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ORIGINAL PAPER

A systematic review of myeloid leukemias and occupational pesticide exposure

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Abstract
Objective To conduct a systematic review and meta-analyses of published studies examining the association between myeloid leukemias (ML) and occupational pesticide exposure.
Methods Studies were identified from a MEDLINE search through 31 May 2006 and from the reference lists of identified publications. Studies were summarized and evaluated for publication bias. Relative risk estimates for ML were extracted from 17 cohort and 16 case–control studies published between 1979 and 2005. Fixed- or random-effect meta-analysis models were used depending on the presence of heterogeneity between studies. Separate analyses were conducted after stratification for study design, occupational group, ML subtype or gender.
Results The overall meta-rate ratio estimate (meta-RR) for the cohort studies was 1.21 (95% confidence interval [CI] 0.99–1.48). Substantial heterogeneity existed among cohort studies ($p = 1.064 \times 10^{-5}$), mainly reflecting the varying occupational categories examined. The meta-RR was 6.32 (95% CI: 1.90–21.01) for manufacturing workers and 2.14 (95% CI: 1.39–3.31) for pesticide applicators. After stratification of cohort studies by specific ML subtype, an increased risk of acute myeloid leukemia (AML) was found (meta-RR: 1.55; 95% CI: 1.02–2.34). No significant heterogeneity was detected among case–control studies and an increased risk of chronic myeloid leukemia (CML) was found among men (meta-RR: 1.39; 95% CI: 1.03–1.88) and farmers or agricultural workers (meta-RR: 1.38; 95% CI: 1.06–1.79).
Conclusion The strongest evidence of an increased risk of ML comes from manufacturing workers and pesticide applicators. Further studies will be needed to correlate reliable exposure data within these specific occupational groups with well-defined subtypes of leukemia to refine this assessment.

Keywords Meta-analysis · Myeloid leukemia · Pesticides · Occupation · Risk

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Introduction

Leukemias are a heterogeneous group of neoplasms derived from hematopoietic cells. Disruption of the normal hierarchy of maturation results in hematological disorders characterized by either excesses or deficiencies of the mature effector cells [1]. Classification of leukemias is broadly related to the cell of origin (e.g., lymphoid or myeloid) as well as to the rapidity of the clinical course (e.g., acute or chronic) but modern categorizations have identified specific leukemias on the basis of biologic, antigenic, and molecular characteristics of these diseases [2, 3].

The causes of leukemia remain largely unknown although several factors have been found associated. They can be broadly grouped into (a) familial and genetic factors including inherited diseases (e.g., Down syndrome) or other chromosomal abnormalities (e.g., Philadelphia chromosome), (b) environmental factors resulting from occupational exposures, ionizing and non-ionizing radiation, chemicals, pesticides, smoking, diet, and other lifestyle

factors as well as (c) medical- and therapy-related factors including radiotherapy, diagnostic irradiation, pharmaceuticals and chemotherapy, viruses [4]. Major identified risk factors that contribute to leukemogenesis are ionizing radiation in high dose, benzene exposure and at least one virus (HTL-1) [5].

There are several arguments in favor of a role of occupational exposures in the development of leukemia: the male excess of leukemia, the consistent increase among older males in many geographic areas, the higher incidence of acute myeloid leukemia in developed countries and industrial metropolitan areas in the US, and the presence of known and suspected hazardous agents in the workplaces [6].

Environmental and occupational exposures to pesticides as a risk factor for hematopoietic tumors have been widely studied mainly among farmers and agricultural workers, in rural communities and in the pesticide manufacturing industry but the results have not been consistent. Most of the earlier studies reported risk for leukemia as a single entity or by classification that did not allow to distinguish specific leukemia categories, partly because of the historical nomenclature but also due to the limited number of cases in individual studies. Failure to take into consideration the diversity of leukemias may account for some inconsistent findings from early epidemiological studies and, moreover, could hide type-specific risk factors. The diversity of leukemias deriving from a variety of stem cells at different hierarchical levels of hematopoietic and lymphoid cell development is indeed likely to be associated with a variety of etiological mechanisms [7]. In addition, as some exposures appear to be related to a specific histological type of leukemia (e.g., benzene most clearly associated with AML [4, 8]), it can be assumed that a family of pesticides could be related to a specific leukemia cell type. As the varying forms of leukemias probably have different etiologies, it is important to have a more precise breakdown of these data to properly assess the results [9].

As myeloid leukemias are the most frequent forms among adults [10], this paper focused on available epidemiologic data dealing these forms of the disease and occupational pesticide exposure to examine whether it is possible to obtain a more accurate estimate of their relationship.

Occupational exposure to pesticides includes a broad range of occupational categories such as end-users (e.g., farmers and applicators) and workers during the manufacturing process (manufacturing workers) both undergoing diverse qualitative and quantitative exposures.

In spite of these variations which make comparisons difficult, we followed in the present paper, a meta-analytical approach to examine subgroups of studies classified by occupational categories to possibly point to settings with the highest risk.

Materials and methods

Study identification and selection

Study identification

A search on MEDLINE (National Library of Medicine, Bethesda, MD) was conducted for the period 1966 to 31 May 2006. The search strategy combined medical subject headings and key words including myeloid, myelogenous, leukemia, chronic, acute, granulocytic, pesticides, occupation, farmers, agriculture, pesticide applicators, manufacturing workers, with no restriction of publication type or publication date. Recent articles in occupational medicine and epidemiology journals were also scanned for relevant publications. Finally, the reference lists of the relevant publications identified were checked for additional studies, limiting the search to studies published in English in the open literature, in peer-reviewed journals. Published studies were used as they are likely to be more reliable than unpublished reports.

Study selection

A study was considered eligible for further review if (1) it referred to an occupational group of interest exposed to pesticides (farmers, pesticide applicators, workers engaged in the manufacture of pesticides and others like horticulturists, greenhouse workers, gardeners, ...), (2) if the outcome included (subtypes of) myeloid leukemia in adults (International Classification of Diseases, 10th revision, code C92) [11] and (3) if the study used a cohort or case–control design. Excluded studies were those that did not report original results (reviews, comments, letters, editorials), experimental studies and proportional mortality ratios (PMR) studies (mainly because of ambiguities in interpreting results) as well as ecological studies (Fig. 1). Exceptions concerning occupational groups are studies on farmers' wives or women living in a farm, also included in our analysis. Although not classified as occupationally exposed, they may be directly engaged in farm activities or be indirectly exposed to pesticides (e.g., household contamination).

Studies were also excluded if they concerned certain forms of pre-leukemia, known as myelodysplastic syndromes (International Classification of Diseases, 10th revision, code D46) [11] in which about 5–40% develop AML [12], if they included subjects already included in another more complete or more recent study examining a greater number of subjects or with longer follow-up duration and if they provided insufficient data to determine an estimator of relative risk (RR) for myeloid leukemia and its confidence interval.

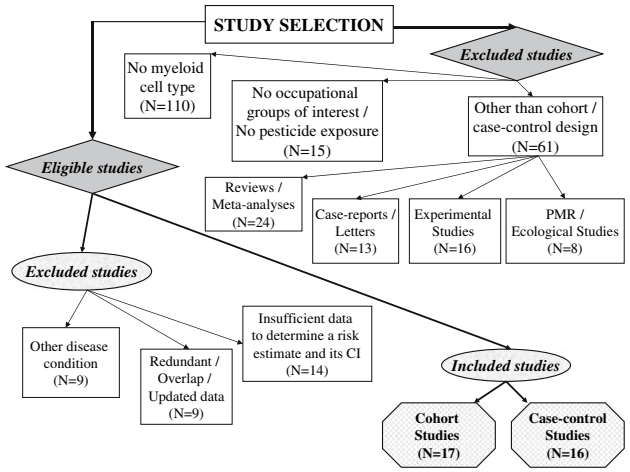

Fig. 1 Study selection. *Note*. N = number of studies

The systematic review and identification of eligible studies was performed by 1 reviewer (GVMF).

Data extraction

A structured abstract was derived for each study identified. Two authors read the reports and independently extracted and tabulated the most relevant RR estimators, with their 95% CIs. The results of this exercise were compared between the authors and consensus was obtained before the meta-analysis. Mortality and incidence outcomes were combined as both are likely to be equally affected by the potential causal factor.

Overall meta-analysis

Cohort studies: if more than one follow-up analysis had been published for the same population, we used the most recently published report. Generally, when multiple estimates of RR were given, we retained (or calculated, see below) the overall data for the total cohort, for any exposure, for the total follow-up period and for all types of myeloid leukemia. Exceptions were papers reporting data justifying their inclusion in other meta-analyses as detailed below (stratifying studies in the meta-analyses). We did not include data resulting from further stratification, e.g., by latency period, by gender, by job title/employee group, by exposure groups, by factory. In some cases, the RR and/or 95% CI was not reported in the publication but we could derive it from the raw data presented [13].

Case–control studies: no overall meta-analysis was performed for case–control studies because when studies reported multiple OR, the available data did not allow to calculate a combined OR e.g., for all types of ML or for both genders. These data were included in stratified meta-analyses.

Stratifying studies in the meta-analyses

Cohort studies: separate meta-analyses were conducted by stratifying data (a) for different occupational groups (manufacturing workers, pesticide applicators, and farmers/agricultural workers), (b) for different types of ML (AML and CML), (c) by gender (men and women) and by gender and ML subtype.

Case–control studies: stratifications were performed for the different types of ML, for occupation (farmers/agricultural workers or occupationally exposed to pesticides when further specification was lacking) and for gender and ML subtype.

Cohort and case–control studies: grouping of cohort and case–control estimates of relative risk was made for ML subtype, for occupation and ML subtype as well as for gender and ML subtypes.

Data analysis

A detailed account of the procedure for data analysis has been published before [14]. In brief, homogeneity among data was evaluated to test between-study comparability. The significance of the between-study variance was evaluated with the ln(RR) statistic test, which has a χ^2 distribution with degrees of freedom equal to the number of studies pooled minus 1. The applied formula is: $\chi^2 = \Sigma\, w_i[\ln(\mathrm{RR})_i - \ln(\mathrm{RR})_p]^2$, for $i = 1$ to N, where N is the number of studies combined, RR_p is the overall pooled RR estimate, RR_i is the RR for the ith study and $w_i = 1/V_i$ where V_i is the variance of the $\ln(\mathrm{RR})_i$. A low p value for this statistic indicates the presence of heterogeneity, which questions the validity of the pooled estimates [15, 16].

In the absence of heterogeneity, we calculated RRs and CIs according to a fixed model [17], which assumes that results across studies differ only by sampling error. The study variance (V_i) was calculated, using the CI given, according to the equation $V_i = [(\ln(\mathrm{CI}_{\mathrm{upper}}) - \ln(\mathrm{CI}_{\mathrm{lower}}))/3.92]^2$. As detailed by Stewart et al. [18] and Dennis [19], the maximum likelihood estimate of the pooled RR in the fixed effect model is the $\exp(\ln(\mathrm{RR})_p)$. The pooled $\ln(\mathrm{RR})_p$ equals $\Sigma\, [\ln(\mathrm{RR})_i/V_i]/[\Sigma(1/V_i)]$, where V_i is the variance for an individual study as described above and $\ln(\mathrm{RR})_i$ is the log RR estimate for study i. This is a variance-weighted least square mean. The variance of the pooled $\ln(\mathrm{RR})_p$, $\mathrm{Var}(\ln(\mathrm{RR})_p)$ or V_p is given by: $[\mathrm{SE}(\ln(\mathrm{RR})_p)] = [\Sigma(1/V_i)]^{-1}$ where SE is the standard error. The pooled variance is used to calculate a 95% CI around the pooled RR estimate.

When data are heterogeneous or if there is reason to believe that publication bias exists, the random effects model is more appropriate. Under this model, the point estimate of the pooled effect measure and its CI incorporate the additional variability due to between-study variance (τ^2). Random effects models were applied, using the method described by Der Simonian and Laird [20]. These authors proposed a non-iterative estimator of τ^2 defined as $\text{est}(\tau^2) = \max\{0, [Q - (k-1)]/[\Sigma w_i - (\Sigma (w_i^2))/\Sigma w_i\}$ where Q is the heterogeneity statistic, k is the total number of studies, and w_i are the inverse variance weights for ln(RR). Potential sources of heterogeneity were evaluated by subset analysis.

The overall meta-analysis for cohort studies is represented by a forest plot where the confidence interval for each study is represented by a horizontal line and the point estimate by a square. The size of the square corresponds to the weight of the study in the meta-analysis. The confidence interval for the total is represented by a diamond.

The influence of study size was explored by plotting the natural logarithm of the estimate of RR (ln RR) versus the inverse of standard error (1/SE). Funnel plot asymmetry was tested by the linear regression method suggested by Egger et al. [21].

We conducted sensitivity analyses by omitting studies reporting imprecise values (weight < 1.5 and $< 10\%$, respectively) to estimate the importance of individual studies in the combined summary statistic and to determine whether any of these had a disproportionate influence [22]. We also conducted influence analyses to reestimate the pooled relative risk while dropping 1 study at a time and examine whether any studies disproportionately influenced the results.

Results

Literature selection and study characteristics

A large number of articles were retrieved from MEDLINE and hand searching in the reference lists of the relevant publications. We reduced these to a list of 251 studies selected for further evaluation (Fig. 1). Among these studies, 186 were excluded for the following reasons: no myeloid cell type ($n = 110$), no pesticide exposure and/or occupational group of interest ($n = 15$), other than cohort or case–control design ($n = 61$): reviews or meta-analyses ($n = 24$), case-reports or letters ($n = 13$), experimental studies and/or cytogenetic abnormalities ($n = 16$), PMR or ecologic studies ($n = 8$).

Among the 65 remaining eligible studies, 32 were excluded because they explored other disease conditions (e.g., myelodysplastic syndrome, thrombocytopenia, preleukemic condition, second primary cancer) but not ML ($n = 9$), the data were redundant/updated/overlapping ($n = 9$), data were insufficient to determine a risk estimate and its confidence interval ($n = 14$). Seventeen cohort studies [23–39] and 16 case–control studies [40–55] were identified as fulfilling the inclusion criteria.

Tables 1 and 2 provide selected characteristics of the cohort and case–control studies used in the analysis, respectively. The studies were published between 1979 and 2005. Studies differed according to the definition of cases, either restricted to AML ($n = 17$) and/or to CML ($n = 12$) or without subtype specification of ML ($n = 12$). Nine cohorts and 7 case–control studies were from Europe, 6 cohorts and 7 case–control studies from USA/Canada, 2 cohorts and 1 case–control studies from Australia/New Zealand and 1 case–control study was from China. Data were presented separately for women ($n = 7$) and for men ($n = 19$) and/or combined for both genders ($n = 15$). Pesticide exposed workers included manufacturing workers (2 cohort studies), pesticide applicators (5 cohort studies), farmers or agricultural workers (9 cohort and 12 case–control studies), horticulturists (1 cohort study) and occupational exposure to pesticides without other precisions (5 case–control studies). Reference populations in the cohort studies represented predominantly national, provincial or regional large populations. Eleven cohort and 3 case–control studies were mortality studies, 6 cohort and 12 case–control studies were morbidity studies and 2 case–control studies reported OR for mortality and incidence.

The estimates of the RR for the pesticide exposed groups of workers to develop or die from myeloid leukemia varied between 0.25 and 9.55 and included from 1 up to 458 cases. Thirteen studies (5 cohort and 8 case–control) reported increased RR estimators for AML with 2 cohort studies presenting a confidence interval that did not contain 1. Four case–control studies had relative risk estimates lower than 1. For CML, increased RR estimators were reported in 9 studies (3 cohort and 6 case–control) with 1 cohort reporting a 95% CI that did not include 1. Decreased CML relative risk estimators were reported in three case–control studies. Among the 10 studies (7 cohort and 3 case–control) reporting increased RR estimators for ML, 1 cohort and 2 case–control studies had a confidence interval that did not contain 1. Reduced risk was reported in 3 cohort and 1 case–control studies, 2 out of the 3 cohort studies presenting a 95% CI that did not include 1. One study reported no association between ML and occupational exposure of agricultural workers with a RR estimator of 1.

Data synthesis

Table 3 summarizes the results of the different meta-analyses of cohort and case–control studies performed.

Table 1 Description of the cohort studies included in the MA of occupational pesticide exposure and myeloid leukemia risk

Reference/exposure group	Location	Occupation or exposure group/ entry criteria/(pesticide type)	Exposure assessment Source of exposure definition Metrics	Gender	ML subtype/N. cases	Estimator of relative risk	95% confidence interval
Manufacturing workers							
Acquavella et al. [23]	USA (Muscatine, Iowa)	Manufacturing workers At least one year of documented employment from plant start up (alachlor)	*Source*: work history information, industrial hygiene judgment and to a lesser extent, recent exposure monitoring data; *Metrics*: qualitative exposure ranking: any alachlor exposure, high alachlor exposure and 5+ years high exposure/ 15+ years since first exposure	Men + women	CML: 2	SIR: 9.55	1.16–34.48
Bueno de Mesquita et al. [28]	The Netherlands	Manufacturing workers Ever employed between 1955 and 1985 or 1965 and 1986 (Phenoxy herbicides and chlorophenols: MCPA, MCPP, 2,4-D, 2,4-DP, 2,4-DCP)	*Source*: job records supplemented with company personnel interviews; *Metrics*: NR	Men	ML: 2	SMR: 4.17	0.50–15.05
Pesticide applicators							
Asp et al. [24]	Finland	Herbicide applicators (chemical brushwood control) At least two weeks during 1955–1971 (Chlorophenoxy herbicides: 2,4-D, 2,4,5-T, MCPA)	*Source*: personnel records of four main Finnish employers involved in chemical brushwood control + mailed questionnaire; *Metrics*: latency between the first exposure and the start of the recording of vital status: no latency, 10 years latency and 15 years latency	Men	ML: 1	SMR: 0.67	0.02–3.71
Blair et al. [26]	Florida	Licensed pesticide applicators (chlorinated hydrocarbons, carbamates, organophosphates, phenoxyacetic acids, phthalimids and coumarins)	*Source*: license application and employee history files + firm certification categories as indicators of likely exposures to specific pesticides; *Metrics*: NR	Men	AML: 3	SMR: 3.33	0.69–9.73*

Table 1 continued

Reference/exposure group	Location	Occupation or exposure group/ entry criteria/(pesticide type)	Exposure assessment Source of exposure definition Metrics	Gender	ML subtype/N. cases	Estimator of relative risk	95% confidence interval
Cantor and Silberman [29]	USA	Aerial pesticide applicators At least once in the period 1965–1980 (e.g., organophosphates, carbamates)	*Source*: records of the Aeromedical Certification Division of the Office of Aviation Medicine; *Metrics*: NR	Men	AML: 5 CML: 3 AML + CML: 8*	SMR: 1.42 1.68 1.51*	0.46–3.32 0.34–4.92 0.65–2.98*
Sperati et al. [37]	Central Italy	Male licensed pesticide users and their wives, age 18–50 years, between 1971 and 1973	*Source*: men date of license; wives Municipal Registry Office of residence of their husbands; *Metrics*: NR	Men Women Men + women	ML: 7 5 12*	SMR: 2.43 3.14 2.69*	0.98–5.00 1.02–7.33 1.39–4.70*
't Mannetje et al. [39]	New Zealand	Sprayers registered between 1973 and 1984 (phenoxy herbicides & dioxins; paraquat; organophosphate)	*Source*: register of New Zealand chemical applicators, exposure history questionnaires; *Metrics*: NR	Men + women	ML: 1	SMR: 1.16	0.03–6.44
Farmers/agricultural workers							
Beard et al. [25]	Australia	Outdoor workers occupationally exposed to insecticides Field officers or laboratory staff for the New South Wales (NSW) Board of Tick Control between 1935 and 1996 (arsenic, DDT, modern chemicals)	*Source*: NSW government records *Metrics*: (1) subject's period of employment: arsenic use (1935–1955), DDT use (1955–1962) and modern chemical use (1963–1996); (2) exposure groups: All (any employment during a particular period), Dose 0 (exposed subjects not yet past ten year exposure lag, Dose 1 (< 5 years employment) Dose 2 (≥ 5 to < 15 years of employment) and Dose 3 (≥ 15 years of employment)	Men	ML: ?	SIR of mortality: 1.15	0.25–5.39

Table 1 continued

Reference/exposure group	Location	Occupation or exposure group/ entry criteria/(pesticide type)	Exposure assessment Source of exposure definition Metrics	Gender	ML subtype/N. cases	Estimator of relative risk	95% confidence interval
Bucci et al. [27]	Northern Italy (Province of Forli Emilia-Romagna Region)	Agricultural workers Residents of the Province of Forli, registered in the records of the National Institute of Social Insurance (INPS) between 1957 and 1993	*Source*: job title (farm owner, hired farm worker), calendar years of contribution by job title crosschecked with population registry; *Metrics*: (1) job title: farm owners and farm workers, (2) time period: 1969–1976, 1977–1984, 1985–1993	Men	ML: 45	ASR: 1.00 (mortality)	0.60–1.68
Dean [30]	Ireland	Agricultural workers Socioeconomic groups: SEG 0 (farmers, relatives assisting farmers and farm managers) and SEG 1 (other agricultural occupations and fishermen, mostly farm laborers) from 1971 to 1987 from censuses	*Source*: occupation recorded on death certificates and censuses; *Metrics*: (1) by socioeconomic groups: SEGO to SEG 9, SEGX, SEGY, (2) by age: 15–64 years and 65+ years	Men Women Men + women	ML: 114 37 151	SMR: 0.81* 0.79* 0.81*	0.68–0.97* 0.55–1.1* 0.69–0.94*
Ji and Hemminki [31]	Sweden	Farmers All economically active individuals from the Swedish Family-Cancer Database 1960 census, 1970 census	*Source*: occupational title (from the national censuses), questionnaires including employment status, job titles and work tasks and industry *Metrics*: NR	Men: Women: Men + women	AML: 242 CML: 145 AML + CML: 387* AML: 47 CML: 24 AML + CML: 71* AML: 289 CML: 169 AML + CML: 458*	SIR: 1.05 1.01 1.035* 0.92 1.06 0.96* 1.026* 1.017* 1.023*	0.92–1.19 0.85–1.18 0.94–1.14* 0.67–1.20 0.68–1.53 0.76–1.22* 0.92–1.15* 0.87–1.20* 0.932–1.123*

Table 1 continued

Reference/exposure group	Location	Occupation or exposure group/ entry criteria/(pesticide type)	Exposure assessment Source of exposure definition Metrics	Gender	ML subtype/N. cases	Estimator of relative risk	95% confidence interval
Kelleher et al. [32]	Western Ireland (Galway, Mayo and Roscommon)	Farmers All male subjects for whom occupational data were available between 1980 and 1990	*Source*: occupation recorded from case notes or from the general practitioner; questionnaire including occupational history, chemical exposure + specific section for farmers detailing manner of use of pesticides; *Metrics*: NR	Men	AML: ?	SIR: 1.81	1.09–2.83
Nanni et al. [34]	Italy (northern Italy, Forli)	Agricultural workers registered with INPS (National Institute of Social Insurance) between 1957 and 1993	*Source*: job title (farm owner, hired farm worker), calendar years of contribution by job title; *Metrics*: (1) job title: farm owners and hired farm workers, (2) time period: 1969–1976, 1977–1984, 1985–1993	Women	ML: 41	ASR: 1.07 (mortality)	0.63–1.83
Semenciw et al. [35]	Prairie provinces of Canada	Farmers (farm operators) identified on the Canadian Censuses of Agriculture and Population between 1971 and 1987 linked to mortality records, at least 35 years (herbicides, insecticides, fertilizer)	*Source*: census records, individual self-reported farm exposures 1970–1971; *Metrics*: NR (except the value for the top exposure quartile)	Men	ML: 127	SMR: 0.78	0.65–0.93
Sinner et al. [36]	USA (Iowa)	Women selected from Iowa 1985 driver's license records, aged 55–69 years, free of prior cancer; living on a farm/not living on a farm from 1986 to 2002	*Source*: questionnaire including location of residence; no information about exposures connected with farms; *Metrics*: (1) live on a farm: yes, no, (2) size of town: rural area or farm, town (population 1,000–10,000) and city (population > 10,000)	Women	AML: 26/53	Relative risk: 1.91 (incidence)	1.19–3.05

Table 1 continued

Reference/exposure group	Location	Occupation or exposure group/ entry criteria/(pesticide type)	Exposure assessment Source of exposure definition Metrics	Gender	ML subtype/N. cases	Estimator of relative risk	95% confidence interval
Stark et al. [38]	USA (New York)	Farm owners and operators from the membership lists of the New York Farm Bureau who were at least 18 years and members for at least one year during 1973–1979	*Source*: data obtained from the membership lists including type of farm; *Metrics*: age categories: 30–59 years and 60+ years	Men	ML: 10	SIR: 0.85	0.41–1.57
Others							
Littorin et al. [33]	Sweden (Southern region)	Horticulturists (market gardeners and orchardists) Members of a national horticulturists' trade association for at least one year during 1965–1982; (pesticides including fungicides, insecticides, herbicides, others were detailed in the paper)	*Source*: association register including job title, type and size of culture; *Metrics*: NR	Men + women	ML: 3	SMorbidityR: 1.1	0.2–3.3

Abbreviations: MA, Meta-analysis; ML, myeloid leukemia; CML, chronic myeloid leukemia; AML, acute myeloid leukemia; NR: not reported for ML with regards to pesticide exposure; DDT, dichlorodiphenyltrichloroethane; 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4-DP, 2,4-dichlorophenoxypropionic acid; 2,4-DCP, 2,4-dichlorophenol; MCPA, 4-chloro-2-methylphenoxyacetic acid; MCPP, 4-chloro-2-methylphenoxypropionic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; SMR, standardized mortality ratio; SIR, standardized incidence ratio; ASR, age standardized (European standard population) mortality rate ratio; ?, number of cases not given or that cannot be calculated; *number of cases and/or estimator of relative risk and/or 95% confidence interval calculated [13]

Table 2 Description of the case–control studies included in the MA of occupational pesticide exposure and myeloid leukemia risk

Reference/exposure group	Location	Occupation or exposure group/case and control definition/(pesticide type)	Exposure assessment Source of exposure definition Metrics	Gender	ML subtype/ N. cases	Estimator of relative risk (mortality and/ or incidence)	95% confidence interval
Farmers/agricultural workers							
Blair and Thomas [42]	USA (Nebraska)	Farmers; cases: white men of 30 years or more with leukemia as recorded on death certificate as cause of death; controls: non-leukemic death; 1957–1974	*Source*: occupation as recorded on death certificate according to the 1950 and 1970 censuses; *Metrics*: (1) year of birth: 1869–1889, 1890–1900, 1901–1943, (2) level of county characteristic: high risk, low	Men	ML: 37 AML: 39 CML: 13 Unspecified ML: 11	OR (mortality): 0.94 1.06 0.88 1.19	0.52–1.70 0.60–1.84 0.37–2.10 0.44–3.27
Blair and White [43]	USA (Wiscontin)	Farmers; cases: white men of 30 years or more with leukemia as recorded on death certificate; controls: died from non-leukemic causes; 1968–1976	*Source*: usual occupation appearing on the death certificate, coded according to the 1960 census; *Metrics*: farming type: dairy or non-dairy farmers	Men	CML: 43 AML: 59	OR (mortality): 1.81 1.05	0.99–3.31 0.68–1.67
Brown et al. [44]	USA (Iowa and Minnesota)	Farmers; cases: all newly diagnosed cases among white men of 30 years or more with leukemia ascertained from tumor registry or hospital records; controls: population-based sample of white men without lymphatic or hematopoietic cancer selected from (a) random digit dialing for living control < 65 years, (b) Medicare records for living control ≥ 65 years, (c) state death certificate files for deceased control; 1981–1984	*Source*: subject or close relatives interviews using a standardized questionnaire; *Metrics*: (1) number of years farmed: 1–9, 10–29, 30–44, 45+, unknown, (2) ever use of type of pesticides: fungicides, herbicides, insecticides, (3) farming type: animal, crop, crop and animal	Men	CML: 27	OR (mortality and incidence): 1.1	0.6–2.0

Table 2 continued

Reference/exposure group	Location	Occupation or exposure group/case and control definition/(pesticide type)	Exposure assessment Source of exposure definition Metrics	Gender	ML subtype/ N. cases	Estimator of relative risk (mortality and/ or incidence)	95% confidence interval
Brownson and Reif [45]	USA (Missouri)	Farmers; cases: white men of 20 years and more as recorded in the Missouri Cancer Registry collecting data from public and private hospitals; controls: other cancer patients in the registry excluding people with smoking-related cancers and prostate cancer; 1984–1985	*Source*: occupational histories appearing on the Missouri Cancer Registry coded using the 1980 US census codes; *Metrics*: age groups: 20–64 years, 65+ years	Men	AML: 4 CML: 3	OR (incidence?): 0.65 1.53	0.23–1.85 0.43–5.42
Burmeister et al. [46]	USA (Iowa)	Farmers; cases: white men of 30 years or more with leukemia as recorded on death certificate; controls: non-leukemic death; 1968–1978	*Source*: usual occupation as recorded on the death certificate coded according to the 1960 census and to the US Bureau of Labor; pesticide usage provided by the 1964 agricultural census; *Metrics*: NR	Men	AML: 86 *CML: 46* Unspecified myeloid: 36	OR (mortality): 1.04 *1.04* 0.80	0.74–1.48 *0.65–1.65* 0.45–1.41
Ciccone et al. [47]	Italy (Torino, Northern Italy)	Farmers; cases: all newly diagnosed AML (50 cases), CML (17 cases) or MDS (19 cases) treated in the Main Hospital of Torino and aged 15–74 years; controls: (a) hospital-based: random sample of all patients newly diagnosed and treated in the hospital for medical or surgical conditions, (b) population-based: random sample of the population living in the city of Torino; 1989–1990	*Source*: occupational history from questionnaire interpreted by one industrial hygienist; exposure assessment based on information contained in the questionnaires, personal experience of the industrial hygienist and the rosters of the Occupational Health Unit where he works; *Metrics*: NR	Women	AML + CML + MDS: ?	OR (incidence): 3.4	1.3–8.9

Table 2 continued

Reference/exposure group	Location	Occupation or exposure group/case and control definition/(pesticide type)	Exposure assessment Source of exposure definition Metrics	Gender	ML subtype/ N. cases	Estimator of relative risk (mortality and/ or incidence)	95% confidence interval
Gajewski et al. [49]	Poland	Farmers; cases: all adults over 18 years old with leukemia residents of 12 towns with more than 100 thousand inhabitants; source: The Central Cancer Register of Institute of Oncology in Warsaw; controls for alive cases: sampled from 1978 Population Census; controls for deceased cases: sampled from the pool of death certificates at the Central Statistical Office of Poland; 1976–1980	*Source*: interviews by trained interviewers; questionnaire: place, type and duration of work, occupied position; *Metrics*: NR	Men + women	ML: ?	OR (mortality and incidence): 1.29	0.48–3.45*
					AML: ?	2.67	0.71–10.04*
					CML: ?	0.25	0.03–2.23*
Järvisalo et al. [50]	Finland	Occupation: agriculture; cases: AML patients aged 20 years and more reported to the Finnish Cancer Registry; controls: patients with another form of cancer (non-AML) except lung, urinary bladder and hematopoietic cancers; 1971–1977	*Source*: occupational title at the time of diagnosis reported on the registry and classified into 17 occupational categories; *Metrics*: NR	Men + women	AML: 114	OR (incidence): 0.96	0.72–1.29*
				Men	61	1.04	0.69–1.56*
				Women	53	0.87	0.57–1.32*
Mele et al. [51]	Italy (Rome, Bologna, Pavia)	Agricultural workers; cases: 15 years or older patients with newly diagnosed AML, ALL, CML and RAEB in three hospitals (Rome, Bologna, Pavia); controls: outpatients either normal or having non-neoplastic hematologic disorders and seen in the same hospitals; 1986–1990	*Source*: environmental exposure histories including occupational exposures from interviews following a questionnaire pilot-tested in a small sample; *Metrics*: selected occupations: agricultural workers, professional use of herbicides, prof. use of pesticides, greenhouse workers	Men + women	AML: 33	OR (incidence): 1.2	0.7–1.9
					CML: 28	1.5	0.9–2.6

Table 2 continued

Reference/exposure group	Location	Occupation or exposure group/case and control definition/(pesticide type)	Exposure assessment Source of exposure definition Metrics	Gender	ML subtype/ N. cases	Estimator of relative risk (mortality and/ or incidence)	95% confidence interval
Reif et al. [52]	New Zealand	Farmers; cases: men aged 20 years or more from The New Zealand Cancer Registry with a recorded occupation; controls: registrants for other sites; 1980–1984	*Source*: occupation defined in the National Cancer Registry as the individual's current or most recent occupation at the time of registration; *Metrics*: age groups: 20–50 years, 60+ years	Men	ML: 52 CML: ? Other ML: ?	OR (incidence): 1.44 1.60 3.33	1.05–1.96 0.93–2.76 1.10–10.04
Speer et al. [54]	USA (California)	Occupation: agricultural, forestry and fishing; cases: patients of all ages residents of Orange County at the time of diagnosis, from the Cancer Registry Information System; controls: patients with colon cancer from CRIS database; 1984–1993	*Source*: occupation coded according to the 1980 census coding system; risk factors coded by a trained professional nosologist; *Metrics*: NR	Men + women	AML: 2	OR (incidence): 1.34*	0.31–5.78*
Terry et al. [55]	USA and Canada	Farmers; cases: adult acute leukemia patients aged 17–79 years recruited through Cancer and Leukemia Group B; controls: selected using random digit dialing procedure; 1986–1989	*Source*: self- and proxy-interviews allowing classification of individuals as having been employed or not in occupational category potentially associated with leukemia risk; *Metrics*: (1) years of employment at occupation: ever, never, ≥ 1 year, (2) years of participation in hobby: never, ever, up to five years, 5+ years	Men + women	AML: 49	OR (incidence): 0.7	0.5–1.2

Table 2 continued

Reference/exposure group	Location	Occupation or exposure group/case and control definition/(pesticide type)	Exposure assessment Source of exposure definition Metrics	Gender	ML subtype/ N. cases	Estimator of relative risk (mortality and/ or incidence)	95% confidence interval
Others							
Adegoke et al. [40]	China (Shangai)	Occupational exposure to pesticides; cases: residents of urban Shangai diagnosed with leukemia at age 15 or older reported to the Shangai Cancer Registry; controls: randomly selected from the general urban Shangai population using the population-based Resident Registry 1987–1989	*Source*: interviews by trained interviewers using standardized Chinese questionnaires; self-reported information combined with job-exposure matrix assessment; *Metrics*: duration of exposure categories: never, ever, < 10 years, ≥ 10 years	Men + women	AML: 13 CML: 6	OR (incidence): 0.9 1.4	0.5–1.9 0.5–3.5
Björk et al. [41]	Sweden (southern)	Occupational, hobby or lifestyle exposures; cases: adult patients with Ph + CML cytogenetically analyzed at the Department of Clinical Genetics; controls: population of southern Sweden; 1976–1993	*Source*: structured telephone interviews; individual exposure assessment performed by occupational hygienists; *Metrics*: NR	Men + women	CML: 22	OR (incidence): 0.75	0.42–1.3
Ciccone et al. [47]	Italy (Torino, Northern Italy)	Occupational exposure to pesticides; cases: all newly diagnosed AML, CML or MDS treated in the Main Hospital of Torino and aged 15–74 years; controls: (a) hospital-based: random sample of all patients newly diagnosed and treated in the hospital for medical or surgical conditions, (b) population-based: random sample of the population living in the city of Torino; 1989–1990	*Source*: occupational history from questionnaire interpreted by one industrial hygienist; exposure assessment based on information contained in the questionnaires, personal experience of the industrial hygienist and the rosters of the Occupational Health Unit where he works; *Metrics*: NR	Women	AML + CML + MDS: 10 + 1 + 2	OR (incidence): 4.4	1.7–11.5

Table 2 continued

Reference/exposure group	Location	Occupation or exposure group/case and control definition/(pesticide type)	Exposure assessment Source of exposure definition Metrics	Gender	ML subtype/ N. cases	Estimator of relative risk (mortality and/ or incidence)	95% confidence interval
Flodin et al. [48]	Sweden	Exposure to pesticides; cases: identified at the hospitals of Linköping, Norrkoping, Orebro, Umea and Jonkoping, aged 20–70, alive, living in the catchment areas of the hospitals involved, and able to answer a questionnaire; controls: (a) from the general population register, (b) randomly selected from the same general population register of the catchment areas of the hospitals; 1977–1982	*Source*: exposure information obtained through a mailed questionnaire; *Metrics*: NR	Men + women	AML: 5	Crude rate ratio (incidence): 1.2	0.44–3.29
Richardson et al. [53]	France	Occupational exposure to pesticides; cases: more than 30 years old and resident in France, hospitalized in Paris and near Paris; controls: hospitalized in the same hospital in other departments 1984–1988	*Source*: exposures analyzed through a detailed questionnaire following a standardized interview and assessed by an industrial hygienist in a similar way to that used when building a job exposure matrix; *Metrics*: type of exposure: weed killers, weed killers: high (> 50% of the working time), medium (5–50% of the working time) exposure, insecticides	Men + women	AML: 16	OR (incidence): 1.38	0.73–2.62

Abbreviations: MA, meta-analysis; ML, myeloid leukemia; CML, chronic myeloid leukemia; AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; NR, not reported for ML with regards to pesticide exposure; OR, odds ratio; ?, number of cases not given or that can not be calculated; *calculated number of cases and/or estimator of relative risk and/or 95% confidence interval; italics: excluded data to avoid redundancy with more recent data

Table 3 χ^2 Woolf and *p*-value for homogeneity, pooled estimates of myeloid leukemia risk and 95% confidence intervals for several groupings of the data concerning pesticide exposed workers

Grouping	N. Studies	Pooled rate ratio	95% CI	Homogeneity	
				χ^2 Woolf	*p*-value
Cohort studies					
ML: All cohort studies	17	***1.21***	0.99–1.48	52.079	1.064×10^{-5}
By occupation					
Manufacturing workers	2	**6.32**	1.90–21.01	0.457	0.500 (fixed)
Pesticide applicators	5	**2.14**	1.39–3.31	2.736	0.603 (fixed)
Farmers/agricult. workers	9	1.03	0.86–1.23	26.795	7.669×10^{-4}
Horticulturists	*1*	*1.1*	*0.2–3.3*		
By ML subtype					
CML	3	2.00	0.62–6.43	7.115	2.851×10^{-2}
AML	5	**1.55**	1.02–2.34	13.748	8.146×10^{-3}
By gender					
Men	12	1.08	0.88–1.32	30.827	1.173×10^{-3}
Women	5	1.20	0.84–1.74	14.095	6.999×10^{-3}
By gender and ML subtype					
Men: AML	4	1.10	0.98–1.25	7.633	0.054 (fixed)
Women: AML	2	1.29	0.63–2.64	6.691	9.691×10^{-3}
Men: CML	2	1.02	0.86–1.20	0.549	0.459 (fixed)
Women: CML	*1*	*1.06*	*0.68–1.53*		
Case–control studies					
By ML subtype					
AML	12	1.00	0.87–1.17	7.391	0.767 (fixed)
CML	9	***1.25***	0.99–1.57	8.927	0.349 (fixed)
ML	4	**1.40**	1.09–1.81	5.065	0.167 (fixed)
By occupation and ML subtype					
Farmers/agric. work.:					
AML	9	0.99	0.84–1.16	6.166	0.629 (fixed)
CML	7	**1.38**	1.06–1.79	5.173	0.522 (fixed)
Occupational exp. to pest.:					
AML	3	1.14	0.75–1.73	0.835	0.641 (fixed)
CML	2	0.88	0.54–1.43	1.182	0.277 (fixed)
By gender and ML subtype					
Men: AML	5	1.00	0.83–1.20	0.865	0.930 (fixed)
Men: CML	5	**1.39**	1.03–1.88	2.660	0.616 (fixed)
Women: AML	*1*	*0.87*	*0.57–1.32*		
Cohort + case–control studies					
By ML subtype					
CML	12	1.11	0.97–1.26	17.598	0.091 (fixed)
AML	17	1.07	0.98–1.17	21.832	0.149 (fixed)
By occupation and ML subtype					
Farmers/agricult. workers:					
AML	12	1.06	0.97–1.16	18.060	0.080 (fixed)
CML	8	1.10	0.97–1.26	8.973	0.255 (fixed)
By gender and ML subtype					
Men: AML	9	1.08	0.97–1.20	8.768	0.362 (fixed)
Women: AML	3	1.12	0.72–1.75	7.770	0.021
Men: CML	7	1.09	0.95–1.26	6.368	0.383 (fixed)

Table 3 continued

Grouping	N. Studies	Pooled rate ratio	95% CI	Homogeneity	
				χ^2 Woolf	*p*-value
Women: CML	*1*	*1.06*	*0.68–1.53*		

Abbreviations: N. Studies, number of studies; 95% CI, 95% confidence interval; (fixed), fixed effects estimates, otherwise random effects estimates; pooled rate ratios are in bold when the 95% CI do not include 1 and in bold italics for borderline CI values (0.99–...); single studies data are presented as indicative in italics; ML, myeloid leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia

Cohort meta-analyses

The meta-RR for all cohort studies was 1.21 (95% CI: 0.99–1.48). A forest plot of the 17 cohort studies is reported in Fig. 2. The study of Ji and Hemminki [31] contributed 54% of the total weight. Removal of this study from the overall meta-analysis resulted in a meta-rate ratio of 1.32 (95% CI: 1.01–1.72). No other studies contributed more than 30% of the total weight. The strong heterogeneity existing among the 17 RR estimates (p value of 1.06×10^{-5}) argues against an overall meta-analysis of the data. Further analyses were therefore carried out to identify sources of heterogeneity, pooling studies according to different stratification variables.

Stratification of the studies by occupation indicated consistency among studies including manufacturing workers and pesticide applicators as evinced by p values for heterogeneity of 0.5 and 0.6, respectively, but not for farmers and/or agricultural workers (p value of 0.0008). For manufacturing workers (mRR: 6.32; 95% CI: 1.90–21.01) and pesticide applicators (mRR: 2.14; 95% CI: 1.39–3.31) relative risk estimators were statistically significantly increased.

Stratification of the studies by myeloid leukemia subtypes (chronic or acute) reduced heterogeneity but some variation across studies persisted as indicated by p values of 0.03 and 0.008, respectively. A significantly increased risk was observed for AML (mRR: 1.55; 95% CI: 1.06–2.26).

Stratification by gender (men or women) yielded no great difference between men (mRR: 1.08; 95% CI: 0.88–1.32) and women (mRR: 1.20; 95% CI: 0.84–1.74) and heterogeneity remained although reduced when compared with all cohort studies combined.

Crossing stratification by gender and myeloid leukemia subtypes strongly reduced heterogeneity for AML and CML in men (p values of 0.05 and 0.46, respectively). Meta-rate ratios higher than 1 were obtained but the confidence intervals included 1.

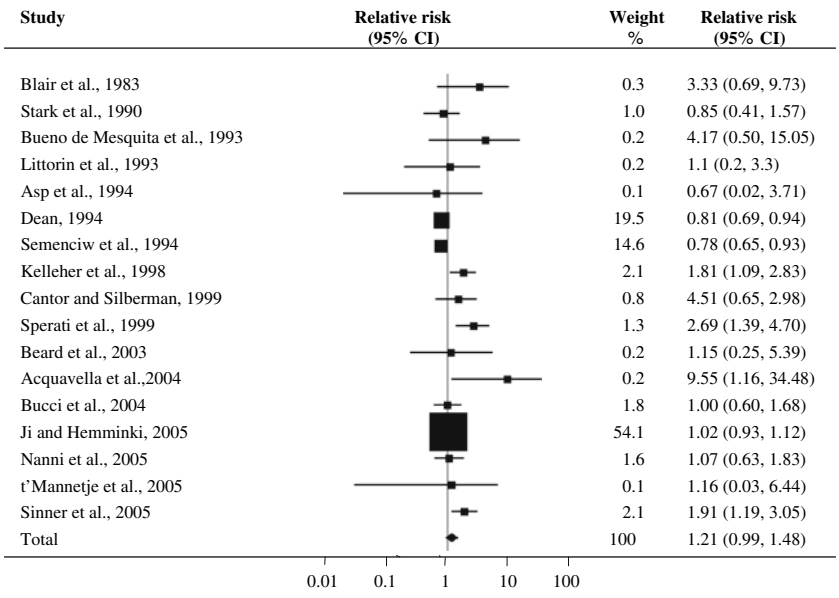

Fig. 2 Forest plot of cohort studies on myeloid leukemia among workers occupationally exposed to pesticides. *Note*. Estimators of RR and 95% confidence intervals (CIs) of cohort studies included in the overall meta-analysis are presented. Each estimator was assigned a weight (w_i) equal to the inverse square of its standard error (SE): $w_i = 1/(\mathrm{SE})^2$

Table 4 Results on ''high exposure to pesticides''

Reference	Study type	Results for any exposure			Results for high exposure			
		ML subtype/N. cases	Estimator of relative risk	95% confidence interval	High exposure*	ML subtype/N. cases	Estimator of relative risk	95% confidence interval
Acquavella et al. [23]	Cohort	CML: 2	SIR: 9.55	1.16–34.48	High exposure	CML: 2	SIR: 11.65	1.41–42.10
Beard et al. [25]	Cohort	ML: ?	SIR: 1.15	0.25–5.39	≥ 15 years employment	ML: ?	SIR: 20.90	1.54–284.41
Semenciw et al. [35]	Cohort	ML: ?	SMR: 0.78	0.65–0.93	Top exposure quartile	ML: ?	RR: 1.63	1.04–2.56
Brown et al. [44]	Case–control	CML: 27	OR: 1.1	0.6–2.0	Duration of farming > 45 years	CML: 5	OR: 1.0	0.4–3.1
Terry et al. [55]	Case–control	AML: 49	OR: 0.7	0.5–1.2	Years of employment at occupation ≥ 1 year	AML: 39	OR: 0.7	0.4–1.2
Adegoke et al. [40]	Case–control	AML: 11 CML: 5	OR: 1.0 1.3	0.5–2.0 0.5–3.7	Duration of occupational exposure ≥ 10 years	AML: 4 CML: 1	OR: 1.6 1.2	0.4–6.1 0.1–10.5

Abbreviations: ML, myeloid leukemia; CML, chronic myeloid leukemia; AML, acute myeloid leukemia; SMR, standardized mortality ratio; SIR, standardized incidence ratio; OR, odds ratio; RR, estimated relative risk; ?, number of cases not given or that can not be calculated

*High exposure definition in the different studies were as follows: Acquavella et al. [23]: each job for each worker corresponded to an occupational exposure category and was assigned a high, medium, low, or negligible qualitative exposure ranking

Beard et al. [25]: a subject's period of employment was used to estimate both the type of chemical he was likely to have been exposed to and the duration of this exposure. This was categorized into exposure group D0, D1, D2 and D3. D3 equates to ≥ 15 years of employment

Semenciw et al. [35]: four exposure categories were created based on exposure quartiles (based on self-reported farming exposure data)

Brown et al. [44]: risk of leukemia according to the number of years farmed (1–9, 10–29, 30–44, 45+) and ever use of pesticides

Terry et al. [55]: individuals were classified as having never or ever been employed in the occupational category (farming). Those with data regarding the duration of employment were further classified as having worked in that occupation less than one year, or one year or more

Adegoke et al. [40]: for self-report of exposures, analyses were by ever exposed versus never exposed and by the total number of years spent on jobs with exposure, i.e., < 10 years, and ≥ 10 years

Case–control meta-analyses

Meta-RR were calculated after grouping studies by ML subtype (AML, CML, ML), by occupation and ML subtype (farmers/agricultural workers and AML or CML; occupational exposure to pesticides and AML or CML) as well as by gender and ML subtype, combined (men and CML; men and AML). Women data were to scarce to allow stratification of the case–control studies. No evidence of heterogeneity existed among the different RR estimators combined. The highest meta-RR estimators with confidence intervals not including one were observed for CML among farmers/agricultural workers and for CML in men. A borderline statistically significant increased meta-RR was observed for CML.

Cohort and case–control studies

Stratification of the studies by ML subtype, by ML subtype and occupation as well as by ML subtype and gender could be performed, resulting in consistency among studies for all groupings except for AML in women. All calculated meta-RR were higher than 1 but none reached statistical significance.

Six studies (3 cohort studies and 3 case-control studies) reported 7 RR estimators of ML according to high exposure to pesticides. These results are summarized in Table 4. In the three cohort studies, higher estimators of relative risk were observed for the high exposure groups, all of them showing confidence intervals not including 1. Among the case–control studies, 1 out of 4 estimators of relative risk increased, 2 were slightly decreased and 1 did not change.

Funnel plot and assymetry

The visual inspection of Fig. 3 suggests some asymmetry arising from a lack of small studies with low RR estimators. The linear regression method of Egger et al. [21] which confirmed the suggested asymmetry (intercept 2.489; 95% CI: 0.4769–4.501; $p = 0.02$).

Discussion

Despite the large number of publications dealing with pesticide exposure and leukemias in general, only a few epidemiological studies focused on specific subtypes of the disease. In most cases, the findings were based on a small

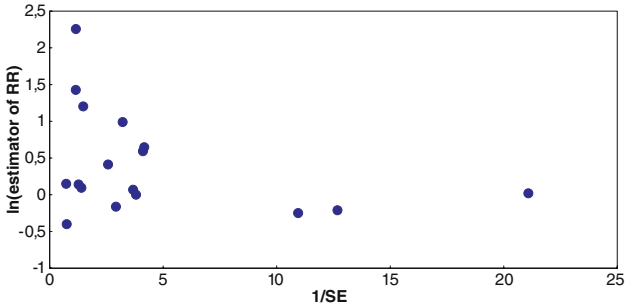

Fig. 3 Cohort studies of occupational pesticide exposure and myeloid leukemias: funnel plot of natural logarithms of relative risk (RR) estimates versus the inverse of their standard errors (1/SE) (lnRR of the 17 cohort studies combined = 0.194)

number of events in each nosological category leading to non-significant and inconsistent results.

The present study is, to our knowledge, the first meta-analytical approach to assess pesticide exposure as a potential occupational risk factor for adult myeloid leukemia.

The results did not clearly indicate evidence of an overall increased risk. Although almost all calculated meta-RRs were higher than 1, only a few showed a clear excess risk. After stratifying the studies by occupational group, evidence of an increased risk emerged from the cohort studies for manufacturing workers and pesticide applicators. From the case–control studies an increased risk of CML emerged for the farmers/agricultural workers. After stratification of the studies by ML subtype, an increased risk emerged for AML in cohort studies as well as a borderline increase for CML in case–control studies. The apparent discrepancy between some of these results does not allow to conclude firmly with regard to the existence of a relationship between myeloid leukemia and overall occupational pesticide exposure. A causal interpretation of the increased risk of ML has generally not been suggested by the authors of the individual studies.

A salient argument in favor of a causal relationship between pesticide exposure and occurrence of ML was that the strongest meta-RRs were observed for both occupational groups (manufacturing workers and pesticide applicators) likely to have been more frequently and intensely exposed to pesticides. Although no heterogeneity was found in the effects measured among cohort studies specifically dealing with these occupational groups, it should, however, be kept in mind that qualitative diversity among studies existed with regard to the likely chemical exposures, the definition of the cohort, the exposure contrast, the comparison population, and the leukemia subtype. This did not allow to isolate a specific pesticide or a particular occupational group within pesticide applicators or manufacturing workers more likely to be related to a ML subtype. The results were obtained by pooling a small number of cohort studies and could not be confirmed by case–control studies but most of the latter concerned farmers/agricultural workers and not manufacturing workers or pesticide applicators.

An increased risk of ML could not be linked to a specific chemical class of pesticide. Manufacturing workers' exposures were specific to alachlor [23] and phenoxy herbicides and chlorophenols [28]. Pesticide applicators handled a wider variety of pesticides (including chlorinated hydrocarbons, carbamates, organophosphates, phenoxyacetic acids, phthalimids, and coumarins) and pesticide use has also changed over the past several decades.

For causal inference it is also important to examine the risk according to a gradient of exposure. In the studies included in our analyses, data were available only for rough exposure-response analyses. Four studies presented exposure-response data using duration of exposure (years of employment, duration of occupational exposure) [25, 40, 44, 55], one study using exposure quartile [35] and one study using qualitative exposure ranking [23]. Duration of employment is often used as a surrogate of an increasing cumulative exposure potential. This assumes that exposure is uniform and continuous over the employment period, especially for pesticide exposure, but many circumstances challenge this assumption. The three cohort studies reported increased estimators of relative risk for high exposure as compared to corresponding results for any exposure.

There are also arguments against a causal interpretation of our results. Control of confounding by other occupational exposures and/or by non-occupational factors remains a concern as it is for virtually all studies in occupational settings. There are, however, few other known risk factors for ML (familial and genetic factors, environmental factors and medical and therapy related factors) and therefore few potential confounders that could have been controlled. Information on these risk factors was generally lacking in studies included in this meta-analysis.

Bias is also a serious concern in meta-analysis. We found evidence of funnel plot asymmetry among cohort studies (Fig. 3) which may lead to overestimate the real effect. The cohort studies that were included in the present meta-analysis did, however, not focus specifically on myeloid leukemia. Myeloid leukemia was reported among other cancer types as part of the results of specific population surveillance. As a consequence, the criticism of the meta-analysis method concerning the limited use of negative findings (less likely to be reported in peer reviewed sources) as well as the opposite criticism that positive studies of occupational hazards could be suppressed by economic forces are probably less relevant in the present meta-analysis. Furthermore, funnel plot asymmetry may have causes other than bias. A funnel plot should be seen as

a mean of examining the tendency for the smallest studies of low quality in a MA to show larger effects [56]. As a consequence, a sensitivity analysis was conducted by removing the smallest study results with imprecise values (weight $< 1.5\%$ and weight $< 10\%$, respectively) [data not shown]. The summary RR based on the remaining 7 and 3 large studies was 1.14 (95% CI: 0.86–1.27) and 0.87 (95% CI: 0.73–1.05), respectively, as compared with the RR of 1.21 (95% CI: 0.99–1.48) based on all the 17 cohort studies. The decreased summary RRs observed after removing studies with imprecise values suggests that ''small study effects'' can partially explain the borderline positive result of the MA of all cohort studies.

The influence of excluding each individual study on the pooled estimator of ML was examined. Pooled RRs obtained after removing each study in turn varied between 1.13 and 1.32. The magnitude of the effect observed varied, with the Sperati study appearing to be the most influential in terms of reduction in the point estimate for the pooled RR (1.13). The 95% CI became narrower when this study was removed because the between-study heterogeneity was reduced. Inference changed when other studies were removed, which was expected given that the initial result was already of borderline significance. A similar situation has been observed for leukemia among workers in the synthetic rubber-producing industry [57].

Exposure assessment is a critical component of epidemiologic research in occupational settings. It varied considerably among the studies included in the present MA. In an attempt to partially reduce this variability, studies were stratified by occupational categories although exposures within a same occupational group might also vary substantially.

The source to identify subjects as occupationally exposed to pesticides are reported in Tables 1 and 2 for cohort and case–control studies, respectively. The plant manufacturing alachlor [23] provided adequate job and department records to identify workers with specific pesticide exposure and the greatest confidence that workers were appropriately included. Manufacturing workers employed in plants producing or formulating a large number of chemicals [28] have a greater potential for misclassification of exposure. Pesticide applicators include various types of users (e.g., aerial pesticide applicators [29], licensed pesticide applicators [26, 37]), involved in different tasks (chemical brushwood control [24], structural pest control [26], agricultural chemicals spraying [29, 37, 39]). Workplace exposure was assessed by (job) records [24, 29] and by license or others registries [26, 37, 39]. Most cohorts of applicators used multiple classes of pesticides (e.g., chlorophenoxy herbicides, organophosphates, carbamates) and therefore contribute little information on the carcinogenic potential with respect to a specific pesticide or pesticide class but rather provide information regarding the health risk of the occupation [58]. Although studies of pesticide manufacturers or pesticide applicators tend to have more objective documentation of exposure (through exposure monitoring and job history), the diversity of exposure conditions cannot be taken into account because of the lack of detailed exposure data in the included studies. The problem is amplified in studies of occupational groups defined broadly as farmers or agricultural workers. Farm practices differ among regions, which leads to differences in type and degree of exposure. In the included studies, none of the farming variables directly measured exposure; all were surrogates. Exposure assessment methods were based on mortality or incidence registries [25, 27, 33, 34], censuses [30, 31], location of residence [36], individual reports [35] and farm membership [38] lists. These methods often suffer from a crude classification of exposure to potentially hazardous agents and potential for misclassification is a major limitation. Exposure overestimation is frequent and this misclassification may distort or dampen disease associations when there is a real underlying relationship between exposure and outcome. This may partially explain the lower risk observed for these occupational groups (Table 3).

All studies included workers ever employed in an occupation related to pesticide exposure but with different exposure assessments. An assumption that underlies our analyses is that all individuals included in these cohorts were exposed in their workplace.

The lack of adequate exposure definition and/or the variations in definitions of exposure across studies is a problem encountered in the vast majority of epidemiologic studies in occupational settings. Influential factors (like those related to pesticide application and behavior) should be incorporated into exposure estimates to reduce measurements error and to allow better resolution of the exposure distribution. Future work to develop exposure metrics that incorporate both chemical and exposure characteristics will contribute to improve these assessments [59].

Disease misclassification has also to be taken into consideration as the reporting of ML data in epidemiological studies has been variable. Most mortality studies refer to codes of the International Classification of Diseases (ICD). However, revisions of the ICD, periodically implemented according to advances in medical science, resulted in the introduction of more sophisticated coding systems. Thus, when ML data are reported, they may refer to some broader or narrower category. Specification of the ML subtypes (e.g., AML or CML) allows to partially reduce disease misclassification but this was made only by few authors. These difficulties with disease nomenclature contribute to

obscure the relationship between leukemia subtype and occupational exposure to pesticides.

Conclusion

Our results from cohort studies indicate some evidence that exposure encountered by manufacturing workers and pesticide applicators increases the risk of ML among these occupational groups. Further studies that would correlate reliable exposure data for these groups with well-defined subtypes of leukemia are needed to confirm this finding. The apparent discrepancy observed between cohort and case–control studies underscores again the need for further studies focusing on well-defined ML subtypes.

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