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ORIGINAL PAPER

Occupational exposure to pesticides and risk of hematopoietic cancers: meta-analysis of case–control studies

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Abstract
Objective In this study we conducted a meta-analysis of 13 case–control studies that examined the occurrence of hematopoietic cancers in pesticide related occupations in order to undertake a qualitative and quantitative evaluation of a possible relationship.
Methods Pubmed databases were searched for case–control studies published between 1990 and 2005 investigating the relation between hematopoietic cancers and occupational exposure to pesticides. Fixed and random effect meta-analysis models were used depending on the presence of heterogeneity between studies.
Results The overall meta-odds ratio obtained after pooling 44 ORs from 13 studies was 1.3 (95% CI: 1.3–1.5). We realized stratified analysis on three different types of hematopoietic cancers (non-Hodgkin lymphoma (NHL), leukemia and multiple myeloma). A significant increased risk of NHL was found (OR = 1.35; 95% CI = 1.2–1.5). Moreover, increased risks of Leukemia (OR = 1.35; 95% CI = 0.9–2) and multiple myeloma (OR = 1.16; 95% CI = 0.99–1.36) were also detected but these results were not statistically significant. Significant heterogeneity existed among the different studies and a publication bias was detected. Therefore, a meta-regression was carried out. Our results showed that a long period of exposure (more than 10 years) provided an increase in the risk of all hematopoietic cancers and for NHL by fractions of 2.18 (95% CI = 1.43–3.35) and 1.65 (95% CI = 1.08–2.51), respectively. Conclusions: The overall meta-odds ratio suggests that there is a significantly positive association between occupational exposure to pesticides and all hematopoietic cancers as well as NHL. A major limitation of our meta-analysis is the lack of sufficient data about exposure information and other risk factors for hematopoietic cancer (genetic predisposition, ethnic origin, immunodepression…). In addition, data concerning specific subtypes of hematopoietic cancers are often confusing. Thus, future epidemiological studies should undertake a major effort to assess the identity and the level of pesticides exposure and should control for the most likely potential confounders.

Keywords Pesticides · Professional exposure · Hematopoietic cancers

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Background

Hematopoietic malignancies are a heterogeneous group of blood disorders that originate in the bone marrow and lymph nodes and are often systemic at diagnosis. The three major groups of hematological malignancies are lymphomas, leukemia, and multiple myeloma (MM). Lymphomas include non-Hodgkin's lymphomas (NHL) and Hodgkin's

disease (HD) with four histological subtypes [1]. The non-Hodgkin's lymphomas are divided into B-cell and T-cell neoplasms based on histologic characteristics. The most common types of NHL are diffuse large B-cell lymphoma (30–40% of lymphomas in western countries) and follicular lymphoma (20–30%) [2]. Four main types of Leukemia are distinguished: acute lymphoblastic (ALL), acute myeloblastic (AML), chronic lymphocytic (CLL), and chronic myelocytic leukemia (CML) [1]. Another type of blood disorder is myelodysplastic syndromes (MDS) which are a heterogeneous group of stem cell malignancies with an increased risk of transformation into acute myeloid leukemia (10–40%) [3]. The etiology of these malignancies is still largely unknown. Viral infections (Epstein-Barr virus, human herpesvirus 8) [4, 5], and some genetic and environmental factors (organic solvents including benzene, ionizing radiation and low frequency electromagnetic fields exposure) have been suggested as established causes of leukemia, lymphoma, and multiple myeloma [6–9]. However, these known risk factors only explain a small proportion of cases of hematopoietic malignancies. Occupational exposure to chemicals, such as petrol and diesel vapors, exhaust gases, metals, solvents, and pesticides, has been established as risk factors for MDS [10]. The maps for leukemia in various countries in particular the USA, suggest a role for certain factors associated with the agricultural environment as high rate areas of leukemia did not include the cities [11]. In addition, employment in farm related occupations has consistently been suggested as a risk factor for myeloma [12].

According to Weisenburger [13], pesticide exposure may have both acute and chronic effects on health. Acute effects in pesticide users, including neurotoxicity, organ damage, irritation, chemical burns, for example, are well documented and could be specifically attributed to different classes of compounds [14, 15]. Chronic toxicity associated with pesticide exposure such as endocrine disruption or immunotoxicity, immunological abnormalities, adverse reproductive and developmental effects, and neurodegenerative diseases, has also been reported but remains to be explored [16–18]. In addition, several studies have suggested that pesticide exposure, independently or in synergy with other risk factors, may be associated with several types of cancer (cancers of lymphatic and hematopoietic system, skin, soft tissue sarcoma, lip, prostate, brain, and stomach cancer). Indeed, insecticides, herbicides, and fungicides could be associated with various cancers including those of the hematopoietic system (leukemia, non-Hodgkin lymphoma, and multiple myeloma) [11, 19–21]. Findings across epidemiological studies that evaluated the risk of NHL among farmers are heterogeneous. In a meta-analysis of 14 studies, Blair et al. [22] reported no significant association between farming and NHL, whereas two other meta-analysis [23–24] reported a significant positive association.

The aim of our study was to perform a meta-analysis of case–control studies in order to clarify the possible relationship between occupational exposure to pesticides and each group and subgroup of hematopoietic neoplasms (leukemia, non-Hodgkin lymphoma, multiple myeloma, and myelodysplastic syndromes). The subjects considered as being potentially exposed to pesticides at work were agricultures, farmers, or employees in chemical industries.

Materials and methods

Study identification

We searched Pubmed databases for studies examining the association between hematopoietic cancers and exposure to pesticides. The search strategy used several combinations of the following keywords: hematopoietic cancer, lymphoma, non-Hodgkin lymphoma, leukemia, myelodysplastic syndromes, pesticides, occupational exposure, agriculture, farmers, and epidemiology. Publications that were not found online were obtained by e-mailing the authors or requested by the Central Documentation Unit (INRA, Versailles-Grignon). We also checked the reference lists of relevant publications for case–control studies treating with occupational exposure to pesticides and hematopoietic cancers.

Study selection

This study is a meta-analysis of case–control studies. In order to select the studies, we defined inclusion and exclusion criteria. Studies were included in the analysis when they complied with the following inclusion criteria:

- Articles published in peer reviewed journals;
- In English;
- Published between 1990 and 2005;
- Studies in adult men or/and women;
- Including any type of hematopoietic malignancies (Leukemia, multiple myeloma, and non-Hodgkin lymphoma);
- Referring to occupations with a potential risk of exposure to pesticides.

Studies were excluded if they:

Were not published in English;
Did not report original results (reviews, letters, and comments);

Did not provide sufficient data (lack of information about the number of cases and controls or about the method used);
Included only deceased individuals or data resulting from accidental exposures.

The subjects considered as being potentially at risk through occupational exposure to pesticides had either agricultural or non-agricultural occupations. Agricultural occupational groups included farmers, farm workers, agricultural workers and pesticide applicators, pesticide mixers and loaders and farm residents. Non-agricultural pesticide exposures included employments with a high probability of exposure to pesticides such as chemical industries. Although the included articles were published between 1990 and 2005, they concern cancer cases that were diagnosed between 1979 and 2003 that could be related to exposures in the 1970s. We avoided cancers that appeared earlier as the pesticides used, the type of protection and the agriculture practices have evolved considerably since 1970. Furthermore, when the study included only deceased individuals, the questions concerning the type and period of exposure were answered by friends or a next-of-kin. We therefore tried to include studies where the exposed persons were interviewed directly. In addition, our aim was not to study the acute effect of pesticide overdoses; we therefore chose not to include articles concerning accidental exposures. Moreover, in order to focus our investigation on pesticides as possible contributing factors, we selected articles concerning not only agricultural pesticide users in a farm (because farmers are also exposed to dust, animals, and fertilizing agents) but also pesticide applicators, and industrial workers.

Data extraction

Once the full text papers of the selected studies were available, two authors separately read the reports and independently created an abstract form of the most relevant information provided (number of cases and controls in each study, occupation, pesticides used, exposure levels and frequency, types and sub-types of hematopoietic malignancies, Odds ratio estimates with their 95% confidence intervals, …). The results of this work were compared and reconciled by the two authors prior to the meta-analysis, they were then tabulated in a data extraction form (Tables 1 and 2).

In some cases we chose overall farming activity rather than specific activities on the farm. Nonetheless, we tried to exclude odds ratio estimates for animal husbandry workers and for exposure due to animal pesticides in order to reduce the risk related to animal viral infections that can have an impact on the development of some types of hematopoietic cancer. In addition, we included data resulting from further stratifications, e.g., level or duration of exposure, types of pesticides used and exposure group when sufficient information was provided. As a consequence, in each study we had more than one Odds ratio estimate to take into consideration.

Data analysis

Statistical pooling

For each study, more than one odds ratio (OR) estimates and their confidence intervals (CI) were provided by the authors (Table 2), but the statistical method that was used varied from one study to the next. In order to calculate the pooled OR estimate and its CI we first used a fixed-effect model (Mantel and Haenszel method [25]). As the homogeneity hypothesis appeared to be irrelevant, we worked with a random-effect model. The estimation was done according to the DerSimonian and Laird method [26] (Table 3). For each model, a test for overall effect was performed. The p values showed for both cases, a significant effect of pesticide exposure on cancer risk.

In the Mantel-Haenszel [25] fixed-effect model the estimated pooled OR $\hat{\theta}$ equals:

$\hat{\theta} = \sum \theta_i \omega_i / \sum \omega_i$ with $\theta_i$the odds ratio for the ith study and its weight $\omega_i = b_i c_i / N_i$

Because of the heterogeneity of our studies, the random effect model is more appropriate. Using this model, the estimate of the pooled effect measure and its CI incorporate the additional variability due to inter-study variance (τ^2). As detailed by DerSimonian and Laird [26], an estimator of τ^2 is defined as $\hat{\tau}^2 = \max\{0, [Q - (K-1)]/[\sum \omega_i - (\sum(\omega_i^2))/\sum \omega_i]\}$ where $Q = \sum w_i \hat{\theta}_i^2 - (w_i \hat{\theta}_i)^2 / \sum w_i$ and K represents the total number of studies.

In the DerSimonian and Laird method [26], the estimated pooled OR $\hat{\theta}$ equals:

$\hat{\theta} = \sum \theta_i \omega_i^* / \sum \omega_i^*$ with $\theta_i$the odds ratio for the ith study and its weight $w_i^* = \left(\hat{\text{var}}(\hat{\theta}_i) + \hat{\tau}^2\right)^{-1}$

Evaluation of homogeneity

The first step was to determine the homogeneity among the studies. The test for this hypothesis is based on a Cochran Q statistical test with a degree of freedom equal to the number of studies minus one and tests the null hypothesis that the intra-study estimates of odds ratio are homogenous across all the studies.

Table 1 General abstract form of the 13 case–control studies included in our meta-analysis

Reference	Sex	Mean age	Type of pesticide	Type and/or subtype of hematopoietic cancer	Source of exposure	Year of diagnostic of cancer	Type of exposure assessment
Kato et al. (2004) USA (NY)	Women	60		B- cell NHL B- cell NHL B- cell NHL T-cell NHL T-cell NHL T-cell NHL	Occupational exposure	1995–98	In-person questionnaire (Duration, frequency of exposure and method of application. History of drug use)
Strom et al. (2005) USA (Texas)	Men	64		Myelodysplasia	Farmers	1999–2003	Mail questionnaire followed by phone calls (job-exposure matrix)
Baris et al. (2004) USA (Atlanta, Detroit, New jersey)	Women and men		Herbicides Herbicides Insecticides Insecticides Fungicides Fungicides	Multiple myeloma	Occupational exposure	1986–89	Interview at home (job-exposure matrix)
Nanni et al. (1998) Italy	Men	64	Herbicides Fungicides insecticides	Multiple myeloma	Occupational exposure	1987–90	In-person structured questionnaire (History of cancer, drug use, smoking, alcohol…)
Cantor et al. (1992) USA (Iowa, Minnesota)	Men			NHL	Farmers	1981–83	In-person interview (method of application of pesticides, use of protective equipment)
Fritschi et al. (2005) Australia (New South Wales)	Women and men		Insecticides organophosphorés Insecticides organophosphorés Insecticides organochlorés Insecticides organochlorés Herbicides Herbicides	NHL	Occupational exposure	2000–2001	Self-administered questionnaire

Table 1 continued

Reference	Sex	Mean age	Type of pesticide	Type and/or subtype of hematopoietic cancer	Source of exposure	Year of diagnostic of cancer	Type of exposure assessment
Chiu et al. (2004) USA (Minnesota, Nebraska, Kansas)	Men		Insecticides	B-cell (Follicular NHL)	Farmers	1979–86	In-person or telephone interview
			Fungicides	B-cell (Follicular NHL)			
			Herbicides	B-cell (Follicular NHL)			
			Insecticides	B-cell (diffuse large NHL)			
			Fungicides	B-cell (diffuse large NHL)			
			Herbicides	B-cell (diffuse large NHL)			
			Insecticides	Other NHL			
			Fungicides	Other NHL			
			Herbicides	Other NHL			
			Insecticides	B-cell (small lymphocytic NHL)			
			Fungicides	B-cell (small lymphocytic NHL)			
			Herbicides	B-cell (small lymphocytic NHL)			
Brown et al. (1990) USA (Iowa, Minnesota)	Women and men	66		Leukemia	Farmers	1980–83	In-person questionnaire
Terry et al. (2005) USA and Canada	Women and men	47		Leukemia	Occupational exposure	1986–89	Phone calls
Clavel et al. (1995) France	Men	56		B-cell NHL	Farmers	1980–90	In-person questionnaire + phone calls
	Women						
Rigolin et al. (1998) Italy	Women and men	65		Myelodysplasia	Occupational exposure	1990–96	In-person questionnaire
Fabbro-Peray et al. (2000) France	Women and men	49		NHL	Farmers	1992–95	In-person questionnaire
Adegoke et al. (2003) Shanghai	Men	51		Leukemia	Occupational exposure	1987–89	In-person questionnaire
	Women						

Six studies concerned both women and men, two studies provided data for women and men separately, four studies concerned only men and one study only women. The different types and subtypes of hematopoietic malignancies are cited. Also, some studies provided information about the type of pesticide used and the type of exposure assessment

Table 2 Authors estimates of odds ratio and study properties for selected publications relating to pesticide applicators and hematopoietic cancers. Some of these studies provided independent data according to the type and level of exposure (period and intensity of exposure, e.g., low or high exposure), type of pesticide used, subtype of cancer and sex of the studied population so we had a total of 44 data (estimates of ORs) to include in our meta-analysis

Reference	Sex	Nb of exposed cases	Nb of exposed controls	Nb of unexposed cases	OR (IC 95%)	Duration of exposure	Level of exposure	Covariates controlled
Kato et al. (2004) USA (NY)	Women	32	51	238	1.06 (0.61–1.82)	<10 years		Age, college education, family history of hematopoietic cancer
		24	20	238	2.48 (1.21–5.08)	10–18 years		
		24	20	238	1.77 (0.90–3.48)	>18 years		
		3	51	17	2.94 (0.61–14.03)	<10 years		
		3	20	17	18.2 (3.47–9544)	10–18 years		
		2	20	17	1.79 (0.25–12.77)	>18 years		
Strom et al. (2005) USA (Texas)	Men	6	3	216	1.58 (0.36–6.87)	>1 years	Low + medium	Age, gender, education smoking and alcohol drinking Exposure to benzene solvent, to Gasoline and family history of hematopoietic cancer
		24	5	216	4.4 (1.55–12.50)	>1 years	High	
Baris et al. (2004) USA (Atlanta, Detroit, New jersey)	Women and men	15	39	511	1.45 (0.78–2.69)		Low	Age, gender, race, state of residence and education
		11	29	511	1.48 (0.72–3.04)		Medium + high	
		46	201	439	0.82 (0.57–1.18)		Low	
		12	28	439	1.6 (0.79–3.25)		Medium + high	
		145	487	406	1.15 (0.91–1.44)		Low	
		4	8	406	2.31 (0.67–7.95)		Medium + high	
Nanni et al. (1998) Italy	Men	4	14	12	1.9 (0.5–7.6)			Gender, age, altitude of municipality, family history of hematopoietic cancer, educational level, previous herpes zoster diagnosis
		5	13	12	2.6 (0.7–9.3)			
		3	12	12	1.7 (0.4–6.9)			
Cantor et al. (1992) USA (Iowa, Minnesota)	Men	356	698	266	1.2 (1–1.5)	>6 months		Vital status, age, state, cigarette smoking, family history of hematopoietic cancer, high risk occupations and high risk exposures
Fritschi et al. (2005) Australia (New South Wales)	Women and men	20	28	662	0.71 (0.39–1.28)		Low	Age, ethnicity and region of residence
		12	6	662	2.11 (0.78–5.68)	>6 months, >8 h/day	High	
		14	13	674	1.07 (0.5–2.32)		Low	
		6	2	674	3.27 (0.66–16.4)	>6 months, >8 h/day	High	
		10	14	679	0.73 (0.32–1.66)		Low	
		5	3	679	1.75 (0.42–7.38)	>6 months, >8 h/day	High	

Table 2 continued

Reference	Sex	Nb of exposed cases	Nb of exposed controls	Nb of unexposed cases	OR (IC 95%)	Duration of exposure	Level of exposure	Covariates controlled
Chiu et al. (2004) USA (Minnesota, Nebraska, Kansas)	Men	73	625	76	1 (0.7–1.5)			Age, state of residence, type of respondents and use of hair dye
		17	203	129	0.9 (0.5–1.6)			
		84	730	70	1 (0.7–1.5)			
		68	625	87	1 (0.7–1.4)			
		17	203	133	0.90 (0.5–1.6)			
		78	730	73	1 (0.7–1.4)			
		79	625	100	1.4 (1–1.9)			
		24	203	156	1.4 (0.9–2.4)			
		92	730	90	1.4 (1–2)			
		36	625	35	1.60 (0.9–2.9)			
		16	203	56	2.80 (1.4–5.6)			
		35	730	38	1.4 (0.8–2.5)			
Brown et al. (1990) USA (Iowa, Minnesota)	Women and men	335	698	243	1.2 (1–1.5)			Vital status, age, state, cigarette smoking, family history of hematopoietic cancer, high risk occupations and high risk exposure
Terry et al. (2005) USA and Canada	Women and men	63	55	716	0.8 (0.5–1.2)			Age, sex, race, education, region of residence, smoking, proxy respondents
Clavel et al. (1995) France	Men	53	58	167	2 (1.3–3.1)	≥6 months		
	Women	8	7	54	2.7 (0.8–8.7)	≥6 months		
Rigolin et al. (1998) Italy	Women and men	48	27	130	2.12 (1.26–3.59)			
Fabbro-Peray et al. (2000) France	Women and men	89	118	356	1.5 (1–2.1)			Age, gender, education level, urban settings
Adegoke et al. (2003) Shanghai	Men	10	17	246	0.6 (0.3–1.3)	<10 years		Age, income
	Women	12	6	218	1.9 (0.7–5.3)	≥10 years		

Table 3 *Pooled-ORs estimates*: This table shows the results of the estimates of pooled-OR and 95% CIs for all hematopoietic malignancies and for every type of cancer before and after correction with "Trim and Fill method"

		All hematopoietic malignancies	NHL	Leukemia	Multiple myeloma
Overall-OR (95% CI)		1.33 (1.19–1.49)	1.35 (1.17–1.55)	1.35 (0.91–2)	1.16 (0.99–1.36)
Between-studies variance t^2		0.06	0.07	0.16	0.02
Test for Heterogeneity	Q statistics	91.43	60.82	19.49	9.78
	p value	0.00	0.00	0.00	0.28
Test for overall effect OR = 1	z	4.91	4.16	1.5	1.87
	p value	0.00	0.00	0.13	0.06
Overall-OR (95% CI) after trim and filled method		1.15 (1.02–1.31)	1.21 (1.03–1.42)	–	1.12 (0.96–1.30)
Between-studies variance t^2		0.11	0.12	–	0.02
Test for Heterogeneity	Q statistics	159.20	97.64	–	14.38
	p value	0.00	0.00	–	0.28
Test for overall effect OR = 1	z	2.22	2.39	–	1.4
	p value	0.03	0.02	–	0.16

The heterogeneity Cochran Q test is useful in order to choose the appropriate model to calculate pooled-ORs. In the cases of heterogeneity ($p < 0.05$), pooled-ORs were calculated according to the random effect model estimated by the DerSimonian & Laird method (all hematopoietic malignancies, Leukemia, and NHL). Fixed effect model (Mantel and Haenszel method) was used to calculate pooled-OR and 95% CI for multiple myeloma ($p = 0.28$, no heterogeneity). In order to test the overall effect, z and p values for normal density were calculated. As detailed in DerSimonian & Laird, tau squared (t^2) estimated the inter-studies variance. When a publication bias was detected the pooled-ORs were recalculated after correction by the "Trim and Fill method." Heterogeneity between the studies persisted after correction of the publication bias

The p value (we considered statistically significant a $p < 0.05$) for this statistical value indicates the presence or not of a heterogeneity between the studies. In the case of heterogeneity a random-effect model (DerSimonian and Laird [26]) has to be used to estimate the pooled OR and its CI.

In order to investigate possible sources of heterogeneity, two different methods were used: meta-regression and stratified analysis. Several meta-regressions were performed to analyze associations between exposure effect and study characteristics. The two methods consist in introducing one or several covariates in the meta-analysis in order to control the heterogeneity between studies. We stratified our data into three groups of hematopoietic malignancies (non-Hodgkin lymphoma (NHL), Multiple myeloma (MM), Leukemia) and we constructed a list of variables believed to influence the development of each group and subgroup of these neoplasms (myelodysplastic syndromes (MDS), B-Cell NHL, T-Cell NHL …). We defined two lists of covariates. The first ones concern exposure parameters: duration of employment for occupational exposures (long period if exposure exceeds ten years, short period otherwise), type of products (pesticides, herbicides, and insecticides) and the type of chemical substance when provided. The second ones concern the study characteristics: sex, geographical location, and date of publication. Source of heterogeneity was considered important if stratification for that source did markedly decrease the inter-study variance.

Publication bias

Publication bias is known to occur in meta-analysis as studies with results that are significant, interesting, from large well-funded studies, or of higher quality are more likely to be submitted, published, or published more rapidly than work without such characteristics. A meta-analysis based on a literature search will thus include such studies differentially, and the resulting bias may invalidate the conclusions. In order to assess publication bias, we explored the effect of the study size by plotting the natural logarithm of the estimator of OR (ln OR) versus its standard error (SE). Publication bias is characterized by an asymmetry in the funnel plot. We used two common statistical methods to assess funnel plot asymmetry. The method of Begg and Mazumdar [27] proposes an adjusted rank correlation method to examine the association between the effect estimates and their variances or standard errors. The Egger et al. [28] approach is a linear regression method where the standard normal deviate (defined as the odds ratio divided by its standard error) is regressed against the estimate's precision (defined as the inverse of the standard error). The intercept provides a measure of asymmetry: the larger its deviation from zero, the more pronounced the asymmetry. We used the Duval and Tweedie [29] non-parametric "trim and fill" method of accounting for publication bias in meta-analysis. The method, a rank-based data augmentation technique, formalizes the use of funnel plots, estimates the number and

outcomes of missing studies, and adjusts the meta-analysis to incorporate the theoretical missing studies.

Software

All analyses were conducted using Stata version 9 SE (Stata Corporation, PC). Stata is a complete integrated statistical software which provides many functions necessary to perform meta-analysis and to deal with publication bias [30].

Results

A total of 36 case–control studies examining the relationship between exposure to pesticides and hematopoietic cancer were found [3, 9, 12, 31–64]. One study [31], was excluded because the data included unseparately both dead and living cases, one study [32], was excluded because data was not specifically limited to hematopoietic cancers, one study [33] was in Italian, 18 studies [9, 34–50] were eliminated because of insufficient data (number of cases or controls not provided, unclear results, unclear method used for the study, …), one study [51] was a review, one study [52] provided data included in another study [49] and one study included only accidental exposure of farm resident cases [53]. Overall, only 13 studies were included in our meta-analysis [3, 12, 54–64] Some of these studies provided detailed data about type and level of exposure or type of pesticide used, we therefore had a total of 44 data (estimates of ORs) to include in our meta-analysis (Tables 1 and 2). Meta-analysis were first performed on all hematopoietic neoplasms pooling together all the 44 author's OR's in order to have a global idea about the overall effect then we did stratification analyses to study the correlation between professional exposure to pesticides and every type of cancer independently, citing non-Hodgkin lymphoma, multiple myeloma and leukemia. Most of the studies included in the analysis were restricted to non-Hodgkin lymphoma (six studies) [54–56, 58, 61, 62]. Two studies were restricted to multiple myeloma [12, 57], two to myelodysplastic syndromes [3, 63] and three to leukemia [59, 60, 64]. One study was restricted to females who had occupations with potential exposure to pesticides [54] four to male workers [3, 55, 56, 57], five studies show data of both male and female workers [12, 58, 60, 62, 63] and two studies presented independent estimates of ORs and 95% CI according to the sex of the exposed person [59, 61]. Among the included data (44 extracted estimates of risk assessment) (Tables 1 and 2), 66% (29 assessments) are from the USA [45–50], 14% (six assessments) are from Australia [52], 16% (seven assessments) are from Europe [51, 44] and 4% from China (two assessments). In all studies, exposure assessment had been performed from questionnaire-based interviews or questionnaire mailings followed in some cases by phone calls. Information about work history and occupational exposure to pesticides were collected. Case subjects were chosen from cancer registers or from hospitals periodic surveys and controls were selected from the general population by random digital dialing or from voter's lists or health care files.

Occupational exposure and incidence of all types of hematopoietic cancers

We have binary outcomes where the event concerns the development of hematopoietic cancer. Tables 1 and 2 show the authors odds ratios for each study. The range of OR is 0.6–18.2. Seven OR estimates report a negative association but the effect is not significant. Among the data that report a positive association, only nine have a 95% CI that doesn't include one, so we can conclude that these studies show a positive significant association. Nonetheless, a descriptive analysis does not show a clear effect of pesticides and our meta-analysis is helpful in summarizing these 44 data and calculating an average OR.

A meta-analysis with a fixed effect model using the method of Mantel and Haenszel [21] was performed. The test was carried out using the Cochran Q statistics in order to test the homogeneity among the studies. The results are presented in Table 3. It produces a Q value of 91.43 with 43 degrees of freedom ($p = 0.000$) demonstrating a strong heterogeneity. As a consequence, the hypothesis of an identical effect for all the studies was rejected, and to take into account this lack of homogeneity, the analyses have been performed with a random model (DerSimonian & Laird [22]). The results are presented in Table 3 and Fig. 1. Both the output and the graph show that pesticide exposure during occupational activity increases the incidence of hematopoietic malignancies. The pooled OR was 1.3 (95% CI = 1.2–1.5). The estimated inter-studies variance σ^2 is 0.06. In order to explain this heterogeneity we have first explored publication bias then we realized stratified analyses and meta-regression using covariates available for each type of cancer.

The asymmetry of the funnel plot obtained in Fig. 2 and confirmed by Begg and Mazumdar [23] (Kendall's tau $z = 2.01$, $p > z = 0.04$) and by the Egger et al. statistical analysis [24] (bias = 1.2, 95% CI = 0.4–2, $p = 0.004$) is a characteristic of publication bias. In order to correct this publication bias, we applied the "trim and fill method" [25] which consists in guessing the number of studies presuming missing, and adjusts meta-analysis to incorporate this imputed missing data (as explained in paragraph

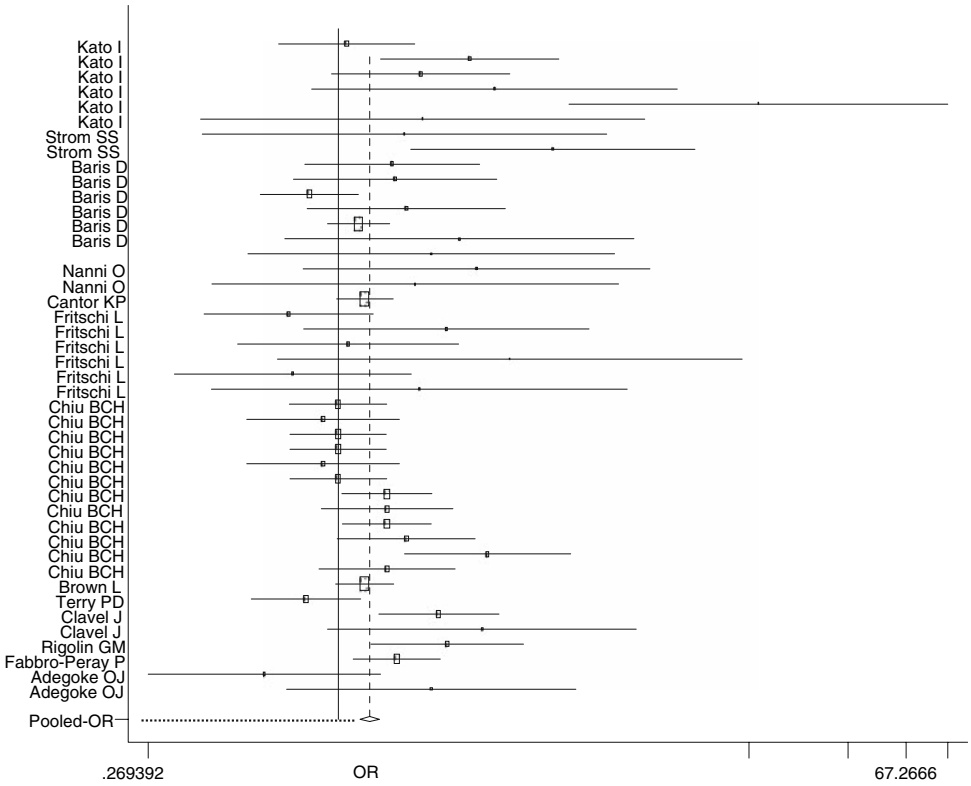

Fig. 1 Forrest plot of all studies. Representation of pooled OR and its 95% CI for all hematopoietic cancers according to a random model as described in Section "Materials and methods"

publication bias in Section "Materials and methods"). To make the funnel plot symmetric, this method added 13 presuming missing studies. The odds ratio decreased from 1.3 (95% CI = 12–1.5) to 1.15 (95% CI = 1.02–1.31) but the results are robust (Table 3). The previous conclusion concerning a positive association between the use of pesticides in occupational activities and the development of hematopoietic cancer is still relevant (a statistically significantly positive OR with p = 0.000). Besides, the heterogeneity test is still significant. Meta-regression was used to investigate possible sources of heterogeneity. We constructed a list of the variables that are thought to influence the development of hematopoietic cancers: duration of employment, (long period if exposure exceeds 10 years), class of products (fungicides, herbicides, and insecticides) and type of the chemical used, sex of cases, geographical location, and date of publication (data not shown). Some of these different variables were not available for all the publications (duration of employment, type of pesticide used), so we performed metaregression only on studies that provided information on covariates.

A source of heterogeneity was considered important if meta-analyses regression for that source did markedly decrease the inter-study variance. The results are shown in Table 4. Some covariates appear to be significant: duration of exposure and geographical location seem to be possible reasons for heterogeneity.

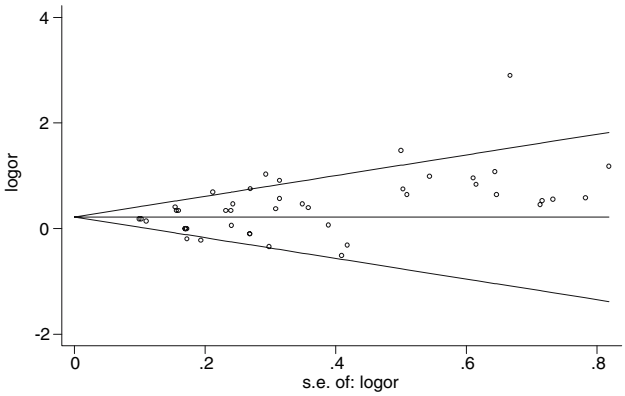

Fig. 2 Analysis of publication bias for all hematopoietic cancers using funnel plot. Studies log (ORs) are represented versus their standard errors according to Begg's method. This figure shows the asymmetry of the funnel plot before correction of the publication bias by the trim and fills method as described in Section "Materials and methods"

With this meta-regression, the inter-studies variance is reduced from 0.06 to 0.01. The coefficients are presented in Table 4, can be interpreted as the estimated increase in the log odds ratio. For example, in Table 4, for the variable "long period exposure", the value 0.78 represents the increase of log OR which means that a long period of exposure increases the risk of hematopoietic cancer by a factor of 2.18 (exponential (0.78)) (95% CI = 1.43–3.35).

Table 4 *Meta-regression*: Covariates coefficients are estimations of log OR and are associated with the p value and the 95% CI

Covariates	All hematopoietic cancers			NHL			Leukemia		
	Coeff	$p > z$	95% CI	Coeff	$p > z$	95% CI	Coeff	$p > z$	95% CI
Long period	0.78	0.000	0.36–1.21	0.50	0.02	0.08–0.92	–	–	–
Short period or duration not mentioned	Ref	–	–	Ref	–	–	–	–	–
Europe	0.44	0.001	0.19–0.69	–	–	–	–	–	–
Rest of the world	Ref	–	–	–	–	–	–	–	–
Subtype of cancer (myelodysplastic syndromes)	–	–	–	–	–	–	1.09	0.00	0.51–1.67

A significant positive association will have a log OR exceeding 0 and the CI will not contain 0. The covariate "long period" exposure shows an effect for all hematopoietic malignancies and for NHL but no significant effect was obtained for multiple myeloma and leukemia. The covariate "Europe" appears only in the case of all hematopoietic cancers. When we preformed meta-regression taking into account the covariate "subtype of cancer" we observed that an effect appeared only in the case of leukemia and for the subtype myelodysplastic syndromes

For the variable geographical location, the meta-regression showed that the incidence of hematopoietic cancers after pesticides exposure is increased by a factor of 1.55 (exponential (0.44)) in Europe compared to other countries included in our study (95% CI = 1.21–1.99).

Occupational exposure and incidence of non-Hodgkin lymphoma

A meta-analysis concerning occupational exposure to pesticides and NHL incidence was performed. 28 data were available for this type of hematopoietic neoplasm. Both the output and the forrest plot (Fig. 3) show that there is a clear effect of pesticide exposure during occupational activities on NHL incidence. The results of Cochran Q statistics (Table 3) showed that an heterogeneity exists between the studies so a random effect model was used to calculate the meta-OR and it's 95% CI. The pooled OR was 1.35 (95% CI = 1.2–1.5). The estimated inter-studies variance σ^2 is 0.07. As described above, we have first explored publication bias then we realized meta-regression using available covariates.

The asymmetry of the funnel plot obtained in Fig. 3 and confirmed by Begg and Mazumdar [23] (Kendall's tau z = 1.8, $p > z = 0.07$) and by the Egger *et al*. statistical analysis [24] (bias = 1.3, 95% CI = 0.1–2.5, p = 0.03) is a characteristic of publication bias. In order to correct this

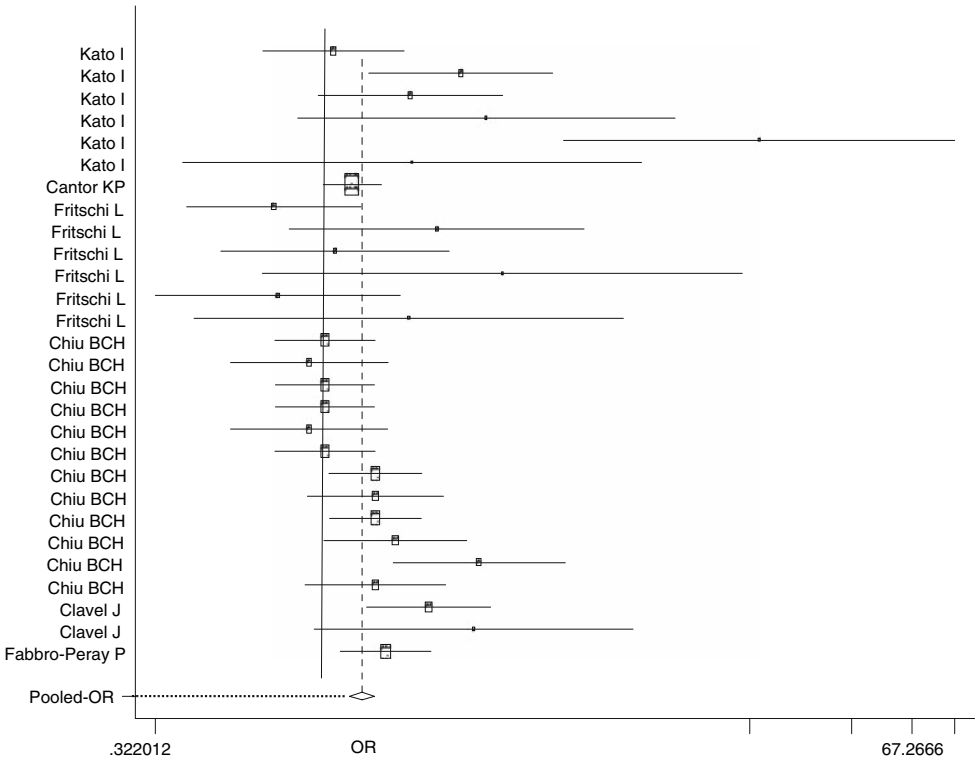

Fig. 3 Forrest plot of studies concerning non-Hodgkin lymphomas. Representation of pooled-OR and its 95% CI for NHL according to a random model as described in Section "Materials and methods"

publication bias the "trim and fill method" added six presuming missing studies. The odds ratio decreased from 1.35 (95% CI 1.2–1.5) to 1.2 (95% CI 1–1.4) indicating that a positive association between the use of pesticides in occupational activity and the development of NHL is still relevant. Besides, the heterogeneity test is still significant. As described above, meta-regression was used to investigate possible sources of heterogeneity. The results showed that the variable "long period of exposure" increased significantly the NHL risk by a factor of 1.65 (exponential (0.5)) (95% CI = 1.08–2.51, $p < 0.05$) (Table 4).

Occupational exposure and incidence of Leukemia

A meta-analysis concerning occupational exposure to pesticides and leukemia incidence was performed on seven data included in our study. Results are presented in Table 3 and Fig. 4. The results of Cochran Q statistics (Table 3) showed that there is heterogeneity between the studies so a random effect model was used. The estimated inter-study variance σ^2 is 0.16. The pooled OR was 1.35 (95% CI = 0.9–2) suggesting that occupational exposure to pesticides may increase the risk of Leukemia. However, the correlation did not show a statistical significance ($p = 0.133$). As described above, we have first explored publication bias then we realized meta-regression using available covariates. No publication bias was assessed for this type of cancer (Kendall's tau $z = 1.8$, $p > z = 0.453$; Egger's test bias = 0.89, 95% CI = –2.2 - 4, $p = 0.493$).

Meta-regression was used to investigate possible sources of heterogeneity (Table 4). The results show that myelodysplastic syndromes incidence is the most related subtype of leukemia to pesticides exposure. The risk is increased by a factor of 2.97 (exponential (1.09)) (95% CI = 1.67–5.31, $p < 0.05$) (Table 4).

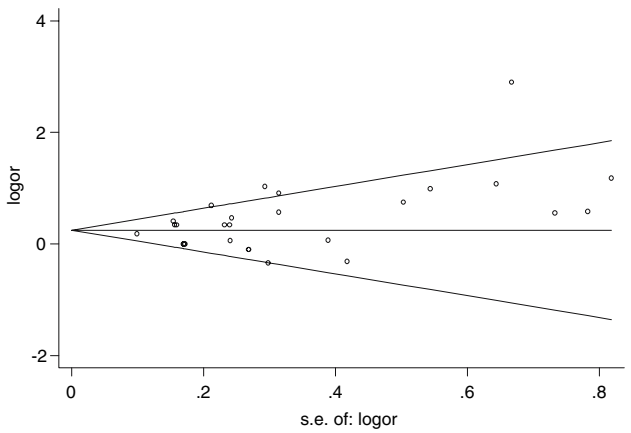

Fig. 4 Analysis of publication bias for non-Hodgkin lymphomas using funnel plot. Studies log (ORs) are represented versus their standard errors according to Begg's method. This figure shows the asymmetry of the funnel plot before correction of the publication bias by the trim and fills method as described in Section "Materials and methods"

Occupational exposure and incidence of multiple myeloma

A meta-analysis concerning occupational exposure to pesticides and multiple myeloma was performed. Nine data were analyzed. Results are presented in Table 3 and Fig. 5. The results of Cochran Q statistics showed that there is no heterogeneity between the studies ($p = 0.281$) so a fixed effect model was used. The pooled OR was 1.16 (95% CI: 0.99–1.36), which means that occupational exposure to pesticides may increase multiple myeloma but this result did not show a statistical significance ($p = 0.06$). The estimated inter-studies variance σ^2 is 0.02. As described above, we have first explored publication bias then we realized meta-regression using the same covariates as above.

The asymmetry of the funnel plot obtained in Fig. 5 and confirmed by Begg's test (Kendall's tau $z = 1.04$, $p > z = 0.3$) and by the Egger's test (bias = 1.25, 95% CI = 0.13–2.37, $p = 0.03$) indicated the existence of a publication bias. In order to correct this publication bias the "trim and fill method" added four presuming missing studies. The odds ratio decreased from 1.16 (95% CI: 0.99–1.36) to 1.12 (95% CI = 0.96–1.30). A positive association between the use of pesticides in occupational activity and the development of multiple myeloma is still relevant but not significant ($p = 0.162$). Besides, the heterogeneity test is still insignificant ($p = 0.230$).

Meta-regression did not show a significant correlation between the covariates controlled and the risk of multiple myeloma [27].

Discussion

Hematopoietic cancers account for nearly 10% of all cancers related deaths in Europe and the USA [1, 65]. The three major groups of hematologic malignancies are lymphomas, leukemia, and multiple myeloma. Lymphomas originate in the lymphoid system. The two primary types of lymphomas are Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL) which is the most well documented haematopoietic disease (for review see Ref. 66). The incidence of NHL largely varied during the last 30 years. Indeed, this malignancy has shown a large increasing incidence in many western countries during the second half of the 20th century. According to the Surveillance, Epidemiology, and End Results (SEER) program (2003) the annual percentage of this malignancy in the US was +3%

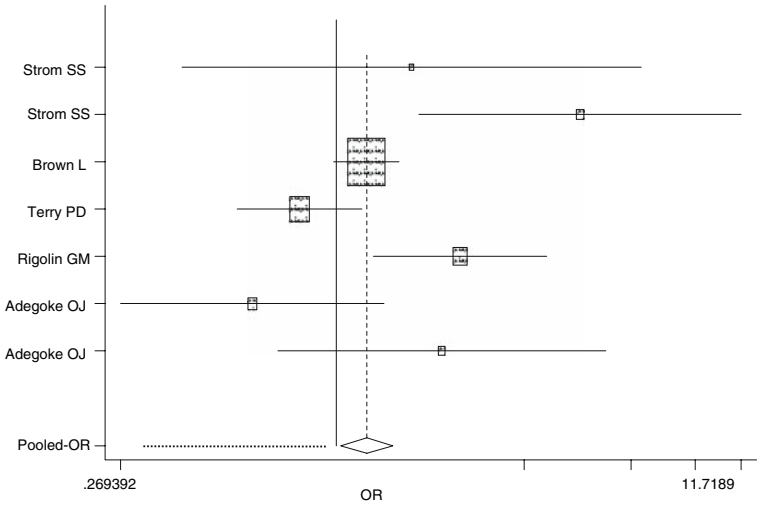

Fig. 5 Forrest plot of studies concerning leukemia. Pooled-OR and its 95% CI for the incidence of leukemia were calculated according to a random model as described in Section "Materials and methods"

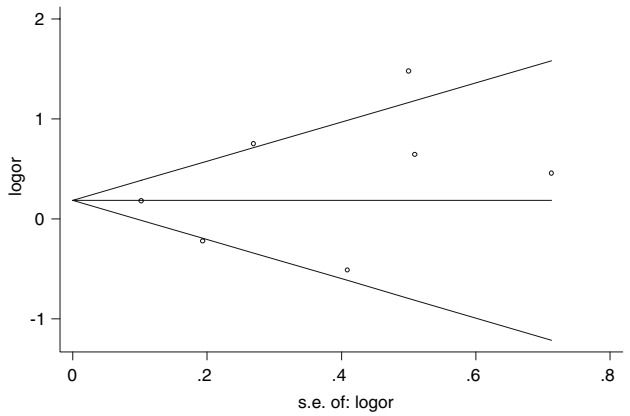

Fig. 6 Analysis of publication bias for studies concerning leukemia using funnel plot. Studies log (ORs) are represented versus their standard errors according to Begg's method. No publication bias was detected for these studies

($p < 0.05$) during 1973–1990 and +1.6% during 1990–1995 [67]. This striking increase in NHL rates was not limited to the US but was also observed in the European Union (EU) and Japan [68]. The increasing incidence of NHL since 1973 clearly leveled off during the 1990s in many European countries and in the US (the SEER program (2003)) [67]. Leukemia is a cancer of the bone marrow and blood that can be acute or chronic. The two primary types of leukemia are lymphocytic leukemia, which involves an increase of white blood cells called lymphocytes; and myelogenous leukemia (also known as myeloid or myelocytic leukemia), which involves an increase in white blood cells called granulocytes [65]. The number of new cases of leukemia diagnosed each year in the US increased steadily from 1975 to 2002, by 0.2% per year [65]. Myeloma is a cancer of the plasma cells that overgrow, forming a mass, or tumour located in the bone marrow. Incidence of myeloma in the US increased by 0.9% per year from 1975 to 2002 [65].

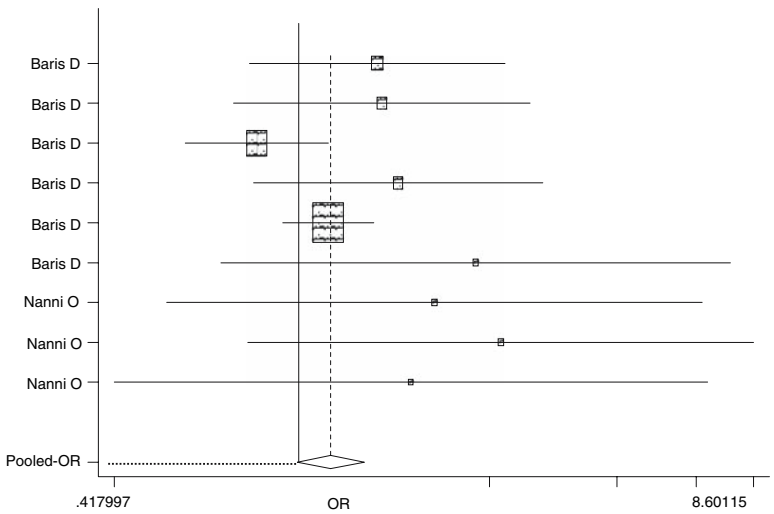

Fig. 7 Forrest plot of studies related to multiple myeloma. Representation of pooled-OR and its 95% CI for multiple myeloma according to a fixed model as described in Section "Materials and methods"

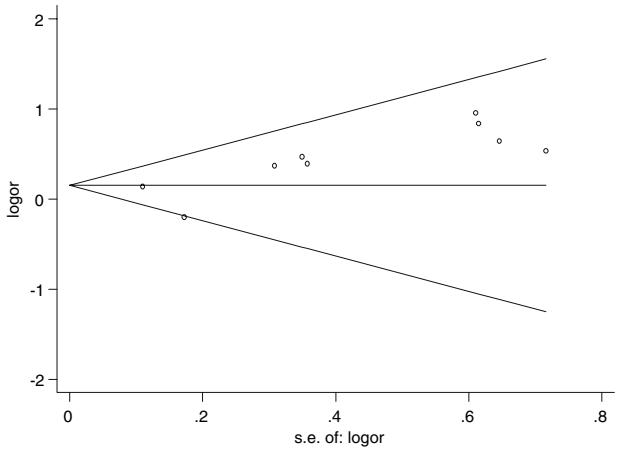

Fig. 8 Analysis of publication bias for multiple myeloma using funnel plot. Studies log (ORs) are represented versus their standard errors according to Begg's method. This figure shows the asymmetry of the funnel plot before correction of the publication bias by the trim and fills method as described in Section "Materials and methods"

Hematopoietic cancers are a heterogeneous group of multifactorial diseases with contributions from genetic, environmental, and lifestyle factors [69]. Drug chemotherapy, viral infections, benzene or radiation are already known to be involved at least in part in the incidence of these pathologies [6, 70–75]. Moreover, some pollutants like dioxine, PCB or pesticides have been often suggested as possible etiological factors. Although concern about the potential hazard of pesticides on human health has been initiated by many epidemiological studies, no consistent conclusion can be drawn and the risk of cancer upon pesticides exposure is frequently discussed. The aim of the present study was to perform a meta-analysis of the relation between hematopoietic malignancies and occupational exposure to pesticides (occupations as farming, agriculture or high incidence exposure as pesticides manufacturers). The originality of this study remains in taking into consideration the different groups and subgroups of hematopoietic neoplasms independently.

We first performed meta-analysis on all hematopoietic cancers by pooling all the data (44 ORs), then, we analyzed independently data concerning every type of hematopoietic malignancy (NHL, leukemia, and multiple myeloma). Our results showed a statistically significant increase in the risk of all hematopoietic cancers and NHL (33% and 35%, respectively). In addition, the incidence of Leukemia and multiple myeloma was increased by 35% and 21.5%, respectively, but these results were not statistically significant ($p > 0.05$).

Pesticides have been repeatedly associated with a risk of NHL and a recent study from Chiu et al. [76] showed that insecticides and herbicides exposure was associated with risk of a subtype of NHL. Moreover, our results are consistent with several prior meta-analysis and reviews, dealing with occupational exposure to pesticides and hematopoietic malignancies. In a meta-analysis based on six studies conducted in the central US, Keller-Byrne et al. [23] reported a weak but significant elevation in NHL risk (meta-RR = 1.4, 95% CI: 1.17–1.55) and in a subsequent meta-analysis of 36 studies Khuder et al. [24] reported a significant positive association (meta-RR = 1.10, 95% CI: 1.03–1.19). Some of the increase of NHL incidence from 1970 to 1990 was attributed to the human immunodeficiency virus (HIV) epidemic and to the acquired immunodeficiency syndrome (AIDS) related NHL [77]. Also viruses, especially Epstein-Barr virus (EBV), have been postulated to be at least in part of etiologic significance. However, this is not sufficient to explain entirely this dramatic increase. Hardell et al. [67] found an interaction between EBV and exposure to immunotoxic chemicals like polychlorinated biphenyls (PCBs), hexachlorobenzene, chlordanes, and dioxins in the etiology of lymphomagenesis with an attributable fraction of 25%. Our results are in agreement with the hypothesis that the initial large increase of NHL incidence and later stabilizing or even decreasing incidence might be related to one or several environmental agents like pesticides with decreasing exposure of the population. Indeed, the highest exposure of the population to persistent organic pollutants such as dioxins, chlorophenols, and PCBs occurred during the 1970s. After that, the concentrations in the environment and thus also in the food chain have declined, although the rate have leveled off during the 1990s. In addition, use of synthetic organic pesticides became widespread during the second half of the 20th century [78] and the incidence of NHL also increased during this time.

Although our results concerning the impact of pesticide exposure on leukemia and multiple myeloma incidence did not allow a firm conclusion, they are strengthened by many studies. Indeed, in a recent systematic review, Van Maele-Fabry et al. [79] have found an increased risk of myeloid leukemia upon pesticide occupational exposure. In addition, prior meta-analysis [80, 81] showed a relationship between farming and the occurrence of multiple myeloma.

Among the 44 data we have collected, some have integrated important details such as the level, the frequency and the duration of exposure among pesticide users, the country, the sex of pesticides user and the hematopoietic cancer type or subtype. As a consequence, in the present study we were able to stratify our analysis after establishing a list of variables thought to influence the development of hematopoietic cancer. The results of our metaregression analyses show, for example, that a long period of exposure (that we defined as more than 10 years) results in an increased risk of developing NHL by a factor of 1.65 (95% CI = 1.08–2.51). Our results also showed that

myelodysplastic syndromes (MDS), considered as a subtype of leukemia, had the most increased risk upon occupational exposure to pesticides (an increase by a factor of 2.97; 95% CI = 1.67–5.31). However, because our results were based on small numbers of data additional studies are necessary to clarify this point. Little is known about the etiology of MDS and concomitant exposure to other classes of toxic agents and genetic or lifestyle factors may have influenced on these findings [3]. Some authors have suggested that insecticides, herbicides or solvents may act as genotoxic agents and exposure to these compounds could be correlated with abnormal caryotype and development of MDS and acute leukemia similar to patients exposed to irradiation or alkylating drugs [82].

Our metaregression also shows that the correlation between the use of pesticides and the incidence of all hematopoietic neoplasms seems more pronounced in Europe than in the USA, although only seven data in EU were compared versus 29 in USA (risk was increased for the covariate Europe by a factor of 1.55; 95% CI = 1.21–1.99). The reason for this could be the type of active compounds that are used, the working habits (protective equipments) and the annually handled quantity in each country. In general, the quantity of pesticides used in these two parts of the world does not appear to be very different but farming practices and pesticide use may differ between countries and even between areas, which means that the exposure varies and that the risk of developing cancer is not the same. However, these details were poorly documented in the epidemiological data. Finally, when we tried metaregression analyses concerning the two covariates year of publication and sex gender, we did not find any relationship between these variables and the risk of developing hematopoietic cancer in exposed groups.

Differentiating the studies according to the chemical classes of pesticides should provide an assessment of the role of each chemical family on the incidence of hematopoietic cancer. However, this information was not well documented in our selected studies and we were not able to identify the contribution of a particular pesticide or group of pesticides as factors involved in an increase of the risk of developing hematopoietic cancers. Nonetheless, an association has been reported among workers that are highly exposed to one type of pesticides. For example, Acquavella et al. [83] showed a high risk was observed in factory workers manufacturing the herbicide Alachlor in Iowa (SIR 18.6). Furthermore, according to the results of the Agriculture Health Study, exposure to Diazinon has been related to an increased risk of developing leukemia [84] and a relationship was observed between Lindane and Chlordane/Heptachlor use and the risk of NHL and leukemia, respectively [85]. In a recent study investigating the association between hematolymphopoietic malignancies and occupational exposure to pesticides, a significant increase risk of NHL was observed for subjects who were exposed to the phenoxy-herbicide 2,4-dichlorophenoxy acetic acid (2,4-D) [86].

Taking into account all the epidemiological data it is important to note that the major limitation to date in investigations on cancer among the agricultural population is the lack of details regarding exposure assessment. In order to improve investigations in this area, it will be important to investigate whether analyses were based only on the job title farmer, whether the risk of disease was compared between farmers with radically different exposure patterns, whether exposures were based on in-person interviews (more real), whether the farmer had used the same pesticides over the exposure period, which pesticide had been applied to the field when they worked and whether the exposure could be qualified as high, medium or low in terms of time spent on the job per year and in terms of the quantity of pesticides handled per year with regard to migrant or seasonal workers.

It is noteworthy that a lot of experimental studies have shown an effect of some pesticides (such as Bisphenol A, Heptachlor, Propanil, and some chlorinated pesticides) on leukocytes maturation [87], on the differentiation of bone marrow cells or human myeloblastic leukemia cells [88], and on the development of human and murine progenitors [89, 90]. Various studies have also demonstrated a genotoxic effect of some compounds (such as Lindane, Azinphos, Mevinphos, and Fos-ethyl-aluminium) on the rat or human hematopoietic system [91, 92]. Thus, experimental data could confirm the risk associated with the use of pesticides.

In conclusion, we found an increased odds ratio of 1.3 (95% CI = 1.2–1.5) for all hematopoietic cancers in pesticide related occupations. These findings were significantly positive when all types of hematopoietic cancers were pooled and also for NHL. However, the reviewed studies contained insufficient qualitative and quantitative information on exposure in order to distinguish the possible influence of pesticides from other occupational, environmental, lifestyle, or genetic factors. In addition, data concerning specific subtypes of hematopoietic cancers are often confusing. Thus, future epidemiological studies should undertake a major effort to assess the identity and the level of pesticides exposure and should control for the most likely potential confounders. Nevertheless, our result strengthens the suggestion that exposure to a common compound, possibly pesticides, is a causal factor.

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