Health impact of occupational pesticide exposure: a review of epidemiological studies in greenspace workers

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Context: The health impact of occupational pesticide exposure has mainly been studied among farmers. Other professionals such as greenspace workers are also extremely exposed, presenting specific exposure features (practices, types of pesticide used). The aim of this review was to summarize epidemiological data on the health impact of pesticides among greenspace workers. **Method:** Six main groups of greenspace workers were identified and examined through a systematic literature review based on PubMed and Scopus. The studies were then grouped according to their design, health outcomes and the type of population studied. **Results**: 66 articles were selected among the 1,619 identified. Thirty-two studies were conducted exclusively among greenspace workers, while 22 also studied these workers with other pesticide applicators. Twelve were cohorts from the general population in which greenspace workers were identified. We analyzed 40 publications focused on cancers, six on neurological and psychiatric diseases, and 20 on reproductive disorders and adverse effects on pregnancy outcomes and children. Elevated risks were found in several studies for leukaemia, soft-tissue sarcoma, multiple myeloma and non-Hodgkin lymphoma. Associations were also found for Parkinson's disease, longer time-to-pregnancy, spontaneous abortions, preterm births and malformations. **Discussion**: The majority of studies used rough parameters for defining exposure such as job titles which could lead to the misclassification of exposure, with the risk of false or positive negative conclusions. Health outcomes were mainly collected through registries or death certificates, and information regarding potential confounders was often missing. **Conclusion:** The review identified only 32 studies conducted exclusively among greenspace workers. Elevated risk was for several diseases. Further epidemiological research is needed, conducted specifically on these workers, to better characterize this population, its exposure to pesticides and the related health effects.

Keywords: occupational epidemiology, greenspace workers, non-agricultural workers, pesticides, occupational exposure

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1. INTRODUCTION

Non-agricultural occupational uses of pesticides concern a large and diverse population, working in green spaces, wood industry, public hygiene, the food industry, etc. Greenspaces themselves include a wide variety of occupations and tasks: creation and maintenance of parks and gardens, maintenance of lawns in public places, golf-course and other sports facilities, maintenance of roadsides, railways and other public facilities, floriculture, horticulture, plant and tree nurseries… While these jobs have often been associated with health benefits due to physical exercise and outdoor work (1), some studies have also shown negative health impacts (2–4). Indeed, greenspace workers are exposed to a large range of occupational hazards, including physical hazards (motor vehicle accidents, falls, injuries, electrocution, noise, vibration, environmental conditions, etc.), biological hazards (diseases linked to microorganisms present in soil or water, such as tetanus, toxoplasmosis, and legionnaires' disease, bites or stings from plants or animals, plant and animals allergens etc.) and chemical hazards such as pesticides, combustion products and heavy metals (4).

Among occupational hazards, pesticide exposure is very likely to impact greenspace workers' health as they are frequently vulnerable to such exposure, with specific outcomes depending on the occupations and tasks. At international level, data on occupational exposure to pesticides among gardeners and greenspace workers are scarce. Epidemiological studies on the effects of pesticides have mainly been conducted among farmers, highlighting associations between pesticide exposure and increased risk of cancer for some specific localisations (prostate (5,6), lung, ovarian, rectal, testicular, skin and breast (5)), as well as Non-Hodgkin Lymphoma (NHL), multiple myelomas and leukaemia (5,7). Neurological diseases (Parkinson's disease (8), Alzheimer's disease and amyotrophic lateral sclerosis), and reproduction disorders (spontaneous abortions, stillbirth and sperm quality) have also been associated with pesticide exposure (5).

However, agriculture does not cover all the exposure situations and specificities encountered in greenspaces. In developed countries, about 10% of pesticides are used for non-agricultural purposes (9). In relation to the surface area treated, it has been suggested that the greenspace sector uses larger quantities of pesticide than the agricultural sector (10–12). In the USA, 50% of the top ten active ingredients used by non-agricultural professional pesticide applicators are herbicides (glyphosate ranks first), 40% insecticides and 10% fungicides (13). Herbicides such as glyphosate and 2,4-D are widely used on turfgrass (11,12,14), sports fields (15) and public facilities such as roads or railroad tracks (16,17). Even if herbicides remain the main treatment on golf courses, fungicides and insecticides are also commonly used to control diseases and insect larvae (11). In floriculture and ornamental plant production, many different pesticides are used. Chemicals such as growth regulators, animal repellents and disinfectants accounted for 47% of the total ingredients applied in nurseries and floriculture in the USA in 2009, followed by fungicides (22.4%), insecticides (17.4%) and herbicides (13%)(18). Pesticide use appears to be higher for greenhouse floriculture in comparison to other types of crops (19). Spraying equipment displays also some specific features, with widespread use of knapsack sprayers, watering cans and hand sprayers. This could result to high exposures, because the distance between the body and the sprayer is very small, and because devices may leak, the worker may not be protected by a cabin like farmers on tractors, and weather conditions such as wind may send the spraying cloud back to the operator (20). Moreover, these workers may spray pesticides in closed environments such as nurseries or horticultural greenhouses, where air containment, lack of ventilation, temperature and humidity will also increase workers' exposure (21). Finally, gardeners and greenspace workers can also be exposed to pesticides through frequent contact with plants during a wide range of manual tasks (planting, sizing, flower picking...)(21,22). Observance and proper use of protective equipment may also differ as, unlike farmers, gardeners often work on different sites in a single day, so they are less likely to have a dedicated place for their equipment (20,23,24). Regarding the pesticides used, some commercial products are the same as those used by farmers, but others are marketed specifically for green spaces, with active ingredients especially dedicated to these uses (e.g., glyphosate...).

Thus, regarding these differences of pesticide use, exposure and equipment between farmers and greenspace workers, the aim of our review was to summarize the epidemiological knowledge available on the health impacts of pesticides on greenspace workers.

2. METHOD

2.1. Literature search

2.1.1. Identification of research terms

Since greenspace workers cover a wide range of occupations, the first step in the literature review was to identify all the terms designating jobs of interest. These were defined according to international classifications of occupations and industrial sectors from 1968 to 2008 (25–30). Six main occupational groups were identified: i) gardeners on public or private property; ii) nursery workers; iii) horticultural farmers; iv) groundsmen and v) municipal workers and vi) road or railroad tracks maintenance workers.

2.1.2. Algorithm

The systematic literature search was conducted in PubMed and Scopus. The following algorithm was built and combined with words related to occupational pesticide exposure and health outcomes:

> (gardener OR greenkeep* OR horticultur* OR floricultur* OR greenhouse worker OR plant nursery OR municipal worker OR road maintenance OR railway maintenance OR flowers OR floricult* OR golf course OR lawn care OR pesticide applicators OR herbicide applicators) AND (Occupational Exposure OR Occupational diseases OR Pesticide* OR Herbicide OR fungicide OR Biological Control Agents OR Agrochemical OR Occupational Health OR Neoplasm OR Mortality OR Morbidity OR Health)

The search in the databases was conducted on 1st April 2020 and updated on 1st March 2021.

2.2. Eligibility criteria

Only articles in English or French were selected, and no restrictions were applied regarding the date. Workers involved in the cultivation of edible products such as fruit and vegetables, identified as *"Market garden workers"*, *"market gardeners and crop growers"* and *"tree and shrubs crop growers"* in the international classifications of jobs and industries, were excluded. Pesticide applicators specialised in pest-control and designated as *"fumigators and other pest and weed controllers"* and *"building structure cleaners"* were also excluded as their tasks differ too much from those of gardeners. Their main task consists of fighting against domestic and environmental pests such as termites, mosquitos, fleas and other parasites. In the literature, they are identified as *"pest-control operators"* or *"pest-control agents"*. Other workers not related to gardeners, horticultural and nursery workers, greenkeepers, and municipal and road maintenance workers were also excluded, as were i) cohorts based on non-occupational populations and exposure, ii) non-epidemiological studies, and iii) studies with no health data.

2.3. Selection method

The first selection of papers was based on titles, then on the abstracts, and finally on a full reading of the articles. The information extracted covered: i) authors, date and country of the study; ii) study design; iii) study population (sample size, characteristics, occupations); iv) assessment of methods of exposure; v) health outcomes; vi) statistical analysis methods, and vii) the main results and associations found.

3. RESULTS

3.1. Literature review

In the first step, 1,713 references were identified (855 from Pubmed, 858 from Scopus), corresponding to 1,619 non-duplicate papers (Figure 1). After title an abstract reading, 1,169 papers were excluded as they were either non-epidemiological studies (N=84) or case studies (N=46), examining exposure other than pesticides (N=146) or focused on exposure assessment (N=302) (biological monitoring (N=243), exposure assessment of agricultural workers (N=31), greenspace workers (N=18) and environmental measures (N=10)), based on non-occupational populations or on workers excluded from our inclusion criteria (N=417) or off-topic (N=174). After reading the abstracts, 450 papers remained and, after full reading, 395 were excluded as they were either based on other populations or did not specify the population concerned (N=265), studied other exposures (N=22), or focused on exposure assessment only (N=25), were non-epidemiological studies (N=26), case studies (N=4), or were off-topic (N=53). In addition, 11 other papers were included, not found in the database search but identified from references in the selected papers, Finally, a total of 66 articles were retained in our review, published between 1974 and 2019, originating from 49 studies.

3.2. General characteristics of the studies

Most of the studies were conducted in Europe (N=37, 56.3%), mainly in Scandinavian countries (N=28), including Sweden (N=7), Denmark (N=7), Finland (N=4) and Iceland (N=1), followed by the Netherlands (N=5), the United Kingdom (N=2) and Italy (N=2). Fourteen studies were carried out in the USA, four in Canada, five in South America (two in Ecuador and three in Colombia), four in Oceania (two in New-Zealand and two in Australia) and one in Asia (Taiwan). Ten studies were multicentric, eight of which were conducted in Scandinavia. Forty studies were cohorts, with 24 case-control and two cross-sectional studies. Sample size ranged from 121 to 347,325. Thirty-two studies were conducted among greenspace workers (19 cohorts, 11 case-control studies and two cross-sectional studies). Twenty-two studies combined greenspace workers and other agricultural workers (nine cohorts and 13 case-control studies) and 12 cohorts were conducted in the general population in which greenspace workers were clearly identified.

Among the thirty-two studies focused on greenspace workers, three cohorts and 10 case-control studies were conducted on gardeners, eight cohorts and three case-control studies on floriculturists, four cohorts on public facilities maintenance, three cohorts on lawn-care and municipal workers, one cohort on golf course employees and. Nine cohorts and 13 case-control studies combined gardeners, horticulturists and nursery workers with agricultural workers. Other studies (12 cohorts) included a large range of occupations, including greenspace workers.

We presented the results according to the main health outcomes explored in the studies: i) cancers (N=40) (Table 1), ii) neurological and psychiatric diseases (Parkinson's disease N=3, suicides N=2, motor neuron disease N=1) (Table 2), iii) reproductive disorders and adverse effects on pregnancy outcomes and children (N=20) (Table 3). In each table, the studies were grouped according to their design and the type of population under study (only greenspace workers, greenspace workers and farmers, and a large range of jobs including greenspace workers)

3.3. Risk of cancer

We identified 15 cohorts (12 historical and 3 prospective) and 11 case-control studies that examined cancer in greenspace workers, described in 40 publications. Measures of association have been summarized for each cancer site (according to the 10th revision of the International Classification of Diseases) in men (Figure 2) and in women (Figure 3).

3.3.1. Cohorts in greenspace workers

In Denmark, a prospective cohort included 4,015 workers (male and female) in plant nurseries, public gardens, parks and cemeteries, recruited in 1975 through the national union of general workers, regardless of age, and followed until 1984 (31) and 2001 (32). Two analyses were performed in this cohort : the first estimated and compared the incidence of cancers in the general population after a nine-year follow-up (31). The second analysis, after a 17-year follow-up, studied the pattern of cancer incidence after changes in pesticide use and regulation, using year of birth as a proxy for exposure levels. Workers born before 1915 were considered highly exposed, while workers born after 1935 were considered less exposed. (32). The first analysis showed a significant excess of soft tissue sarcoma (STS) (SIR = 526 [109-1538], 3 observed cases) and chronic lymphocytic leukaemia (CLL) (SIR=275 [101-599], 6 observed cases) among men. A non-significant increase in NHL was also noted (SIR=173 [63-376], 6 observed cases). Regarding the risk of cancer among women, the sample size was too small for any conclusive result. In the second analysis, where only men were considered, the overall risk of cancer decreased, compared to the general population (SIR=0.86 [0.76-0.94], 521 observed cases). The risk of STS and CLL remained high, but did not differ statistically from the general population However, risk increased in the highly exposed group: SIR=5.9 [1.9-18.2] (3 observed cases) for STS and SIR=2.3 [1.3-4.1] (12 observed cases) for CLL. An increase in the risk of cancer of the reproductive organs (code 177-9 ICD 7th revision) was also observed, although not statistically significant (SIR=1.3 [1.0 – 1.8], 39 observed cases)

In the Netherlands, a retrospective cohort included 1,341 herbicide applicators licensed for "public park work" before 1980, with no details of their exact job, and followed their mortality until 1988 (33). Type and quantity of pesticides were collected from the municipalities where they were employed. Most pesticides used were herbicides (96%), mainly simazine, chlorothiamide, dalapon, dichlobenil and diuron. Overall mortality was significantly lower than in the general population (SMR=76 [58-97], 63 observed cases). However, mortality from cancer was higher for specific locations: pancreas, intestine, skin, brain and Hodgkin lymphoma, with statistical significance reached only for multiple myeloma (SMR=815 [164-2382], 1 case observed). In a subgroup of 921 workers considered as highly exposed (excluding subjects that were only supervisors, based on job titles at the time of licensing), the risk of multiple myeloma increased dramatically (SMR=1 299 [261-3 795], 3 cases observed). Analyses were updated after 12 years, corresponding to a 20-year latency period: the risk of multiple myeloma remained high, but no longer significant (SMR=214.3 [43.1-614.7], 3 cases observed) and the risk of skin cancer increased for herbicide applicators (SMR=357.4 [115.1-827.0], 5 cases observed) (34).

In Finland, a prospective cohort was examined to explore mortality and morbidity among chlorophenoxy herbicide applicators along railroad tracks, highways, electric lines and in forests (35). Almost 2,000 male workers, exposed to pesticides for two weeks or more between 1955-1971, were included in 1972 and followed-up for mortality until 1980. When compared to the general population, mortality was lower in the overall cohort and also in the most exposed subjects. The results, updated until 1988, confirmed a decreased risk of cancer (SMR=0.8 [0.7-1.0], 77 cases observed), even for the most exposed workers (SMR=0.8 [0.4-1.3], 49 cases observed) (36). It is noteworthy that the risk of prostate cancer was found to be low in this population (SIR=0.3 [0.1-0.8], 5 cases observed).

In Sweden, a cohort of 348 herbicide (amitrole and phenoxy herbicides including 2,4-D and 2,4,5-T) applicators on railroad tracks assessed the incidence of tumours (37). Four sub-cohorts were formed according to the type of herbicide used for more than 45 cumulative days over the period 1957-1972: 207 were exposed to phenoxy herbicides, 152 were exposed to amitrole and 28 were exposed to other herbicides. An excess in cancer mortality was observed in workers exposed to amitrole when a 5-year latency was considered ($p<0.03$) as well as in those exposed to other herbicides when no latency was taken into account or for latency periods of 3 and 5 years ($p<0.01$). The risk of lung cancer increased in amitrole users -regardless of latency periods ($p<0.05$) and in other herbicide users - significantly for 3 to 5 years latency ($p<0.05$). In a nested case-control study including workers with more than 45 days overall herbicide exposure, the risk of tumour (codes 140-205, ICD 7th revision) increased in amitrole users with exposure duration (RR=3.4 for exposure 1 to 45 days and RR=4.1 over 90 days). For phenoxy herbicide, no such pattern was observed. The updated analysis (follow-up until 1978, a latency period of 10 years or more) showed a significantly doubled in overall cancer mortality for individuals exposed to amitrole and a trebling in those exposed to phenoxy herbicides (38). Workers exclusively exposed to phenoxy herbicides had six times greater risk of developing stomach cancer than the general population. These risks were more pronounced for exposures during the 1957-1961 period.

In the United States, mortality among pesticide applicators specialized in turf and lawn care was studied in a retrospective cohort (39). Over 18,000 pesticide applicators hired in a national lawn-care service company were included, and approx. 16,000 of them specialised in lawn, trees and shrubs. Female and male workers were followed from 1969 to 1990. Cancer risk was lower in men employed as applicators than in the general population (SMR=0.7 [0.4-1.1], 16 cases observed). When stratified on tasks and duration of work as lawn applicators, a significant increased risk of NHL was observed in workers who had applied herbicides for more than three years (SMR=7.1 [1.8-28.5], 2 cases observed) and in men employed after the age of 26, but non significantly (SMR=2.4 [0.3-8.8], 2 cases observed).

A retrospective cohort of 682 male golf course superintendents in the United-States explored causes of death between 1970 and 1992 in comparison with the mortality of white males from the general population (12). Excess mortality was observed for overall cancers (Proportionate Mortality Ratio: PMR=135 [121-151], 203 cases observed) and for tobacco smoking-related diseases like arteriosclerotic heart (PMR=140 [127-155], 236 cases observed), respiratory diseases (PMR=176 [135-230], 49 cases observed), and emphysema (PMR=186 [101-342], 10 cases observed). No data was available on smoking habits. An excess of risk was observed for prostate cancer (PMR=293 [187-460], 18 cases observed), NHL (PMR=237 [137-410], 12 cases observed), brain tumours (PMR=234 [121-454], 8 cases observed), tumours of the nervous system (PMR=202 [123-333], 15 cases observed) and large intestine cancer (PMR=175 [125-245], 32 cases observed).

3.3.2. Scandinavian cohorts based on population census with specific focus on greenspace workers

Thanks to a personal identity number for all inhabitants in Scandinavian countries, census data such as demographic information and occupations have been linked to Nordic cancer registries. This allowing analysis benefiting from a very large number of people; however, exposure assessment was only based on job titles.

3.3.2.1. Analyses in the NOCCA Study

Seven of the papers reviewed here are based on the Nordic Occupational Cancer (NOCCA) Study, a large cohort including workers who participated in national population censuses in Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) between 1960 and 1990.

Within the NOCCA cohort, each cancer site was analysed in relation to occupations from 1960 to 2005 (40). The only cancer occurring statistically more frequently among male gardeners was lip cancer (SIR=1.6 [1.5-1.7], 677 cases observed). This result was confirmed by additional analyses of avoidable cancers (due to poor life habits such as smoking or drinking alcohol) from 1960 to 2005 (41), and in analyses adjusted to alcohol and tobacco consumption (42).

A decrease in cancer risk in Scandinavian gardeners was also found in the NOCCA population i) in a specific analysis conducted in 2015 in Finland, Iceland, Sweden and Norway on skin and oesophagus cancer (SIR=0.8 [0.6-1.0], 83 cases observed) and oesophageal squamous-cell carcinoma (SIR=0.7 [0.6-0.8], 212 cases observed) (43), ii) in an analysis on bladder cancer until 2005 (SIR=0,8 [0,8-0,8], 3,162 cases observed)(44) and in the risk of kidney malignancies (SIR=0.7 [0.6-0.8], 195 cases observed)(45). Regarding female gardeners from 1961 to 2005, the risk of breast cancer was found to be one of the lowest, regardless of the subtype (SIR=0.8 [0.7-0.8], 7,300 cases observed) (46).

3.3.2.2. Other Scandinavian studies

Four other cohort studies conducted among Scandinavian workers also linked census data with national cancer and death registries.

The risk of gastric cancer was studied in more than six million Swedish workers, followed from 1961 to 2002 (47). In the 1960s, gardeners had the same incidence as the general population (SIR=1.0 [0.9-1.1], 329 cases observed). Between 1960 and 1980, their incidence of gastric cancer increased (SIR=1.5 [1.0-1.9], 39 cases observed), and it rose even more for cardia cancers (SIR=2.4 [1.3-3.8], 14 cases observed). Gardeners were the occupational group with the highest risk of these cancers.

In another retrospective analysis of the Swedish in the period 1971-1989, the link between occupation and multiple myeloma was explored (48). Farmers and horticulturists were pooled, with a distinction made between managers and employees. Among men, managers had a higher risk of developing multiple myeloma, compared to other workers (RR=1.2 [1.1-1.4], 317 cases observed) and a trend was observed for employees (RR=1.7 [1.0-2.9], 166 cases observed). Farmers, horticulturists and foresters belong to one of the most at-risk occupational group. Exploring the role of chemical groups through two job exposure matrices, a relation with pesticide exposures was observed (RR=1.2 [1.1-1.3], 350 cases observed).

The risk of melanoma among more than one million female workers was also studied in Sweden from 1960 to 1989 (49). When compared with the general population, horticulturists had significantly more melanoma (RR=1.6 [1.1-2.3], 30 cases observed) than farmers, even when adjusting UV exposure (RR=1.7 [1.1-2.7]).

Another study in Norway, Sweden, Denmark and Finland analysed the incidence of cancers among 10 million workers from 1970 to 1991 (50). Cancer risk overall and site-specific was lower for gardeners, horticulturists and nurserymen, both for women (SIR=83 [81-84], 15,306 cases observed) and men (SIR=86 [84-88], 8,927 cases observed).

3.3.3. Cohorts based on population census with specific focus on greenspace workers

In Canada, Gallagher et al. (1986) conducted a retrospective cohort study assessing occupational mortality from cutaneous malignancies, including over 600 deaths in British Columbia from 1950 to 1978 (51). Again, gardeners and nurserymen experienced a higher incidence than the general population (PMR=430 [157-937], 6 deaths observed). The results for farmers and other workers exposed to pesticides were not described. The occupational groups with the highest incidence were architects and chemical engineers.

3.3.4. Case-control studies with a focus on greenspace workers

Five case-control studies (52,52–56) in the United States and in Europe, exploring occupational factors of multiple myeloma, were included in a meta-analysis (57). Overall, 1,959 multiple myeloma cases and 6,192 control subjects enrolled from 1977 to 2004 were analysed. In the pooled analysis, gardeners and nursery workers tended to show an increased risk of developing multiple myeloma compared to the control subjects selected from the general population (OR=1.5 [1.0-2.3], 121 cases). However, in three of these studies, the risk decreased for gardeners and/or farmers and associated workers (52–54).

In New Zealand, a case-control study including 291 incident cases of NHL from the national cancer registry in 2003-2004 and 471 control subjects investigated the risk of NHL in various agricultural sectors (58). Using job titles, patients with NHL were three times more likely to be nurserymen (OR=3.2 [1.0-9.7], 10 cases) and five times more likely to be nurserywomen (OR=5.2 [1.0-28], 6 cases). When pooling gardeners and nursery workers, the risk of NHL only remained in women (OR=2.5 [0.9-9.4], 8 cases). Another study analysed the link between leukaemia and occupation with the same control group: patients with leukaemia were four times more likely to have been employed in a plant nursery than patients without any disease (OR=4.2 [1.3-13.5], 9 cases) (59). In females, the odds ratio was even higher: OR=11.7 [2.3-59.9] (8 cases). On the other hand, grounds and greenkeepers to have a very low risk of leukaemia (OR=0.2 [0.0-1.6]), even though the analyses were based on a very limited numbers of subjects

(1 case and 10 control subjects). Analyses by leukaemia subtypes showed an increased risk of CLL in nursery workers (OR=3.9 [1.1-13.9], 6 cases). The number of acute myeloid leukaemia cases was too low for any conclusion.

In Montreal (Canada), a case-control study was conducted on the risk of renal cell carcinoma in relation to occupations among 142 patients diagnosed between 1979 and 1985, and 533 population control subjects (60). Patients hospitalized for a renal cell carcinoma were more frequently employed as farmers or horticulturists (OR=1.6 [1.0-2.6], 22 cases) than the population-based control groups. The risk was even higher for gardeners (OR=4.1 [1.7-10.3], 6 cases). Chemicals used by these workers were analysed and an excess risk of cancer was observed in those exposed nitric acid (OR=2.1 [0.7-6.1], 4 cases) and phosphoric acid (OR=3.4 [1.3-9.2], 5 cases) fertilizers.

A case-control study in Finland included 1,419 incident case of primary malignant pancreatic neoplasms diagnosed between 1984-87 and 3,519 control subjects with stomach, colon or rectum cancer, and highlighted differences between gardeners and farmers (61). Both cases and control subjects were known to have died by 1990. Patients with pancreatic cancer were four times more likely to have worked in the gardening sector (OR=4.1 [1.4-11.8], 8 cases). Conversely, farmers had a decreased risk of developing pancreatic cancer (OR=0.8 [0.7-1.0], 144 cases).

In Sweden, the role of herbicide exposure in STS occurrence was examined in a case-control study including 96 men diagnosed between 1975 and 1982 (64 alive and 32 dead) and 200 control subjects with another type of diagnosed cancer (62). Among workers occupationally exposed to pesticides, wood preservatives, solvents and other chemical, patients with STS were four time more likely to have worked as gardeners (OR=4.1 [1.0-14], 6 cases).

In British Colombia (Canada), the risk of nasal and bladder cancer was investigated according to occupational exposure (63). From 1990 to 1992, 48 cases of nasal cancer, 105 cases of bladder cancer and 159 control subjects from the general population were included. Gardeners appeared to have a higher risk of nasal cancer (OR=2.9 [0.4-19.8), 3 cases] and bladder cancer (OR=3.7 [0.7-25.0], 6 cases). On the other hand, in another study carried out in the US, male groundskeepers and gardeners had a lower risk of bladder cancer (OR=0.8 [0.5-1.4]) (64). In this study, 1,402 cases of bladder cancer diagnosed in 2001-

2004 were included, together with 1,418 control subjects from the general population. However, when the industry code (ISIC) (instead of only the job title) was considered, the risk of bladder cancer was statistically higher for men working in the landscape and horticultural services industry (OR=2.4 [1.2-4.8]).

In the US, the link between occupation and the risk of keratinocyte cancer was studied among 889 cases diagnosed with basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) in 1994-1995, together with 524 healthy control subjects from the same area (65). Male groundskeepers and gardeners had a significantly higher risk of BCC (OR=3.2 [1.5-6.8] (37 cases) and the same applied for SCC (OR=3.3 [1.4-7.8] (16 cases).

In the United Kingdom, a case-control study analysed the risk of STS among farmers, gardeners and groundsmen and foresters, comparing 1,961 male STS cases diagnosed between 1968-76 and 1,961 control subjects with another type of cancer (considered non-related to pesticide exposure), matched for age and area of residence (66). The risk of STS increased between 1968 and 1976 but remained non-significant. After a stratification based on occupations, the relative risk was higher in farmers but not in gardeners/groundmen: RR=1.7 [1.0-2.9] (42 cases observed) and RR=0.7 [0.4-1.4] (17 cases observed) respectively.

3.3.5. Cohorts pooling greenspaces workers and other pesticide applicators

In a Swedish retrospective cohort, 1,856 gardeners or nurserymen and 547 orchardists, members of the national association of horticulturists, were followed from 1965 to 1986 (67). When compared to the general population, a significant decrease in mortality was observed for overall cancer (SMR=0.8 [0.7-0.9], 542 cases observed), for lung cancer, and also respiratory diseases and for cardiovascular diseases. However, mortality was significantly greater for central nervous system tumours (SMR=2.9 [1.1-6.2], 6 cases observed) and melanoma (SMR=2.1 [1.2-3.5], 15 cases observed) in men aged 60 and over. In the overall cohort, non-significant excess risks were also observed for stomach cancers, female reproductive organ cancers (uterus, ovaries and tubes), Hodgkin lymphoma and myeloma. The morbidity ratio for brain tumour was even higher over the period 1975-1979 (SMR=3.5 [1.3-7.7], 6 cases observed), a result that the authors attributed to a possible role of pesticides used after 1960 (e.g., DDT, diquat, metam).

In Iceland, 2,449 horticulturists, orchardists and farmers were enrolled in a prospective cohort to study cancer (68). Six subgroups were defined according to pesticide use and time-period enrolment (from 1941 to 1985). The first subgroup was composed of licenced applicators such as farmers, considered highly exposed, especially to phenoxy acetic acids. The second subgroup enrolled horticultural students, and the others featured members of associations (the Market Gardener's Association, the Horticulturist's Association, the Association of Vegetable Farmers, and the Farmer's Association), all considered as low-exposure groups. At the 1993 follow-up, the incidence of overall cancer was lower than in the general population, both in men (SIR=0.8 [0.6-1.1], 59 cases observed) and in women, (SIR=0.7 [0.4-1.3], 12 cases observed). Nevertheless, in men, the cancer incidence tended to be higher for rectum (SIR=2.7 [0.9-6.4], 5 cases observed) and skin (SIR=2.8 [0.9-6.6], 1 case observed). When both genders were combined, SIR for rectum cancer became significant (SIR=2.9 [1.1-6.4], 6 cases observed) and the association was stronger in the highest exposure subgroup: SIR=4.6 [1.5-10.8] (5 cases observed). In a case-control study nested in this cohort, workers with adenocarcinoma in villous or tubulo-villous adenomas were twenty times more likely to have been occupationally exposed to pesticides than people without this kind of rectal cancer (OR=19.5 [1.5-181.0]). The same results were observed when rectal and colon cancer with the same histology were combined (OR=20.0 [1.8-127.4], 1 case). Within this cohort, the risk of lymphatic and hematopoietic cancers also increased statistically in women (SIR=5.6 [1.1-16.2], 3 cases observed).

A retrospective cohort included around 30,000 male and female workers (greenspace workers as well as farmers and ranchers), identified through the list of pesticide applicators licenced in the State of Florida (US) from 1975 to 1993 (69). For private and commercial greenspace workers (floriculturists, orchardists, public operators), overall mortality was significantly lower in men (SMR=0.7 [0.7-0.8], 1,776 cases observed) and in women (SMR=0,4 [0,4-0,5] (98 cases observed), as well as overall cancer mortality (SMR=0,8 [0.7-0.9] in men (498 cases observed) and SMR=0,6 [0,4-0,8] in women(34 cases observed)) and for some specific cancers mortality: mouth and pharynx (SMR=0.5 [0.2-1.0] for men (7 cases observed) and SMR=0.7 [0.0-4.1] for women (1 case observed), and lymphatic cancers (other than lymphosarcoma, Hodgkin lymphoma and leukaemia) in men (SMR=0.6 [0.4-1,0] (18 cases observed)). On the other hand, a twofold excess in mortality was observed for prostate cancer (SMR=2.4 [1.8-3.0], 64 cases observed), only in men licenced for less than 4 years (SMR=2.6 [1,6-4.0] (21 cases observed) versus

SMR= 0.5 [0.0-2.8] (1 case observed) in those licenced for 16-20 years). Analyses according to the employment status (private vs. commercial/public) did not show any difference. In the same cohort, cancer incidence was also studied and the findings were in line with those mentioned above (70). In addition, the incidence of cancers of the reproductive organs was higher than in the general population: prostate (SIR=1.9 [1.7-2.1], 353 cases observed), testis (SIR=2.5 [1.6-3.7], 23 cases observed), all female genital organs (SIR=2.1 [1.3-3.1], 23 cases observed), cervix (SIR=3.7 [1.8-6.6], 11 cases observed) and uterus (SIR=1.4 [0.7-2.6], 11 cases observed)

Causes of death were analysed in 1977 in 3,827 pesticide applicators in Florida – with a specific focus on lung cancer – and compared to the local population (71). Applicators were identified from the licences delivered by the Florida Department of Health and Rehabilitative Services in 1965-1966, and pooled greenspace workers and home pest killers. Overall mortality was comparable to that of the reference population. However, white men tended to have an increased incidence of lung, skin and brain cancers, and a lower risk of digestive cancers, respiratory diseases and cirrhosis. Moreover, lung cancer mortality increased with the number of years of licence and became significant over 20 years (SMR=289, $p<0.05$, 8 cases observed). The risk was also higher for people aged below 30, described by the authors as less experienced and more prone to pesticide misuse. Workers specialised in lawn-care did not show an excess risk of lung cancer (SMR=93, non-significant, 7 cases observed), while pest-control operators specialized in household pests and rodents did (respectively SMR=168 and 165, $p<0.05$)These results on lung cancer were updated in 1982, taking into account tobacco smoking (72). After adjustment for the number of packs of cigarettes smoked per year, the risk of lung cancer increased significantly in workers licenced before the age of 40 (OR=2.4 [1.0-5.9], 38 cases), those who had worked for more than 20 years (OR=2.1 [0.8-5.5] (13 cases) and those who had started their exposure more than 20 years earlier (OR=2.2 [0.8-5.8], 19 cases). In a nested case-control analysis, an elevated risk of lung cancer was observed in workers exposed to diazinon (OR=2.0 [0.7-5.5], 17 cases), DDT (OR=2.6 [0.5-14.3], 5 cases) and carbamates (OR=16.3 [2.2-122.5], 7 cases).

3.3.6. Case-control studies considering greenspace workers pooled with other pesticide applicators

In a case-control study in the United States, the risk of STS and NHL was investigated among herbicide applicators (in or outside agriculture) (73). The cases involved men diagnosed with STS (N=128) or NHL

(N=576) between 1981 and 1984. The 694 control subjects were frequency-matched by vital status and age. Landscapers, who were considered as low-exposed, did not have an excess risk of STS (OR=0.9 [0.3-2.8]) but presented a non-significant excess risk for NHL (OR=1.7 [0.9-3.1]). On the other hand, gardeners, considered as moderately exposed, did not have any excess risk for STS (OR=1.1 [0.5-2.2] or NHL (OR=0.8 [0.5-1.4]). When all workers were pooled in the analysis, the risk of NHL doubled for workers with more than 15 years of herbicide exposure prior to a 25-year latent period.

In Taiwan, a case-control study was conducted in order to determine occupations associated with the risk of oesophagus cancer (74). In this study, 326 patients with oesophageal squamous cell carcinoma (ESCC) diagnosed between 2000 and 2005 and 386 age-matched control subjects were included. After adjustment for known risk factors such as tobacco and alcohol consumption, gardeners and farmers had a higher risk of developing oesophagus cancer (OR=2.1 [1.0-4.2], 46 cases) than the general population.

3.4. Risk of neurological and psychiatric diseases

3.4.1. Parkinson's disease

3.4.1.1. Cohort in greenspaces workers

In the prospective Danish cohort described above (31,32), the risk of Parkinson's disease among male gardeners was analysed from 1975 to 2008 (75). The 3,124 gardeners from the cohort were linked with the hospital registry to identify Parkinson's patients. Compared with the general population, the risk of hospital care in relation to Parkinson's disease increased slightly and non-significantly (SHR=1.1 [0.8-1.7], 28 cases observed). However, the risk was higher in greenspace workers born before 1915 (SHR=1.6 [0.8-2.8], 11 cases observed), assumed to have been exposed to more toxic pesticides and/or at a higher dose.

3.4.1.2. Cohort in greenspace workers and other pesticide applicators

Also in Denmark, another prospective cohort followed more than 2 million workers from enrolment in 1981 until 1993, exploring the association between Parkinson's disease and agricultural occupations (76). Exposure to pesticides was extrapolated from the name and code of occupation. Hospitalisation in relation to Parkinson's disease was 30% more prevalent in farmers and horticulturists (SHR=132 [111-156], 134 cases observed) than in the general population. Self-employed landscape gardeners experienced the highest risk (SHR=448 [54-1617], even if non-significant (2 cases among 553 subjects).

3.4.1.3. Case-control studies in greenspace workers

In Canada, the role of environmental factors on Parkinson's disease occurrence was investigated among 372 patients recruited in 1988 (77). When compared with patients with heart conditions, patients with Parkinson's disease were significantly twice more likely to have been exposed to pesticides (OR=2.0 [1.0-4.1], 33 cases), a result even more pronounced when the general population was considered as the reference (OR=2.3 [1.1-4.9]). Analyses based on occupations demonstrated that male patients with Parkinson's disease were more likely to be gardeners (OR=1.7 [0.9-3.4], 39 cases). No association was found when chemical groups of pesticides were considered (defined by mechanisms of action). The authors suggested that this negative result could be explained by the role of associations of pesticides rather than single ones.

3.4.2. Suicides

3.4.2.1. Case-control studies in greenspaces workers and other pesticide applicators

A case-control study, nested in an Australian cohort of farmers, greenspace workers (sports fields and municipal facilities), horticulturists, nurserymen and employees of pesticide manufacturing, explored the risk of suicide among workers occupationally exposed to pesticides (78). In this study, 90 subjects whose cause of death was intentional self-harm between 1983 and 2004, and 270 living control subjects from the original cohort were considered (thus, the control subjects were also occupationally exposed to pesticides). The risk of dying from suicide was lower for gardeners, horticulturists or nurserymen (OR=0.7 [0.4-1.2], 24 cases). After adjustment for reported pesticide exposure, overexposure to organophosphate/carbamate pesticides and occupational groups, this ratio narrowed to 1 (OR=0.9 [0.5-1.8]). In addition, a non-significant increased risk was observed among those who had been overexposed (i.e., subjects who had a biomonitoring test outside the reference range) to carbamates or organophosphates (OR=2.1 [0.8-5.3], 8 cases).

In the United States, a case-control study analysed the risk of suicide among farmers, animal caretakers, gardeners, nurserymen and veterinarians (79). The study included 4,991 deaths coded as suicide between 1990 and 1999, and 107,692 control subjects who died from other causes. Women occupationally exposed to pesticides were twice as likely to commit suicide than non-exposed women (OR=2.0 [1.0-3.9]). For men exposed to pesticides, the elevation in risk was very slight (OR=1.1 [1.0-1.3]). In this analysis, no stratification was made for the type of occupation.

3.4.3. Other neurological disease

A New Zealand study including greenspace workers focused on motor neuron disease. In this case-control study, 295 incident and prevalent cases of motor neuron disease diagnosed between 2013 and 2016 were included and 605 population controls were included (80). Patients with motor neuron disease were more likely to have worked as gardeners or horticulturists (OR=2.0 [1.0-3.8], 20 cases) than the control subjects, and the risk increased with the length of time in the job: OR=4.5 [1.3-16.3] for exposure longer than 10 years (p trend=0.03, 7 cases). For grounds and greenkeepers, the results were comparable (OR=3.0 [1.1-8.0], 12 cases).

3.5. Adverse effects on reproduction and foetal development

3.5.1. Adverse effects on reproduction:

3.5.1.1. Greenspace worker cohorts

A study conducted in the Netherlands analysed the time-to-pregnancy (also known as fecundability) among men working in flower production greenhouses (81). 694 exposed men were compared with 613 workers non-exposed to pesticides (cleaners, market stall retail workers...). Couples with men exposed to pesticides took slightly shorter time to conceive than the reference group (Fecundability ratio: FR=1.1 [1.0-1.23]). After adjustment on confounders, time-to-pregnancy (first pregnancy) was longer in floriculturists (FR=0.7 [0.5-0.9]). In 2006, the study extended to women (398 greenhouse workers vs. 524 referents) and observed that women who had been working over 32 hours a week had a non-significant lower fecundability in comparison with women working part-time (FR adjusted=0.8 [0.6-1.0]). Primiparous and workers who picked up flowers also had a decrease in fecundability (FR=0.5 [0.2-1.2]) (82).

These results correlated with the findings from a Finnish study on the association between floriculturists and horticulturists' fertility and pesticide exposure before and during pregnancy (83). 178 couples with men working in greenhouses for one month or more between 1980 and 1990 were included and those who applied pesticides or handled treated plants were considered as exposed. Workers who had applied pesticides only once a month or had worked with treated plants less than once a week were considered to have low exposure, while those who had sprayed at least once a week or had worked with treated plants 3 days a week were declared as highly exposed. Time to pregnancy was non-significantly longer in exposed workers in comparison with non-exposed workers: the Fecundability Density Ratio (FDR was below unity which reflected reduced fertility (FDR = 0.8 [0.6-1.0]). This association was even stronger in primiparous women (FDR=0.4 [0.2-0.8] and FDR=0.3 [0.1-1.0] for low and high exposure respectively). Furthermore, exposure to pyrethroids was significantly associated with lower fecundability (FDR=0.4 [0.2-0.8]). A non-significant decrease in fecundability was also found with organophosphates (FDR=0.7 [0.4-1.2]) and carbamates (FDR=0.6 [0.3-1.1]).

In Italy, a comparable study was conducted in women who had worked for six months or more in floriculture at the time of conception (84). Overall, 717 women were included, and 713 pregnancies were considered for the analysis. No decrease in fecundability was observed in women exposed during the month when conception took place (HR=1.0 [0.8-1.1], 287 cases).

Another study in Italy compared fertility between 127 exposed men and 173 administrative workers (85). Greenhouse workers were classified according to the number of hours of pesticide applications per year. A significant increase in time-to-pregnancy was observed in men exposed to pesticides for more than 100 hours a year (OR=2.4 [1.2-5.1], 46 cases). In addition, analyses using the life table technique showed a statistically significant difference between the cumulative non-conception rate of the exposed vs. the unexposed workers (p=0.006, Mantel-Cox test), which means that greenhouse workers had a longer time-to-pregnancy than non-exposed workers.

In 2000, Abell et al. compared the time to pregnancy between floriculturists and female members of the Danish gardeners trade union (86). The duration of exposure was defined as the number of hours spent treating flowers. No difference was observed between the floriculturists and the non-exposed workers (FR=1.1 [0.9-1.4], 253 pregnancies). However, when duration of exposure was taken into consideration, time-to-pregnancy was longer in women working more than 20 hours per week (FR=0.7 [0.5-1.0], 220 cases), in those applying pesticides (FR=0.8 [0.6-1.1], 82 cases) and, more especially, in those not wearing gloves (FR=0.7 [0.5-1.0], 156 cases). Combining all these characteristics, fecundability was clearly reduced:

FR=0.6 [0.5-0.9] (202 cases). Moreover, time-to-pregnancy in floriculturists and female members of the gardeners' trade union was found to be longer in comparison with women from the general population (FR=0.8 [0.7-1.0]).

3.5.1.2. Cross-sectional study in greenspaces workers

In Colombia, the fecundability of 2,084 women who had worked in floriculture for 2 years or more before trying to get pregnant was studied, defining exposure levels with a matrix that combined work status and duration of work in floriculture (87). Exposed women had a lower rate of fecundability when compared to women who were unemployed or had another job (fecundability Odd Ratio: fOR=0.9 [0.8-1.0]), and even lower when duration of work in floriculture exceeded 2 years (fOR=0.7 [0.6-0.8]). However, the lowest ratio of fecundability was observed in non-exposed administrative workers (fOR=0.7 [0.5-1.0]).

3.5.1.3. Cohorts in greenspace workers and other pesticides applicators

A study conducted in France and Denmark on the effect of pesticides on fecundability pooled two cohorts of farmers (vine-growers and other farmers) and greenhouse workers (88). In France, exposure was defined as using pesticides during the calendar year before the birth of the youngest child (N=142), and the reference group consisted of rural workers from the same geographic area (N=220). In Denmark, the exposed workers were conventional farmers (N=326) and greenhouse workers (N=123), who were compared to organic farmers (N=123). Danish gardeners had the lowest fecundability ratio (FR=0.9 [0.6-1.2]). No individual information on pesticide use was available but the description of pesticide sales led to the conclusion that gardeners in greenhouses – with the lowest fecundability - were more exposed to fungicides, insecticides and growth regulators.

3.5.2. Adverse effects on pregnancy outcomes

3.5.2.1. Cohort studies in greenspace workers

In Equator, Handal et al. studied the reproductive history of 217 mothers working in floriculture and exposed to pesticides and the risks of adverse pregnancy outcomes between 2003-04 (89). Information about work in floriculture, duration of work during pregnancy, job activities and use of pesticides in the workplace was collected. Women who had worked in floriculture in the past 6 years had an increased risk of spontaneous abortion (OR=2.6 [1.0-6.7]) and the increase was more pronounced if they had worked more than 3 years in floriculture within the past 6 years (OR=3.4 [1.3-8.8]).

3.5.2.2. Cohorts in greenspace workers and other pesticide applicators

In a prospective cohort study in Denmark conducted between 1997 and 2003, adverse effects on pregnancy outcomes were compared between female gardeners (N=226) and farmers (N=214), with 62,164 women working in other occupations as reference (90). Gardeners experienced the highest incidence of highly preterm births (OR=2.6 [1.1-5.9], 6 cases), but other adverse pregnancy outcomes were not significantly more frequent. Female farmers had no elevation for any risk.

3.5.2.3. Cross-sectional study in greenspace workers

In Colombia, the prevalence of adverse pregnancy outcomes among floriculturists exposed to pesticides was estimated in the 1990s (91). Adverse outcomes were compared among 8,867 workers during pregnancy and at birth in couples where one of the parents had been working in floriculture for at least six months. Exposure was considered high in workers in small companies and levels were also assigned according to the quantity of pesticides used per hectare, the type of job and tasks, and the time spent in the company. In women working in floriculture, a significant increase in spontaneous abortion (OR=2.2 [1.8-2.7]), premature birth (OR=2.9 [1.6-2.2]) and malformation (OR=1.3 [1.1-1.7]) was observed, but the highest increase in adverse outcomes was observed among those who were not occupationally exposed to pesticides (OR=3.2 [1.5-6.7]).

3.5.2.4. Case control studies in greenspace workers

In a case-control study nested the Colombian study mentioned above (91), the risk of birth defects among 222 children with parents occupationally exposed to pesticides in floriculture (443 referents) was analysed (92). Exposure levels were assigned according to the duration of work in floriculture, the size of the company, the types of job during pregnancy, a history of pesticide poisoning, and the use of personal protective equipment. Paternal exposure was statistically associated with an elevated risk of malformation (RR=1.7, $p<0.01$). Maternal exposure during pregnancy was also associated with a higher risk of congenital malformations (RR=1.8 [1.2-2.7]), especially of haemangioma (RR=6.6, $p<0.05$).

3.5.3. Adverse effects in children

3.5.3.1. Cohorts studies in greenspace workers

In the same study of Handal et al. mentioned previously, the link between maternal occupation and pesticide exposures in floriculture and neurobehavioral development in 121 infants (aged 3 to 23 months) was explored (87). Children whose mothers worked in floriculture suffered from impaired neuro-behavioural development, with a lower score in fine motor skills (-13%), higher odds of having poor visual acuity (OR=4.7 [1.1-20]), and a low score for prehension (OR=0.5 [0.2-0.9]). This result was confirmed when considering pesticide use in the workplace.

3.5.3.2. Case-control studies in greenspace workers and other pesticide applicators

In Denmark, several national databases were merged (fertility database, patient registry, malformation registry) to investigate the risk of cryptorchidism and hypospadias among boys born of parents occupationally exposed to pesticides (farmers and gardeners) (93). Compared to 23,273 control subjects from the general population, the 7,522 boys diagnosed between 1983 and 1992 were significantly more likely to have a mother working as a gardener during pregnancy (OR=1.7 [1.1-2.5]). The risk was more pronounced than for mothers working on farms (OR=1.3 [0.9-1.7]). However, definitions of the groups overlapped: greenhouse workers and market gardeners were not considered as farmers, while landscapers were in the non-exposed reference group. Father's occupation was not related to any congenital malformation. Parental occupations were considered only during conception and pregnancy, excluding previous exposures.

In the United States, a case-control study was conducted in children with a diagnosis of acute lymphoblastic leukaemia (ALL) in order to determine the role of parental occupational exposures (94). Analysing 669 children with ALL between 1995 and 2008 and 1,021 referents, no association was found with maternal exposure either during or after pregnancy. Conversely, in children whose fathers had worked in greenspaces or in nurseries, the risk of developing an ALL tended to increase (OR=1.5 [0.7-3.3], 446 cases).

Another US case-control study examined the risk of paediatric multiple sclerosis (MS) in relation to parental occupations (95). Compared to 412 healthy control subjects, 265 children with MS were twice as likely to have a father who worked as a gardener before pregnancy and before the children's first birthday (OR=2.2 [1.1-4.2], 24 cases).

In the Netherlands, the association between child neuroblastoma and parents' occupation at the time of conception, during pregnancy and throughout early childhood was analysed in a case-control study including 504 children diagnosed with neuroblastoma between 1992 and 1996 and 504 matched healthy control subjects (96). Children with neuroblastoma were twice as likely to have a father who had worked as a gardener or landscaper (OR=2.3 [1.0-5.2]). This association was not found in male farmers (OR=0.9 [0.4-1.8]), while a trend was observed in female farmers (OR=2.2 [0.6-8.8]).

In the United States, the associations between paternal occupations and 60 types of birth defects were studied in 9,998 children (birth defects diagnosed between 1997 and 2004) and 4,066 healthy control subjects (97). Children whose fathers had worked in greenspaces (three months before pregnancy until birth) had an excess risk of amniotic band syndrome (OR=1.9 [0.9-4.4], 2 cases), anencephaly (OR=1.4 [1.0-2.1], 8 cases), oesophageal atresia (OR=1.2 [0.9-1.8], 8 cases), biliary atresia (OR=1.7 [1.0-2.8], 3 cases) and total anomalous pulmonary venous return (OR=1.8 [1.2-2.8], 7 cases).

In the United Kingdom, the association between neural tube defect (NTD) and paternal occupation was investigated in 694 pregnancies with a diagnosis of neural tube defect between 1970 and 1987 (98). Paternal exposure to agrochemicals increased the risk of NTD (OR=2.7 [1.1-6.7]), in relation to the job of farmer (15 cases versus 5 control subjects) and gardener (5 cases versus 1 control subjects). Another case-control study in the United States, analysed 538 NTD cases and 539 healthy control subjects between 1989 and 1991 and found that children whose fathers were gardeners or groundsmen three months before or after the conception, had a slight non-significantly increased risk of NTD (OR=1.5 [0.7-3.2], 16 cases), while the risk doubled in children of farmers (OR=2.1 [1.2-3.9], 34 cases) (99).

4. DISCUSSION

Reviewing the existing literature on the health impact of pesticide use in greenspace workers, we found 66 publications, but only 32 specifically dedicated to greenspace workers. Indeed, in many studies, these professionals were combined with farmers or other pesticide applicators such as pest control workers. Our review consequently identified six primary occupations in the literature: i.e., gardeners, golf course workers, lawn-care and municipal workers, public facilities maintenance, floriculturists and horticulturists.

4.1. Main results

As with farmers, numerous studies found an elevated risk of lymphatic and hematopoietic cancers among greenspace workers. When subtypes of leukaemia were combined (code C91-C95 ICD10), five studies showed elevated risks in women (48,50,59,68–70) and eight in men (12,31–34,36,68,69,72). Only three studies found decreased risks for men (50,59,70). Among women, three studies found an increase in the risk of multiple myeloma in greenspace workers (48,50,68), while four studies showed elevated risks in men (33,36,48,50) and two found decreased risks (12,72). For NHL, most studies concluded there was an increased risk among male (12,31,39,58,68) and female gardeners (31,58,68), although two studies contradicted these results (50,73). Results for Hodgkin lymphoma appear controversial as two studies found an elevated risk in women (50,69) and one found a decreased risk (70). In men, two studies found an elevated risk (36,50) and three found a decreased risk (69,70,72). The risk of STS appeared elevated among greenspace workers when both genders were combined in the analyses (31,62,67) and in women only (69,70). In men, two studies found an elevated risk (31,73), and three studies showed a decreased risk (66,69,70).

In women, many studies showed a lower risk for several cancer sites: oesophagus (41,43,50,69,70), pancreas, larynx, bladder (41,50,69,70), colon (41,50), liver, brain (50,69,70) and breast (41,46,50,69,70), and for some other sites (tongue, mouth, pharynx, gall bladder, nose and ovary) in a single study (50). An elevated risk was found for other sites of cancer, although in single studies (digestive organs and peritoneum (31), lip (50)). The risk of cervix cancer was found to be more elevated in two studies (69,70), while one study showed the opposite (50).

In men, the results were less consistent. Ten studies found a decrease in the risk of bladder cancer (12,33,36,41,44,50,64,69,70,75). The risk of genital organ cancers (code C60-63 ICD10) was higher in three studies (31,67,70), although differing when risks were calculated for specific sites such as prostate or testis. Indeed, three studies found significantly elevated risk for prostate cancers (12,69,70), while four showed the opposite (36,50,68,72). For testis cancers, four found an elevated risk (68–70,72), while one found a lower number of cases among gardeners (50).

Non-cancerous diseases were also reported in this review. Several studies (four studies in men (12,75–77) and two studies in women (76,77)) have pointed to a positive association between working in greenspaces and Parkinson's disease, and suggested a dose-response relationship. Results regarding reproductive disorders also showed some consistency. Regarding men, pesticide exposure in floriculture was linked to an elevated risk of longer time-to-pregnancy (81,83,85,88), with an impact related to the duration of work. The same applies in studies focused on women's exposure (82–84,86,87). Other adverse effects on reproduction were highlighted, such as spontaneous abortion (89,91), preterm birth and malformations (90,91), and neural tube defect (98,99). Some of those studies suggested more elevated risks in greenspace workers in comparison with farmers (90,93,96) which could suggest a possible role of specific pesticides used or how they are used in this sector (materials, work environment, use of personal protective equipment etc.).

4.2. Strengths of the studies

Cohorts of workers were assembled in several countries, but only three studies were conducted exclusively among gardeners (31,32,75), one among golf-course workers (12) and two among herbicide applicators along railroad tracks (37,38). Cohort studies, especially prospective ones, are more likely to take the temporal sequence between exposure and outcome into account than case-control studies. However, most of these cohort studies were retrospective (N=33) for time-efficiency reasons. Consequently, recall bias and exposure misclassification cannot be ruled out. NOCCA cohorts included large population sample sizes of up to 15 million and therefore benefit from high statistical power. However, there is still very little information on exposure, and the risk of exposure misclassification is high. This weakness also applies to other cohorts adopting the same methodology, i.e., only using available information rather than data collected specifically for the study. In this review, 24 case-control studies were identified, a very efficient design for rare or long-latency diseases. This type of study provides good case identification with comprehensive medical diagnosis.

The study population was selected in different ways. In most studies, greenspace workers were identified through worker unions, municipalities and greenspace or floriculture companies. Thanks to company records, there was a lot of generally available information including tasks performed, number of years in the company, hours per week, and demographic information such as age and gender. Direct recruitment through companies and unions provided a good selection of subjects who had worked in greenspaces for many years. Scandinavian countries have reliable national censuses and a unique personal number which is given to every citizen, enabling large numbers of greenspace workers to be identified (both male and female) and, consequently, investigation of specific health issues with high statistical power (87,94). Some studies also included workers based on their licence to use pesticides (71,72).

In terms of exposure assessment, many studies only relied on job title. However, some used additional information from questionnaires or company records to assign exposure levels, such as gender (31), year of birth (32,75), number of years in the company (39,60,72,74,80,89), number of days of exposure (35–38), number of hours worked per week or per month (81,82,86,91,100), tasks performed (73,81–83,86,87,91), types of pesticide used (37,38,72,78), use of personal protective equipment (83,86), and size of the company (91). When individuals were identified on the basis of their licence to use pesticides, the age when the licence was first granted was used to calculate the duration of exposure (69–71). In other studies, exposure assessment was based on data derived from job-exposure matrices, suitable when only the job and/or the industry is known, or in very large studies. Moreover, job-exposure matrices make it possible to consider multiple exposures for a given job.

To determine health status, cancer registries were the most main source of information (31,32,37,38,40,41,43–50,58,61–63,66–70,73), followed by hospital registries (60,74,76,80,83,90,93–97,99) and death certificates (33–36,51,69–72,78,79). These sources of information are considered reliable and provide comprehensive identification of all cancers or deaths, reducing information bias related to self-reporting health status. However, questionnaires were usually the only source of information for non-cancerous health outcomes, such as on fecundability, adverse reproductive outcomes and birth defects (81,82,84–89,91,92,100), and Parkinson's disease (77).

4.3. Limitations of the studies

Pesticide exposure was frequently implied by job title and/or industry. However, classification of greenspace workers and floriculturists for exposure to a specific pesticide through a 'yes' or 'no' answer remains approximate. Information on individual exposure and work conditions, such as the use of protective equipment, tasks, number of hours worked in contact with pesticides, would be more accurate. The same applies to studies using licences as a proxy. In several countries, the licence is mandatory for all entities engaged in applying pesticides, with variations in the period of validity of the licence. Studies using the licence as a surrogate for exposure assessment assume that workers used pesticides throughout the period of licence validity, which could lead to exposure misclassification. Some studies combine job title and/or licence information with data on sales or the quantity of products used by companies or municipalities. This can help to improve the classification in relation to exposure levels. Studies that base their exposure assessment on information derived solely from job title or pesticide licence might miss past exposure in other jobs and complex professional careers could not be taken into account. As the latency period between exposure and onset of the cancer can be long, especially for solid tumours, this represents a serious limitation. However, collecting information on past exposure is a real challenge as commercial products and practices fluctuate over time. Pesticide applicators in general are also exposed to a very high number of diverse active substances, adjuvants, and different associations. Systematic traceability of product use can be incomplete and may depend on the activity sector.

Some studies assess exposure through questionnaires which leads to dichotomous classification ("exposed" vs. "non-exposed") or level classification ("low", "medium" and "high" exposure). This type of classification also remains highly imprecise as it does not take into account protective equipment, spraying equipment, or even the specific molecules applied. Few studies asked the participants which pesticides they have used. On the other hand, this type of method is likely to be biased as it mostly relies on memory. This method is even more complicated for employees in plant nurseries, greenhouses or municipalities who might not even know what kind of pesticides they used or were exposed to. In most of our review studies, there is a general lack of data on individual exposure. Information on the dose, type of pesticide, equipment and tasks performed are generally incomplete, making it difficult to compare studies. Job definition can also differ from one study to another, and in some cases is also incomplete (e.g., the type of culture can be missing for horticulturists or nurserymen). Five studies from the NOCCA cohort used "gardeners" as a denomination, but only Pukkala et al. (2009) clearly stated the ISCO code used. Two other Scandinavian studies outside the NOCCA project also used the term "gardeners", although without defining it. Moreover, in most studies, greenspace workers were associated with other pesticide applicators such as farmers, pest-control operators or foresters.

Another important limitation is that information on the tasks performed by workers is often missing, even though the work varies and is associated with very different levels of exposure. This is likely to generate inconsistencies. For instance, one of the studies found that floriculturists had a higher risk of adverse pregnancy outcomes, but the highest odds ratios were seen for clerical workers who were less likely to be exposed than field floriculturists. Field studies have demonstrated that some tasks involve more exposure than others, such as spraying pesticides (82) and handling plants and flowers after treatment (83).

Our review highlighted several positive associations between pesticide exposure in greenspaces and specific cancer sites, Parkinson's disease and reproductive disorders. However, uncertainty remains in several cancer sites, especially among men. These include oesophagus, stomach, rectum, colon, liver, pancreas, kidney, lung, prostate, testis, thyroid, skin and brain cancers.

As the data regarding health outcomes were mostly collected through cancer registries or death certificates, information regarding potential confounding factors is often missing. Only 27 studies (15 case-control studies and 12 cohorts) included them in the analyses. More specifically, information on occupational exposure – other than pesticides - was considered in only 25 studies. Adjustment for tobacco consumption, for instance, was performed in only 13 studies (58,61–63,74,80,84–86,88,97,99) and alcohol consumption in only five studies: four assessing birth defects among workers (61,84,90,95) and one studying oesophagus cancer (74). Moreover, known risk factors for hematopoietic cancer, such as history of chemotherapy or radiation treatment, BMI, presence of genetic diseases or exposure to other pollutants, were not considered. All these shortcomings could have led to bias in the measurement of associations.

5. CONCLUSION

In this review, the studies indicated associations between the greenspace sector and several health outcomes such as lymphatic and hematopoietic cancers (such as NHL, HL, leukaemia, MM and STS), Parkinson's disease, and some adverse effects on reproduction. Other health outcomes are questioned, but the studies remain controversial. Better knowledge of pesticides exposure in greenspace workers is crucial for studies on their health, since many studies used rough parameters to define exposure, like job title or holding a pesticide-use license. To better understand the role of pesticide exposure in the onset of diseases among greenspace workers, further research based on more precise assessment of exposure is needed. In addition, other occupational exposure should also be assessed to determine the role of each exposure on the onset of diseases. Further studies should also gather information on sociodemographic characteristics, occupational histories and life habits in order to have a better understanding of this population and adjust results on potential cofounders when needed.

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Figure 1: Flow diagram of study selection

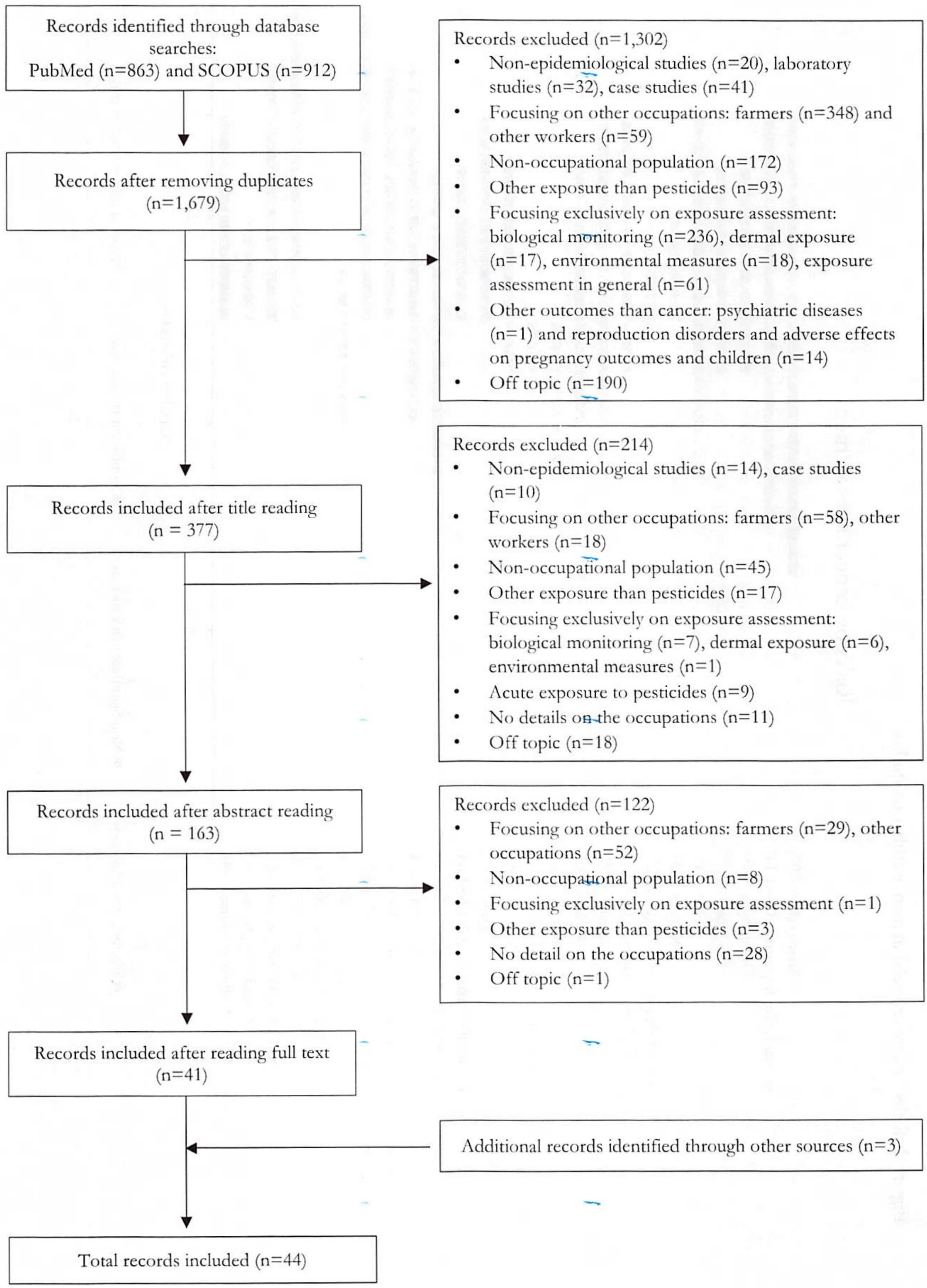

Figure 2: Risks by cancer site(s) in men: number of studies

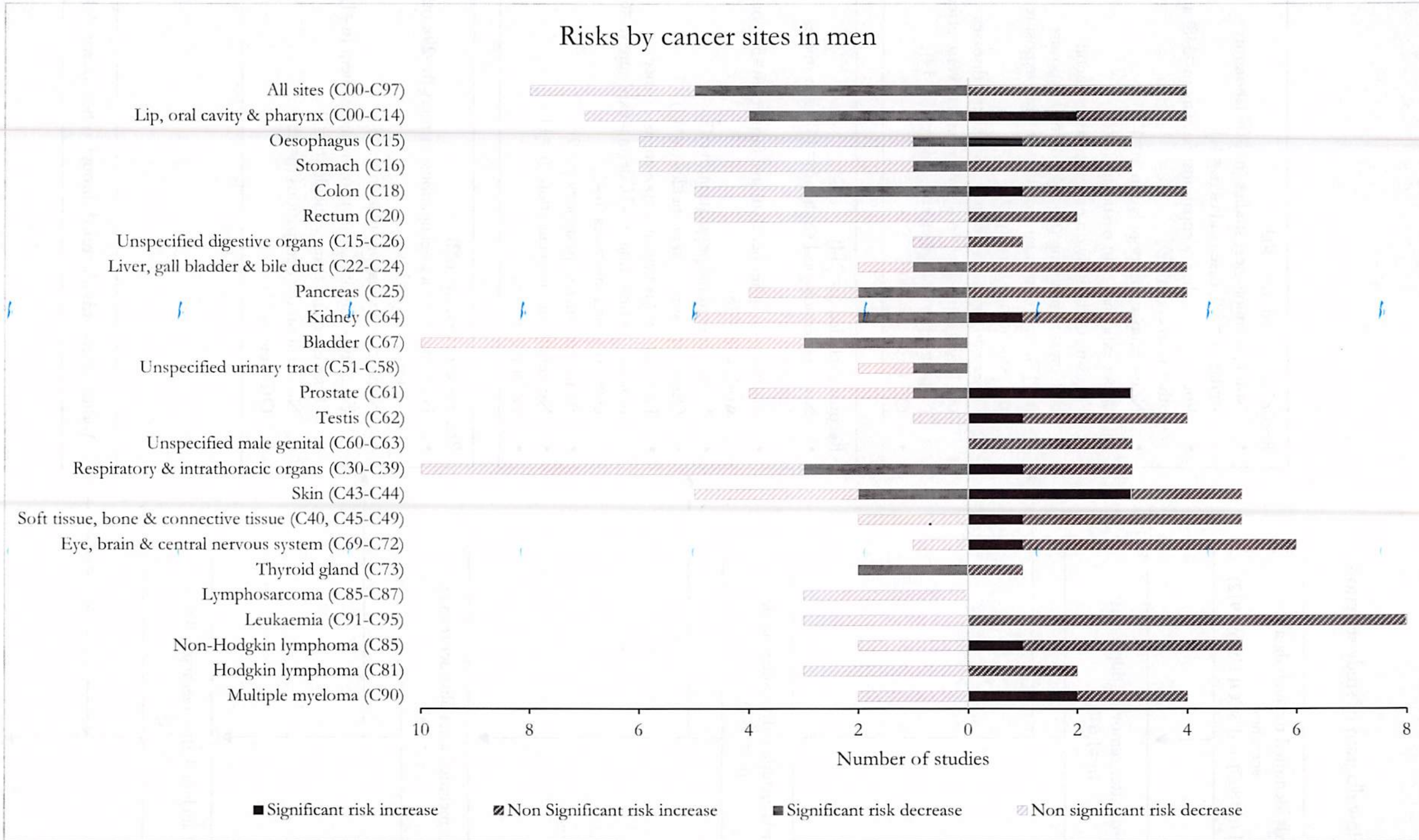

Figure 3: Risk by cancer site(s) in women: number of studies

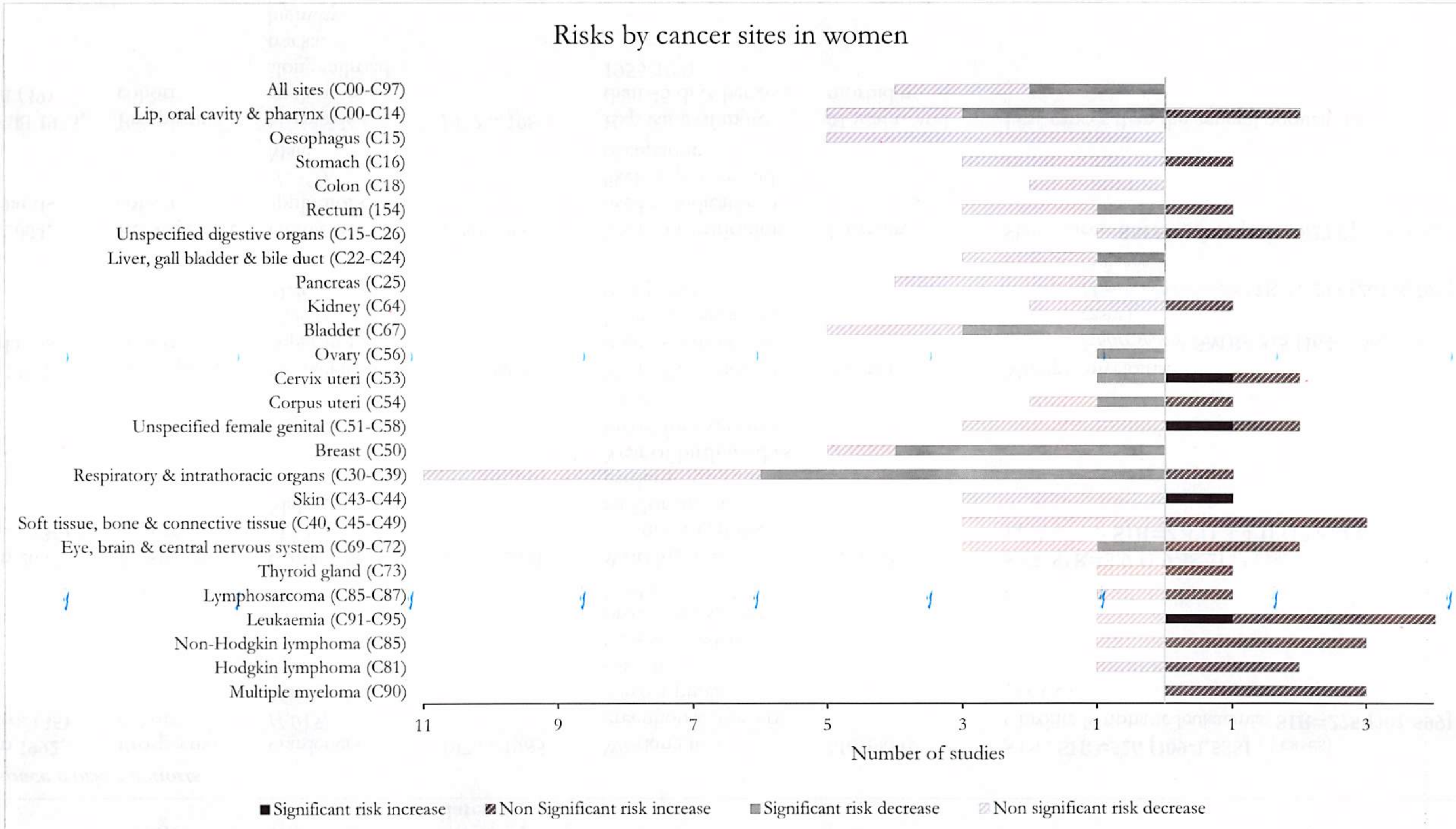

Table 1: Studies assessing cancer risk among greenspace workers and affiliated pesticide applicators

First author	Study design	Population (N)	Inclusion and follow-up dates	Exposure	Health Effects	Main results	R b:
Greenspace worker cohorts							
Hansen 1992, Denmark (35)	Prospective cohort	Gardeners *(4,015)* Male and female	1975 - 1985	Working in a greenhouse, nursery and/or public gardens Gender used as proxy for exposure levels	Morbidity	STS[a]: **SIR=526 [109-1,538]** (3 cases) Chronic lymphatic leukaemia: **SIR=275 [101-599]** (6 cases)	H
Hansen 2007, Denmark (36)	Prospective cohort	Gardeners *(3,156)* Male	1975 - 2001	Working in a greenhouse, nursery and/or public gardens Year of birth used as proxy for exposure levels	Morbidity	STS: **SIR=5.9 [1.9-18.2]** (3 cases) Leukaemia: **SIR=2.3 [1.3-4.1]** (12 cases)	M
Swaen 1992, Netherlands (37)	Retrospective cohort	Herbicide applicators *(1,341)* Male	1980-1988	Year of certification used as indicator of likely exposure and occupation	Mortality	Multiple myeloma: - *Entire cohort*: **SMR=815 [164-2,382]** (3 cases) - *Higher exposition:* **SMR=1,299 [261-3,795]** (3 cases)	H
Swaen 2004, Netherlands (38)	Retrospective cohort	Herbicide applicators *(1,341)* Male	1980 - 2001	Year of certification used as indicator of likely exposure and occupation	Mortality	Skin cancer: **SMR=357.4 [115.1-827.0]** (5 cases)	H
Riihimäki 1983, Finland (39)	Prospective cohort	Herbicide applicators along railroad tracks, highways,	1972 – 1980	Exposure of more than 45 days between 1955-1971	Mortality and morbidity	Less cancer than the general population	H

		electric lines and forests *(1,971)*					
Asp 1994, Finland (40)	Prospective cohort	Herbicide applicators along railroad tracks, highways, electric lines and forests *(1,909)* Male	1972 – 1988	Exposure of more than 45 days between 1955-1971 Questionnaires on exposure after 1972	Mortality and morbidity	*All cancer*: SMR=0.8 [0.7-1.0] (77 cases) *Prostate*: **SIR=0.3 [0.1-0.8]** (5 cases)	M
Axelson, 1974, Sweden (41)	Retrospective cohort	Herbicide applicators on railroad tracks *(348)* Male	1957 - 1972	Exposure > 45 days between 1957 and 1972 Amitrol and phenoxy herbicides	Mortality and morbidity	*Amitrol exposure:* - Lung: obs > exp **(p<0.03)** (2 cases) - Tumours: obs > exp **(p<0.03)** (4 cases) *Exposure to every herbicide:* Tumours: obs > exp (p<0.03) (15 cases)	H
Axelson, 1980, Sweden (42)	Retrospective cohort	Herbicide applicators on railroad tracks *(348)*	1957 - 1978	Exposure > 45 days between 1957 and 1972 Amitrol and phenoxy herbicides	Mortality	*Amitrol & phenoxy exposure:* - Mortality: **RR=2.1 (p<0.01)** (15 cases) - Cancer: **RR=3.4 (p<0.005)** (6 cases) *Phenoxy exposure:* - Stomach: **RR=6.1 (p<0.05)** (2 cases)	H
Zahm 1997, USA (43)	Retrospective cohort	Pesticide applicators on lawns *(18,576)* Male and female	1969 - 1990	Working in a lawn care company	Mortality	*Worked more than 3 years:* - NHL[b]: **SMR=7.1 [1.8-28.5]** (2 cases)	H
Kross, 1996, USA (12)	Retrospective cohort	Golf course superintendents *(686)* Male	1970-1992	Working on a golf course	Mortality	*Cancers:* - All cancers: **PMR=135 [121-151]** (203 cases) - Brain: **PMR=234 [121-454]** (8 cases) - NHL: **PMR=237 [137-410]** (12 cases) - Large intestine: **PMR=175 [125-245]** (32 cases)	H

						- Prostate: **PMR=293 [187-460]** (18 cases) - Nervous system: **PMR=202 [123-333]** (15 cases)	
Scandinavian cohorts based on population census and considering greenspace workers							
Pukkala 2009 Scandinavian countries (44)	Retrospective cohort	NOCCA cohort Workers (*15 million*) Male and female	1960 – 2005	Job title	Morbidity	Gardeners: *Lip cancers*: **SIR=1.6 [1.5-1.7]** (677 cases)	M
Kjaerheim 2010, Scandinavian countries (45)	Retrospective cohort	NOCCA cohort Male and female	1960 – 2005	Job title	Avoidable cancers - morbidity	Gardeners: all SIR < 1	M
Kjaerheim 2018, Scandinavian countries (46)	Retrospective cohort	NOCCA cohort Male and female	1960 – 2005	Job title	Morbidity (adjusted on alcohol and tobacco use)	Gardeners: all SIR ≤ 1	M
Jansson 2015, Scandinavian countries (47)	Retrospective cohort	NOCCA cohort Male and female	1960 – 2005	Job title	Oesophageal adenocarcinoma and squamous-cell carcinoma - morbidity	Gardeners: all SIR<1	M
Hadkhale 2016, Scandinavian countries (48)	Retrospective cohort	NOCCA cohort Male and female	1960 – 2005	Job title	Bladder cancer - morbidity	Gardeners male/female: **SIR=0.8 [0.8-0.8] / 0.8 [0.7-0.8]** (3,162 cases)	M
Michalek 2018, Scandinavian countries (49)	Retrospective cohort	NOCCA cohort Male and female	1960 – 2005	Job title	Renal pelvis cancer – morbidity	Gardeners male/female: **SIR=0.8 [0.6-0.9] / 0.7 [0.5-0.9]** (52 cases)	M
Katuwal 2018, Scandinavian countries (50)	Retrospective cohort	NOCCA cohort Female	1960- 2005	Job title	Breast cancer - morbidity	Gardeners: - *By country*, all SIR < 1 except for Iceland: SIR=1.1 [0.3-2.7] (4 cases)	M

Ji 2006, Sweden (51)	Retrospective cohort	Workers (*6.1 million*) Male and female	1961 - 2002	Job title	Stomach cancer - morbidity	Gardeners male/female: - *Gastric cancer:* SIR=1.0 [0.9-1.1] (329 cases)/ 0.9 [0.7-1.2] (65 cases) - *Corpus cancer:* SIR=1.0 [0.8-1.1] (159 cases)/ 0.9 [0.6-1.2] (33 cases) - *Cardia cancer:* SIR=1.2 [0.9-1.6] (42 cases)/ 0.7 [0.2-1.5] (5 cases)	M.
Lope 2008, Sweden (52)	Retrospective cohort	Workers (*2,992,166*) Male and female	1971 – 1989	Job title	Multiple myeloma - morbidity	Horticultural workers (male): - *Entire cohort:* RR=1.3 [0.9-1.8] (35 cases) - *Subcohort 1960-70:* RR=1.4 [0.8-2.4] (13 cases) Agricultural, horticultural and forestry enterprisers (female): - *Entire cohort:* RR= 1.7 [1.0-2.9] (13 cases) - *Subcohort 1960-70:* RR=1.8 [0.7-4.8] (4 cases)	M.
Pérez-Gomez 2005, Sweden (55)	Retrospective cohort	Workers (*1,101,669*) Female	1960-1989	Job title	Cutaneous melanoma - morbidity	Horticultural workers: - *Entire cohort*: **RR=1.6 [1.1-2.3]** (30 cases)	M.
Andersen 1999, Scandinavian countries (56)	Retrospective cohort	Workers (*10 million*) Male and female	1970-1991	Job title	Morbidity	Gardeners all SIR ≤ 1 except for (male/female): - *Lip:* **SIR= 165 [145-187]** (232 cases) - / 111 [82-149] (46 cases) - *HL*[c]: SIR=102 [80-129] (71 cases)/ 110 [88-136] (85 cases) - *MM*[d]: SIR=110 [95-128] (176 cases)/ 103 [91-115] (277 cases) For female only: - *Acute leukaemia:* SIR=105 [90-121] (177 cases) - *Other leukaemia:* SIR=102 [90-117] (210 cases)	M.

Cohorts studies based on population census and considering greenspace workers

Gallagher 1986, Canada (57)	Retrospective cohort	Death certificates of workers (*626*) Male and female	1950 – 1978	Job title	Melanoma - mortality	Gardeners and nursery workers: - *Males 20 and over:* **PMR=430 [157-937]** (6 cases)	H
Case-control studies considering greenspace workers							
Perrotta 2013, Consortium (63)	Meta-analysis of case-control studies	1,959 cases – 6,192 control subjects	1977 – 2004	Job title	Multiple myeloma - morbidity	Gardeners and nursery workers: OR=1.5 [1.0-2.3] (121 cases)	H
Mannetje 2007, New Zealand (64)	Case-control	291 cases – 471 control subjects from the general population	1977 – 2004	Job title	NHL - morbidity	Gardeners and nursery workers (all/male/female) - OR=1.3 [0.6-2.6] (17 cases)/ 0.8 [0.3-1.9] / 2.5 [0.9-9.4] (8 cases) Nursery grower (all/male/female) - **OR=3.2 [1.0-9.7]** (10 cases)/ 1.8 [0.4-8.5] / 5.2 [1.0-28.0] (6 cases) Horticulture and fruit growing (all/male/female) - **OR=2.3 [1.4-3.8]** (41 cases)/ 1.6 [0.8-3.3] (17 cases)**/ 3.2 [1.5-6.6]** (24 cases)	M
McLean 2008, New Zealand (65)	Case-control	225 cases – 471 control subjects from the general population	2003-2004	Job title	Leukaemia - morbidity	Gardeners and nursery workers (all/male/female) - OR=1.5 [0.7-3.0] (15 cases)/ 0.7 [0.3-1.8] (7 cases)/ **OR=5.0 [1.4-18.6]** (8 cases) Horticulture and fruit growing (all/male/female) - **OR=2.6 [1.5-4.6]** (32 cases)/ 1.4 [0.7-3.1] / **4.7 [2.1-10.6]** (19 cases)	M
Parent 2000, Canada (66)	Case-control	142 cases – 1,900 control subjects with other cancer + 533 control subjects from the general population	1979 – 1985	Job titles	Renal cell carcinoma - morbidity	Nursery workers (gardening): **OR=4.1 [1.7-10.3]** (6 cases)	M

Partanen 1994, Finland (67)	Case-control	1,419 cases – 3,519 control subjects with stomach, colon or rectum cancer	Diagnosed between 1984-87 and dead by 1990	Job title and sector of activity	Pancreatic cancers - morbidity	By industrial branch: - *Gardening:* **OR=4.0 [1.4-11.8]** (8 cases) By job title: - *Gardeners/groundsmen:* **OR=3.6 [1.1-12.0]** (5 cases)	H
Wingren 1990, Sweden (68)	Case-control	71 cases – 164 control subjects with other cancer + 315 from the general population	1975 – 1982	Job title and job exposure matrix for herbicide exposure (phenoxy acids and chlorophenols)	STS – morbidity & mortality	Gardeners (cases vs control subjects from the general population): OR=4.1 [1.0-14.0] (6 cases)	M.
Teschke 1997, Canada (69)	Case-control	153 cases – 159 control subjects from the general population	1990 – 1992	Job title	Nasal and bladder cancers - morbidity	Gardeners, nasal cancer: - *Ever employed:* OR=2.9 [0.4-19.8] (3 cases) - *Most recent 20 years removed:* OR=2.0 [0.2-16.1] (2 cases) Gardeners, bladder cancer: - *Ever employed:* OR=3.7 [0.7-25.0] (6 cases) - *Most recent 20 years removed:* OR=2.7 [0.5-19.8] (5 cases)	M.
Colt 2010, USA (70)	Case-control	1,402 cases – 1,418 control subjects from the general population	2001 – 2004	Job title and sector of activity	Bladder cancer - morbidity	Occupation: *Groundskeepers and gardeners (men):* OR=0.8 [0.5-1.4] (31 cases) Industry: *Landscape and horticultural services (men):* **OR=2.4 [1.2-4.8]** (25 cases)	M.
Marehbian 2007, USA (71)	Case-control	889 cases – 524 control subjects from the area	1994 – 1995	Job title	Keratinocyte cancer (BCC[e] & SCC[f]) - morbidity	Groundskeepers and gardeners: - *BCC male/female:* OR=**3.2 [1.5-6.8]** (37 cases) / 0.3 [0.0-4.0] (1 case) - *SCC male:* **OR=3.3 [1.4-7.8]** (16 cases)	M.
Cohorts pooling greenspace workers and other pesticide applicators							
Littorin 1993, Sweden (72)	Retrospective cohort	Farmers, gardeners, foresters &	1965 - 1986	Name and code of occupation	Mortality et morbidity	Under the age of 60: - *Tumours in the central nervous system:* **SMR=2.9 [1.1-6.2]** (6 cases)	M.

		arborists *(2,378)* Male and female				- *Brain tumours:* **SMR=3.2 [1.6-5.7]** (11 cases) - *Meningiomas:* **SMR=6.8 [1.9-17.4]** (4 cases) Entire cohort: - *Melanomas:* **SMR=2.1 [1.2-3.5]** (15 cases)	
Zhong 1996, Iceland (73)	Prospective cohort	Horticulturists, orchardists and farmers (*2,449*) Male and female	Inclusion date between 1941 and 1985. Follow-up ending in 1993	Occupation (pesticide applicators considered to have the highest exposure)	Morbidity	Entire cohort: - *For women, lymphatic and hematopoietic tissues*: **SIR=5.6 [1.1-16.2]** (3 cases) - *For men and women, rectum*: **SIR=2.9 [1.1-6.4]** (6 cases) Most exposed group: - Rectum: **SIR=4.6 [1.5-10.8]** (5 cases)	H
Fleming 1999a, USA (74)	Retrospective cohort	Pesticide applicators *(30,155)* Male and female	1975-1993	Holding a licence used as indicator of likely exposure	Mortality	Prostate cancer: - *Overall cohort:* **SMR=2.4 [1.4-3.0]** (64 cases) - *Exposed < 4 years:* **SMR=2.6 [1.6-4.0]]** (21 cases)	H
Fleming 1999b, USA (75)	Retrospective cohort	Pesticide applicators (*33,658*) Male and female	1975 - 1993	Holding a licence used as indicator of likely exposure	Morbidity	Male: - *Prostate:* **SIR=1.9 [1.7-2.1]** (353 cases) - *Testis:* **SIR=2.5 [1.6-3.7]** (23 cases) Female: - *All genital organs:* **SIR=2.1 [1.3-3.1]** (23 cases) - *Cervix:* **SIR=3.7 [1.8-6.6]** (11 cases)	H
Blair 1983, USA (76)	Retrospective cohort	Pesticide applicators *(3,827)* Male and female	1965 - 1977	Year of pesticide certification used as indicator of likely exposure	Lung cancer - mortality	Certified for more than 20 years*:* - *Lung cancer:* **SMR=289** (*$p<0.05$*) (8 cases) Certified between 10 and 19 years: - *Emphysema:* **SMR=321** (*$p<0.05$*) (5 cases) Certified before the age of 40*:* - *Lung cancer:* **SMR=234** (*$p<0.05$*) (11 cases)	H
Pesatori 1994, USA (77)	Retrospective cohort and	Pesticide applicators (*4,251*)	1965 - 1982	Year of pesticide certification used as	Lung cancer – mortality	Entire cohort:	M

	nested case-control	Male and female		indicator of likely exposure		- *Lung cancer:* **SMR=1.4 [1.0-1.8]** (54 cases). *Increased with the number of years exposed: >20 years:* **SIR=2.2 [1.1-3.0]** (13 cases) Case-control study: - *Licensed < 40yo:* **OR=2.4 [1.0-5.9]** (27 cases) - *Carbamate exposure:* **OR=16.3 [2.2-122.5]** (7 cases) *and propoxur:* **OR=12.4 [1.5-100.3]** (2 cases)	
Case-control studies considering greenspace workers pooled with other pesticide applicator							
Balarajan, 1984, United Kingdom (78)	Case-control	1,961 cases – 1,961 control with another type of cancer Male	1968 – 1976	Name and code of occupation	STS – mortality	Gardeners and groundmen: RR=0.7 [0.4-1.4] (17 cases) Farmers and orchardists: RR=1.7 [1.0-2.9] (42 cases)	H
Woods, 1987, USA (79)	Case-control	704 cases – 694 control subjects from the general population		Name and code of occupation Occupation used as an indicator of likely herbicide exposure	STS and NHL – morbidity	Landscapers (low exposure*)*: - *STS:* OR=0.9 [0.3-2.8] * - *NHL:* OR=1.7 [0.9-3.1] * Gardeners (medium exposure): - *STS:* OR=1.1 [0.5-2.2] * - *NHL:* OR=0.8 [0,5-1.4] *	M
Huang 2012, Taïwan (80)	Case-control	326 cases – 386 healthy control subjects from the Department of Preventive Medicine Male	2000 – 2005	Working in one of the 33 occupations whose environments are known to have potential exposure to hazards related to cancer development	Oesophageal cancer – morbidity	Farmers or gardeners: **OR adj = 2.1 [1.0-4.2]** (46 cases)	M

[a] Soft Tissue Sarcoma
[b] Non-Hogkin's Lymphoma
[c] Hodgkin's lymphoma
[d] Multiple Myeloma
[e] Basal Cell Carcinoma

[f] Squam Cell Carcinoma
* No data available on the number of cases

Table 2: Studies assessing neurological and psychiatric diseases

First author	Study design	Population (N)	Inclusion and follow-up dates	Exposure	Health Effects	Main results	R b:
Cohorts in greenspace workers							
Kenborg, 2012, Denmark (81)	Retrospective cohort	Gardeners *(3214)* Male	1975 - 2008	Year of birth used as proxy for exposure levels	Parkinson	Entire cohort: SHR=1.1 [0.8-1.6] (28 cases) Born between 1900-14: SHR=1.6 [0,8-2,8] (11 cases)	M
Cohort in greenspace workers and other pesticide applicators							
Tüchsen, 2000, Denmark (82)	Prospective cohort	Farmers, horticulturists & gardeners *(2 273 872)* Male and female	1981 – 1993	Name and code of occupation	Parkinson	Farmers: **SHR=132 [111-156]** (134 cases) Gardeners: SHR=448 [54-1617] (2 cases)	M
Case-control studies in greenspace workers and other pesticide applicators							
Hertzman, 1994, Canada (83)	Case-control	127 cases – 245 control subjects (with cardiac disease or from the gen. pop.)	1988	Name and code of occupation Use of pesticides and solvents Classification of pesticides by chemical group	Parkinson	Entire cohort: - *Comparison with cardiac controls*: **OR=2.0 [1.0-4,1]** (33 cases) - *Comparison with the gen. pop.*: **OR=2.3 [1,1-4,9]** (33 cases) Gardeners*:* OR=1.7 [0.9-3.4] (39 cases)	H
Chen, 2018, New-Zealand (84)	Case-control	295 cases – 605 control subjects from the gen. pop.	2013-2016	Name and duration of occupation	Motor neuron disease	Gardeners/horticulturists: **OR=2.0 [1.0-3.8]** (20 cases) > *10 yrs of exposure:* **OR=4.5 [1.3-16.3]** (7 cases) Grounds/green keepers: **OR=3.0 [1.1-8.0]** (12 cases)	M