



Occupational exposure to pesticides and multiple myeloma in the AGRICAN cohort

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Abstract

Purpose Epidemiological studies have found an increased risk of multiple myeloma (MM) in farmers. Few studies have investigated the detailed circumstances of occupational pesticide exposure which could explain these increased risks (pesticide use on crops, seeds or on animals, contact with treated crops) and the role of other exposures. In the Agriculture and Cancer cohort (AGRICAN), we assessed the associations between MM and crop- or animal-related activities, with specific attention to pesticide exposure via use on animals and crops or contact with treated crops and to disinfectant exposure.

Methods Analyses concerned 1,55,192 participants, including 269 incident MM identified by cancer registries from enrolment (2005–2007) to 2013. Cox models using attained age as time scale were run to calculate hazard ratios (HR) and 95% confidence intervals (CI).

Results MM risk was increased in farmers (i) who started using pesticides on crops in the 1960s, especially among those applying pesticides on corn (≥ 20 years: HR 1.73, 95% CI 1.08, 2.78, p for trend < 0.01) and (ii) using insecticides on animals (HR 1.48, 95% CI 1.11, 1.98), especially among horse farmers (≥ 10 years: HR 2.77, 95% CI 1.22–6.27, p for trend = 0.01). We also observed significant elevated risks with disinfectant use in animal barns.

Conclusions Findings support the role of pesticide use on crops and animals in the occurrence of MM risk in farmers.

Keywords Multiple myeloma · Farming · Occupational exposure · Cohort · Pesticides · Insecticides · Corn

The members of AGRICAN-group are listed in Acknowledgement section.

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Multiple myeloma (MM) is one of the most common hematological cancers in both men and women. Age-standardized incidence rates have increased from 1980 to 2015 in some countries such as France and the United States [1, 2]. Although MM is a rare cancer, incidence in France is one of the highest in the world, behind Australia/New Zealand, United States, and Northern Europe, with age-standardized

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incidence rates in France of 4.2 and 2.9 per 1,00,000 among men and women, respectively, in 2018 (World Standard) [2] and an intermediate survival rate (age-standardized net 5-years survival: 53%, France, 2012) [3]. Its etiology remains largely unknown, apart from some risk factors such as age, gender, ethnicity, obesity, familial history of lymphohaematopoietic cancers, and history of monoclonal gammopathy of undetermined significance [4–6]. Several meta-analyses have found an increased risk of MM from 10 to 40% among farmers [7–10] that was recently reported in cohorts from Nordic countries (Nordic Occupational Cancer project) [11], Great Britain (the Pesticide Users Health Study) [12], France (AGRICAN cohort) [13], and in the USA in the Agricultural Health Study (AHS) [14]. Overall pesticide exposure has been associated with an increased risk of MM in several case–control studies in the North America [15–17], in France [18], in other European countries [19–24], and in New Zealand [25]. Few studies have investigated the role of specific pesticides on MM risk [15, 17, 18, 20, 25–29]. However, most of them investigated pesticide exposure by crop treatments or less frequently via use of insecticides on animals, and they provided no information on other exposure circumstances such as seed treatment, secondary exposure via re-entry tasks, harvesting, and sowing.

In the AGRICAN cohort, we estimated MM risk associated with (i) exposure to pesticides via various uses (on crops, seeds or on animals), (ii) secondary exposure to pesticides via re-entry tasks, harvesting, and sowing, considering the type of crops and animals, and (iii) other farming tasks such as disinfectant use.

Methods

Study population

The AGRICAN cohort is a prospective cohort of 1,81,842 individuals affiliated to the *Mutualité Sociale Agricole*, the French health insurance scheme in agriculture [30]. Briefly, participants were men and women aged 18 and older at enrolment, active or retired, living in one of the 11 French areas covered by a population-based cancer registry at the time of enrolment. Most of the participants had worked on a farm during their lifetime as farm owners or farmworkers (87%). Individuals were followed from the date of reception of the questionnaire (1st November 2005–31st December 2007) until diagnosis of first incident cancer, date of death, date they left the study areas, or date they were lost to or ended follow-up (31st December 2013), whichever came first. Participants were followed for 6.7 years (± 1.9 years) on average. Participants lost to follow-up and deceased individuals were identified annually by crossing with the *Mutualité Sociale Agricole* files and the French National Death

Index. Primary incident tumors were identified by matching the AGRICAN database to all cancer registries covering the study areas and cases were coded according to the International Classification of Diseases for Oncology, 3rd edition (code: 9732/3 for MM).

Exposure data and potential confounders

The enrolment questionnaire collected a complete job calendar with a lifetime history of 13 types of crops (grassland, wheat/barley, corn grain or for silage, vineyard, potato, sugar beet or mangle, fruit-growing, rape, sunflower, tobacco, peas/field beans, field-grown vegetables, greenhouse). We collected data on occupational use of pesticides on each crop, on pesticide treatments of seeds on the farm, on potential secondary exposure to pesticides via sowing for all crops except for fruit-growing (pruning and harvesting), for winegrowing (re-entry tasks, harvesting and park maintenance), and for potato- and tobacco-growing (sowing and harvesting). Based on field studies, a quantitative variable for secondary exposure to pesticides was created considering re-entry tasks in vineyards (pruning, thinning) and pruning in fruit-growing as a high level of exposure, other tasks with secondary exposure to pesticides as a low level of exposure and no secondary exposure [31, 32]. Years of beginning and end were collected for each task as well as surface area. Data on use of personal protective equipment (protective gloves, disposable or Tyvek[®] coverall, masks with filter cartridges) during occupational life were collected (ever use and frequency of use: never, occasionally, and systematically for each equipment). For five types of farm animals (cattle, sheep/goats, pigs, horses, poultry), we collected information on year of beginning and end, number of animals and tasks (use of insecticide on animals, care to animals, milking and disinfection of milking equipment for cattle and sheep/goats only, and disinfection of barns). Some demographic and lifestyle characteristics, such as level of education, height, weight, diet, alcohol consumption, and smoking, were also collected.

Statistical analyses

Exclusion criteria were as follows: suffering from any cancer except non-melanoma skin cancers before the date of enrolment and after the date of creation of the most recent registry in the study area (1st January 2005) ($n = 2,755$); incomplete data on history of agricultural exposures ($n = 24,263$). This left 1,55,192 subjects for analysis. We fitted Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (95% CI), with attained age as time scale.

We assessed associations between MM and each type of crop and animal, tasks on crops and animals with their

duration, crop surfaces, and number of animals. The reference group consisted of farmers who had never worked on a given crop or animal. We used categorical variables for duration of exposure (10-year interval) and quartiles from the whole population for the number of animals and surface area of crops. Tests for trend used median of categories as a continuous variable.

Sensitivity analyses were performed (i) considering the use of personal protective equipment, with special attention to the systematic use of protective gloves, among pesticide users; (ii) for main associations by mutual adjustment for correlated exposure or by estimating the association of an exposure in the subgroup of non-exposed subjects for the other correlated exposure; (iii) with additional adjustment for gender and body mass index; (iv) considering a 10-year latency between exposure and date of end of follow-up; (v) considering the reference group as people having never worked on a farm; (vi) excluding incident cases diagnosed less than two years after enrolment; (vii) excluding all prevalent cases ($n = 10,449$), whatever the date of diagnosis. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina).

Results

The study population was mainly composed of men (56%). The median age at enrolment was 66 years. Half of the population had a level of education lower than middle school. Nearly 42% of participants were overweight and 15% were obese. Nearly 87% had worked on a farm (56% as farm owners and 44% as farmworkers). We identified 269 incident MM cases (159 male, 110 female) with a mean age at diagnosis of 75.9 years (± 9.8 years).

Exposure to crop-related tasks

The most frequent types of crops cultivated were grassland (54%), wheat or barley (42%), vine (34%), and corn (29%). Nearly 50% of farmers used pesticides on crops (70% for men and 16% for women) for an average of 26.9 years from adulthood to enrolment, 37% used pesticides on seeds and 82% were potentially exposed via secondary exposure (high level of exposure: 35%, low level of exposure: 47%). The proportion of farmers using pesticides on crops ranged from 30% in fruit-growing and grassland to more than 60% for rape, sunflower, and corn. Nearly 55% of pesticide users wore personal protective equipment, mainly gloves (51% of pesticide users), but not systematically as only 18% of pesticide users systematically wore them.

We found an elevated risk associated with pesticide exposure via use on crops (HR 1.24, 95% CI 0.93–1.65), or seeds (HR 1.17, 95% CI 0.82–1.66) but not via secondary

exposure (HR 1.06, 95% CI 0.71–1.57), whatever the level of secondary exposure (low: HR 1.15, 95% CI 0.76–1.74; high: HR 0.94, 95% CI 0.60–1.46) (Table 1). We did not observe any relationship with duration of pesticide use on crops (p for trend = 0.41) or on seeds (p for trend = 0.33) or with duration of secondary exposure (p for trend = 0.90). However, we found an increased risk among farmers who used pesticides on crops for a duration of 20 to 40 years (HR 1.56, 95% CI 1.05–2.32, 35 exposed cases) and in those who started to use pesticides in the 1960s (HR 1.60, 95% CI 0.97–2.66, 19 exposed cases) (Supplementary Table 1). No major changes in associations were observed considering the use of personal protective equipment. We also found a positive association among farmers who used pesticides on seeds for a duration of 10 to 20 years (HR 2.04, 95% CI 1.05–3.95, 10 exposed cases) with an elevated risk for those who started to use pesticides on seeds in the 1970s (HR 1.96, 95% CI 0.83–4.63, six exposed cases).

We found an elevated risk among corn farmers (HR 1.32, 95% CI 0.99–1.76) that was especially high among the longest exposed (≥ 20 years: HR 1.67, 95% CI 1.13–2.47, 33 exposed cases, p for trend < 0.01). Risks were slightly more pronounced among corn-growers who used pesticides on corn (HR 1.47, 95% CI 1.04–2.08, 44 exposed cases), especially among those exposed for 20 years or more (HR 1.73, 95% CI 1.08–2.78, 21 exposed cases, p for trend < 0.01), for pesticide-treated surface areas exceeding 16 hectares (HR 1.84, 95% CI 0.92–3.68, nine exposed cases, p for trend 0.03) and among applicators who had started using pesticides in the 1960s (HR 2.22, 95% CI 1.22–4.03, 12 exposed cases) or in the 1970s (HR 1.77, 95% CI 0.96–3.23, 12 exposed cases) (Table 1 and Supplementary Table 1). We also found an elevated risk of MM among farmers who treated their corn seeds (HR 1.48, 95% CI 0.93–2.36), those with secondary exposure to pesticides on corn (sowing: HR 1.36, 95% CI 0.97–1.89) (Table 1) and those harvesting corn (HR 1.32, 95% CI 0.96–1.80, 58 exposed cases). The risk was higher among pesticide users (on corn or seeds) who had not performed sowing or harvesting (HR 3.07, 95% CI 1.56–6.04, nine exposed cases).

An elevated MM risk was also observed (i) for users of pesticides on wheat or barley (HR 1.36, 95% CI 0.96–1.92), especially among those who had applied pesticides for less than 30 years (HR 2.23, 95% CI 1.36–3.65, 20 exposed cases) and among those who started to apply pesticides in the 1950s (HR 1.58, 95% CI 0.90–2.78, 14 exposed cases) (ii) for users of pesticides on potatoes (HR 1.51, 95% CI 0.95–2.40), and (iii) for potential secondary exposure to pesticide on rape via sowing (HR 1.43, 95% CI 0.87–2.35) (Table 1 and Supplementary Table 1).

Table 1 Associations between multiple myeloma risk and exposure to pesticides and disinfectants, AGRICAN, 2005–2013

Farming activities	Ever worked on the activity			Ever use pesticides on crops or animals			Ever use treatments on seeds on farm			Ever performed other tasks with secondary exposure to pesticides ^a			Ever use disinfectants on barns		
	No. of cases	HR	95% CI	No. of cases	HR	95% CI	No. of cases	HR	95% CI	No. of cases	HR	95% CI	No. of cases	HR	95% CI
Crops															
Any crops	199	0.94	0.55 1.59	97	1.24	0.93 1.65*	56	1.17	0.82 1.66	149	1.06	0.71 1.57	NA		
Grassland	139	0.98	0.73 1.32	38	1.12	0.75 1.67	NA			NA			NA		
Wheat/barley	111	1.20	0.91 1.59*	51	1.36	0.96 1.92**	45	1.33	0.93 1.91*	64	1.21	0.87 1.66	NA		
Corn	79	1.32	0.99 1.76**	44	1.47	1.04 2.08***	21	1.48	0.93 2.36**	49	1.36	0.97 1.89**	NA		
Winegrowing	77	0.91	0.68 1.21	24	0.82	0.53 1.27	NA			67	0.87	0.64 1.17	NA		
Potato	69	0.98	0.72 1.34	22	1.51	0.95 2.40**	5	0.88	0.36 2.17	37	0.97	0.67 1.42	NA		
Beets	53	1.07	0.78 1.47	13	1.21	0.69 2.13	4	0.68	0.25 1.83	33	1.06	0.73 1.55	NA		
Fruit-growing	44	1.01	0.71 1.44	9	0.95	0.48 1.87	NA			35	1.06	0.72 1.55	NA		
Rape	24	1.33	0.87 2.04*	9	0.97	0.49 1.89	4	1.12	0.41 3.01	17	1.43	0.87 2.35*	NA		
Sunflower	14	1.10	0.64 1.90	7	0.97	0.46 2.08	1	0.46	0.06 3.28	10	1.18	0.62 2.23	NA		
Tobacco	23	0.96	0.62 1.49	8	1.01	0.50 2.07	NA			21	0.97	0.62 1.53	NA		
Peas/field beans	14	1.13	0.65 1.94	3	0.61	0.19 1.90	3	0.91	0.29 2.84	8	1.18	0.58 2.41	NA		
Field-grown vegetables	21	0.98	0.62 1.55	NC			NC			NC			NA		
Greenhouse	6	0.84	0.37 1.90	NC			NC			NC			NA		
Animals															
Any animals	193	1.06	0.66 1.71	83	1.48	1.11 1.98***	NA			NA			88	1.40	1.05 1.86***
Cattle	175	1.00	0.70 1.44	69	1.31	0.88 1.95*	NA			NA			70	1.31	0.88 1.96*
Sheep/goats	26	0.83	0.55 1.25	7	1.03	0.49 2.20	NA			NA			10	1.22	0.65 2.30
Pigs	72	1.03	0.77 1.38	14	1.27	0.73 2.20	NA			NA			29	1.27	0.85 1.90
Horses	59	1.14	0.84 1.55	11	1.52	0.82 2.80*	NA			NA			NC		
Poultry	84	0.91	0.68 1.21	21	1.23	0.78 1.97	NA			NA			36	1.25	0.86 1.82

CI confidence interval, HR hazard ratio, NA not applicable, NC not collected

* p value ≤ 0.20 ; ** p value ≤ 0.10 ; *** p value ≤ 0.05

^aVia sowing for all crops, except for tobacco and potato (sowing, harvesting), fruit-growing (pruning, harvesting), vineyard (re-entry tasks, harvesting, and park maintenance)

Exposure to animal-related tasks

Cattle farmers accounted for 65% of the cohort members in our analysis, poultry farmers for 31%, pig farmers for 24%, horse farmers for 18%, and sheep/goat farmers for 11%. Nearly 38% of farmers used insecticides on animals (from 19% in horse farming to 37% in cattle farming) and 39% used disinfectants in animal barns. No association between MM and each type of animal farming was observed (HR from 0.83 to 1.14, Table 1). However, use of insecticides on animals was positively related to MM risk (HR 1.48, 95% CI 1.11–1.98), especially among farmers who applied insecticides on animals for less than 20 years (HR 2.17, 95% CI 1.21–3.89, 13 exposed cases), for a duration of 20 to 40 years (HR 1.70, 95% CI 1.06–2.74, 21 exposed cases), and who started to use insecticides before the 1960s (HR 1.79, 95% CI 1.13–2.82, 23 exposed cases) and in the 1980s (HR 2.93, 95% CI 1.26–6.82, 7 exposed cases) (Table 1 and Supplementary Table 1). We also found an increased risk with use of insecticides on horses with (i) duration of use of insecticides on horses (≥ 10 years: HR 2.77, 95% CI 1.22–6.27, 6 exposed cases, p for trend 0.01) and (ii) number of horses treated (≥ 4 horses: HR 5.46, 95% CI 2.02–14.74, 4 exposed cases, p for trend < 0.01). Applying insecticides on cattle was also positively associated with MM risk (HR 1.31, 95% CI 0.88–1.95), especially on more than 70 cattle (HR 1.80, 95% CI 0.90–3.58, 11 exposed cases, p for trend 0.09). Use of disinfectants in barns was positively related to MM (HR 1.40, 95% CI 1.05–1.86, 88 exposed cases), whatever the type of animal farming, with an elevated risk among those exposed for less than 20 years (HR 1.74, 95% CI 0.97–3.12, 13 exposed cases) and for a duration of 20 to 40 years (HR 1.44, 95% CI 0.86–2.41, 17 exposed cases). When associations were adjusted mutually for insecticide use on animals and disinfectant use, both associations were attenuated (insecticide use: HR 1.30, 95% CI 0.89–1.91; disinfectant use: HR 1.20, 95% CI 0.82–1.75). Insecticide use on animals remained positively associated with MM among farmers who did not use pesticides on corn (HR 1.40, 95% CI 0.99–1.98, 39 exposed cases). However, 80% of cases among users of pesticide on corn also applied insecticides on animals.

For all associations, no changes in HR higher than 20% were observed after adjustment for gender or body mass index, considering a 10-year latency, using non-farmers as the reference group, or after excluding all prevalent cases, whatever the date of diagnosis, or incident cases diagnosed less than 2 years after enrolment.

Discussion

The present findings suggest that the use of pesticides on some crops (corn: grain or for silage, wheat/barley and potato), insecticides on animals (especially horses

and cattle), and disinfectants in barns contributes to the risk of MM in farmers. The use of pesticides on crops in the 1960s, especially on corn, was associated with an increased risk of MM. We found positive associations with the risk of MM and the duration of pesticide use only on corn and insecticide use on horses. Globally, there was no increased risk associated with potential secondary exposure to pesticides, apart from corn and rape.

Our analysis was based on 269 incident MM cases diagnosed in farmers, a number in the range of those included in the pooled analyses conducted by the international consortium of MM (170 cases among farmers) [33] and the North American Pooled Project (340 cases among people who lived or worked on a farm) [26]. We used a prospective design limiting the differential information bias on exposure and relying on validated data on cancer incidence from population-based cancer registries. Moreover, fewer than 1% of the participants were lost to follow-up for cancer incidence and vital status, limiting the selection bias. We were able to assess the risk of MM in various farm environments thanks to the collection of the lifetime history of agricultural activities for 13 types of crops and 5 animal species. Several tasks were also investigated, enabling (i) global assessment of exposure to pesticides via application on crops, animals, or on seeds as well as potential secondary exposure to pesticides, and (ii) other tasks to be investigated such as the use of disinfectant products. Moreover, the availability of the years when exposures began and ended allowed us to estimate exposure–response relationships with duration and periods of exposure. However, for some infrequent agricultural practices and/or for more complex analyses concerning tasks or duration, we were limited by the number of cases.

To date, few studies have assessed the risk of MM according to detailed information on farming (types of farming, duration, periods of exposure, direct and secondary pesticide exposure), and they frequently relied on a limited number of exposed cases. Our results on corn and wheat/barley farming are in line with some case–control studies that reported an increased risk of MM among crop farmers in New Zealand (OR 2.0, 95% CI 0.6–6.0, 5 cases) [25], among cereal farmers in Italy (OR 1.2, 95% CI 0.5–2.7, 20 cases) [29] and among cereals (OR 2.2, 95% CI 1.0–5.2, 11 cases) and corn farmers in France (OR 2.7, 95% CI 1.0–7.2, seven cases) [18].

We also found an increased risk among farmers who started using pesticides on crops in the 1960s and among pesticide users on some crops (corn, wheat or barley, potato). Most case–control studies until now have investigated associations between MM and overall occupational use of pesticides and have reported positive associations (11 studies out of 12). Some of them reported significant associations (OR from 1.2 to 5.2) [16, 18–20, 24] while others reported

non-significant positive associations [15, 17, 21–23, 25] or no association [34].

A few studies have looked at associations between specific pesticides and MM [15, 17, 18, 20, 25–29], and most of them considered insecticide use on crops. Significant associations were found for some organochlorines such as DDT and lindane [15, 20, 26, 29], the carbamate insecticide carbaryl [26], and the pyrethroid insecticide permethrin [27–29]. Other studies reported positive and significant associations with the fungicide captan [26] and phenoxy herbicides [15, 20]. We reported increased risks associated with the early use of pesticides on corn in the 1960s and 1970s. Most of these pesticides studied in the literature have been applied on corn or for seed treatment since the 1960s or 1970s in France such as DDT, lindane, carbaryl, 2,4-D, and captan, but were not used only on corn as they were also authorized on other crops like vine, fruit, potato, rape, and beet [35]. Herbicides have been widely used on corn, especially atrazine and dinoterb, in volumes greatly exceeding those of insecticides (mostly lindane for soil treatment) and fungicides (no fungicide except for seed treatment), in France [36], but they have seldom been studied.

We found positive associations between MM and insecticide use on animals, especially among farmers who had started using them before the 1960s and in the 1980s. Insecticides that have been linked to MM such as DDT, lindane, carbaryl, and permethrin have been used both on crops and on animals in France [35], but associations between insecticide use on animals and MM have been seldom studied, apart from permethrin use in the AHS study [27] and use of chlordane, coumaphos, and dichlorvos in Iowa [17]. In France, the list of insecticides that were authorized for use on animals has been available since 1979. However, DDT and lindane have been used on animals probably since the 1950s. In the 1980s, lindane, carbaryl, permethrin, and coumaphos were authorized for use on animals.

We also found a positive association between MM and the use of disinfectants in barns that has never been reported in the literature to our knowledge. Unfortunately, our questionnaire did not collect the names of molecules that were used. Types of barn disinfectants used in France included quaternary ammonium, phenol derivatives, and aldehydes (including formaldehyde). Some of them (formaldehyde) have already been used in cattle barns by fumigation, leading to the exposure of cattle farmers [37].

It is not possible to rule out the impact of biological exposure in farming, which is thought to be a risk factor for some hematological cancers in the meat industry [38]. In addition, some findings might be due to chance or correlations between exposures. However, even though multiple exposures were frequent, specific correlations between insecticide use on animals and pesticide use on corn or between insecticide use on

animals and disinfectant use were moderate, with Pearson correlation coefficients of 0.44 and 0.65, respectively.

These findings provide support not only for the role of pesticide use on some frequent crops in France but also for the role of insecticide use on animals, on MM risk. Thus, they throw light on the etiology of MM among French farmers. In future analyses in the AGRICAN cohort, we will use PESTIMAT, a crop-exposure matrix, to investigate the associations between pesticides like the triazine herbicides and organochlorine insecticides and the risk of MM [35].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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