td>
<td>4</td>
<td>0.42 (0.12–1.09)</td>
</tr>
<tr>
<td>Mouth</td>
<td>145–148</td>
<td>2</td>
<td>0.31 (0.04–1.11)</td>
</tr>
<tr>
<td>Pharynx</td>
<td>150</td>
<td>3</td>
<td>0.36 (0.07–1.05)</td>
</tr>
<tr>
<td>Stomach</td>
<td>151</td>
<td>38</td>
<td>0.89 (0.63–1.22)</td>
</tr>
<tr>
<td>Colon</td>
<td>153</td>
<td>36</td>
<td>0.81 (0.57–1.13)</td>
</tr>
<tr>
<td>Rectum</td>
<td>154</td>
<td>26</td>
<td>0.83 (0.54–1.21)</td>
</tr>
<tr>
<td>Liver primary and biliary passages</td>
<td>155</td>
<td>7</td>
<td>0.45 (0.18–0.93)</td>
</tr>
</tbody>
</table>

### Table 3  SIR and observed number of cases (O) for some cancer diagnoses in Swedish licensed pesticide applicators by years since license

<table>
<thead>
<tr>
<th>Tumour site</th>
<th>0–4 SIR (O)</th>
<th>5–9 SIR (O)</th>
<th>≥10 SIR (O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td>0.79 (100)</td>
<td>0.92 (177)</td>
<td>0.85 (281)</td>
</tr>
<tr>
<td>Stomach</td>
<td>1.09 (10)</td>
<td>1.01 (13)</td>
<td>0.72 (15)</td>
</tr>
<tr>
<td>Colon</td>
<td>0.81 (5)</td>
<td>1.17 (15)</td>
<td>0.70 (16)</td>
</tr>
<tr>
<td>Rectum</td>
<td>0.35 (2)</td>
<td>1.23 (11)</td>
<td>0.78 (13)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.66 (3)</td>
<td>0.28 (2)</td>
<td>0.57 (7)</td>
</tr>
<tr>
<td>Trachea, bronchus, and lung</td>
<td>0.31 (4)</td>
<td>0.49 (11)</td>
<td>0.56 (23)</td>
</tr>
<tr>
<td>Prostate</td>
<td>1.13 (12)</td>
<td>1.10 (26)</td>
<td>0.92 (52)</td>
</tr>
<tr>
<td>Testis</td>
<td>0.94 (4)</td>
<td>1.43 (6)</td>
<td>2.54 (8)</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.29 (2)</td>
<td>0.59 (6)</td>
<td>1.60 (10)</td>
</tr>
<tr>
<td>Urinary organs</td>
<td>1.28 (10)</td>
<td>1.16 (15)</td>
<td>0.84 (20)</td>
</tr>
<tr>
<td>Malignant melanoma of skin</td>
<td>1.27 (7)</td>
<td>0.52 (4)</td>
<td>1.47 (17)</td>
</tr>
<tr>
<td>Skin carcinoma</td>
<td>0.75 (2)</td>
<td>1.80 (6)</td>
<td>2.10 (11)</td>
</tr>
<tr>
<td>Nervous system</td>
<td>0.72 (6)</td>
<td>1.50 (14)</td>
<td>1.47 (18)</td>
</tr>
</tbody>
</table>
Table 4  SIR and observed number of cases (O) for some cancer diagnoses in Swedish licensed pesticide applicators by year of birth

<table>
<thead>
<tr>
<th>Tumour site</th>
<th>Year of birth</th>
<th>-1914 SIR (O)</th>
<th>1915-34 SIR (O)</th>
<th>1935- SIR (O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites</td>
<td></td>
<td>0.88 (250)</td>
<td>0.81 (252)</td>
<td>1.07 (64)</td>
</tr>
<tr>
<td>Stomach</td>
<td></td>
<td>1.10 (24)</td>
<td>0.57 (11)</td>
<td>1.92 (3)</td>
</tr>
<tr>
<td>Colon</td>
<td></td>
<td>0.83 (13)</td>
<td>0.81 (17)</td>
<td>0.67 (2)</td>
</tr>
<tr>
<td>Rectum</td>
<td></td>
<td>0.88 (13)</td>
<td>0.78 (12)</td>
<td>0.75 (1)</td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td>0.53 (6)</td>
<td>0.50 (6)</td>
<td>0.00 (0)</td>
</tr>
<tr>
<td>Trachea, bronchus, and lung</td>
<td></td>
<td>0.61 (21)</td>
<td>0.36 (14)</td>
<td>1.07 (3)</td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
<td>1.04 (64)</td>
<td>0.90 (26)</td>
<td>0.00 (0)</td>
</tr>
<tr>
<td>Testis</td>
<td></td>
<td>2.33 (1)</td>
<td>1.63 (6)</td>
<td>1.47 (11)</td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td>0.41 (5)</td>
<td>0.67 (13)</td>
<td>0.00 (0)</td>
</tr>
<tr>
<td>Urinary organs</td>
<td></td>
<td>1.23 (24)</td>
<td>0.71 (16)</td>
<td>2.05 (5)</td>
</tr>
<tr>
<td>Malignant melanoma of skin</td>
<td></td>
<td>0.92 (4)</td>
<td>1.48 (21)</td>
<td>0.48 (3)</td>
</tr>
<tr>
<td>Skin carcinoma</td>
<td></td>
<td>1.50 (12)</td>
<td>1.21 (8)</td>
<td>1.01 (1)</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td>1.00 (7)</td>
<td>1.46 (23)</td>
<td>1.21 (8)</td>
</tr>
</tbody>
</table>

Relative risk for different cancer sites according to Seventh International Classification of Diseases for pesticide applicators and agricultural workers, respectively.

0.88 (0.78–1.00) for those born before 1915 and 0.81 (0.71–0.91) for those born in 1915–34. For applicators born 1935 or later SIR was 1.07 (0.83–1.37). The risk for testicular cancer was increased, though not statistically significantly, in the two youngest year of birth groups. Only one case was found in the oldest groups.

There was no statistically significant difference in risks of cancer between farmers and applicators, \( \chi^2(26) = 34.56 \) (\( p = 0.13 \)). When individual cancer sites were compared statistically decreased risks of cancer in both cohorts were found for all sites together and also for liver (ICD7 = 155), pancreas (157), lung (162), and kidney (180) (figure). Increased risks were seen for lip cancer (140). Relative risks of cancer at about unity in both studies were observed for prostate (177), connective tissue and muscle (197), and for non-Hodgkin’s lymphoma (200 + 202). Decreased or relative risks about unity among farmers and
increased risks in pesticide applicators were observed for testicular cancer (178), tumours in the nervous system (193) and endocrine glands (194, 195), and for Hodgkin's disease (201).

Discussion

In the present study licensed pesticide applicators who have used the most acutely toxic pesticides in agriculture were found to have a decreased overall risk of cancer compared with the whole population.

An explanation for the decreased overall risk could be that the cohort was selected in such a way that, for example, the applicators were brought up on farms and were healthy when they began their working careers. About 70% of those in the studied cohort were engaged in agriculture or forestry, or both. It is not possible to estimate the extent to which this selection has affected the results.

The lowest risks for pesticide applicators and for agricultural workers were found for those cancers that are considered to be associated with the use of tobacco and alcohol—oesophagus, liver, pancreas, larynx, and lung. A mail survey on smoking habits in Sweden in 1963 showed that 34% of the workers in farming, forestry, or fish industry smoked tobacco daily compared with 54% in other occupations. In 1981 the corresponding figures were 21% and 38% respectively. In the survey in 1984 among the pesticide applicators 21% smoked daily, 33% were ex-smokers, and 46% were never smokers (J Dich et al, unpublished data).

The increased risks, found in both groups, for lip and skin cancers are supposed to be due to exposure to sunlight.

No increased risk for multiple myeloma was found among pesticide applicators. In a study of Swedish farmers a raised risk but no time trend, nor any difference between different age groups, was found. This suggested that probably no important carcinogen for multiple myeloma had been introduced during the past decades. The result from the present study does not contradict the hypothesis that modern pesticides are not a risk factor for this disease.

Higher risks for pesticide applicators than for agricultural workers were found for testicular tumours, tumours in the nervous system and endocrine glands, and for Hodgkin's disease. In a study of time trends in the risk of cancer among Swedish agricultural workers increasing trends were found for testicular and nasal cancer, where the relative risk increased from less than to above unity. Among pesticide applicators and two cases respectively were found for these sites and for testicular cancer the risk tended to be raised. The results from these studies indicate that an aetiological factor for testicular cancer could have been introduced some decades ago and that the effects are seen in the late 1970s. Pesticides are one of many plausible risk factors. In a study on percutaneous penetration of pesticides (parathion, malathion, and carbyral) in man the scrotum had almost total absorption and the ratio in comparison with the forearm was about 12. There may, however, be other risk factors in the farmer's environment for this type of cancer.

For pesticide applicators a non-significant increased risk was found for tumours of the nervous system. Such increased risks were seen among those who were born in 1915 or later and also five or more years after the licence was issued. When dividing the cohort according to licence year only those who had a licence issued in 1965 or 1966 tended to have an increased risk. Swedish farmers had an increased risk in 1961–73 but later the risk decreased to below unity. Metallic inorganic mercury has been suspected of being a carcinogen of the nervous system. In Sweden mercury compounds have since the 1920s been used as seed disinfectants. Since their environmental hazardous effects became known the use has successively been reduced and in the middle of the 1960s alkyl mercury compounds were forbidden and special limitations were placed on mercury disinfection. A study of applicators of mercury and other seed disinfectants showed no increased risk for tumours in the nervous system.

Much attention has been paid to the association between the use of phenoxy acid herbicide and soft tissue sarcoma and malignant lymphoma. Several studies of farmers and other cohorts of exposed workers and several case-control studies concerning these cancers have been performed.

Studies on soft tissue sarcoma and malignant lymphoma in the cohort have been published elsewhere. No statistically significantly increased risk was found for any of these sites. All patients, or relatives if the patient is dead, in the cohort with these cancers are questioned about the use of pesticides and protective clothing, smoking and dietary habits, occupational history, or use of drugs and will be compared with controls within the cohort.

The increased risks for prostatic cancer and for leukaemia among farmers found in other studies have not been confirmed for Swedish farmers or pesticide applicators.

A high risk for lung cancer has been found among United States pesticide applicators in Florida and California, as in the German Democratic Republic. Another study has shown increased risk for stomach cancer. No excess risks for any of these cancer sites can be seen among the Swedish pesticide applicators.

These specially educated pesticide applicators have
used protective clothing only slightly more frequently than farmers in general. The survey among applicators showed that 92% had used pesticides one day or more in the period 1950–79. It may thus be concluded that the applicators in this cohort have been exposed to pesticides. Average time since first exposure to pesticides is longer than the follow up time of 12-2 years. As many as 20% in the cohort used pesticides in the 1950s. There is a difference in this respect between year of birth groups. For those born in 1934 or earlier and 1935 or later the corresponding percentages were 33-3 and 8-2, respectively. The latency time may anyhow be too short to detect increasing risks of cancer and the cohort will be followed up in SCR for the period 1983–6 when the Data Inspection Board has approved the completion. A follow up is important, especially for those cancer sites where higher risks than among farmers were observed and thus may be due to the use of pesticides.

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References
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