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Meta-analysis of Chemical exposure and increased risk of hematologic malignancies.

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Meta-analysis of Chemical exposure and increased risk of hematologic malignancies.

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Meta-analysis of Chemical exposure and increased risk of hematologic malignancies.

Abstract

Background: Exposure to environmental risk factors may be associated with the development of hematologic malignancies, as pointed by evidence in the literature. Despite this, most studies refer to a specific risk factor or disease.

Objective: To assess this issue globally, in this study we performed a meta-analysis.

Methods: A searched PubMed database was done in 2020 and a selection of 35 case-control and cohort studies published between 1990 and 2020 was done.

Results: Was observed a significant adverse association between exposure to organic solvents such as benzene and incidence of myeloid malignancies. For agricultural

chemicals (pesticides, herbicides, insecticides), an adverse association was found for both lymphoid and myeloid malignancies.

Conclusions: The results suggest that activities in chemical industries or agriculture pose greater risk and should be closely monitored. Prospective occupational surveys are needed to identify exposure–response relationships and clarify disease mechanisms.

Keywords: lymphoid; myeloid; risk; benzene; agriculture; smoking; indoor tanning; paint.

Introduction

Occupational and lifestyle-related exposures have been suggested as risk factors for the development of a multitude of hematologic malignancies. Generally, the associations tend to increase with longer duration of exposure, so that prolonged follow-ups are usually necessary to validate the exposure-outcome relationship [1]. Hematologic malignancies are characterized by the proliferation of clonal mature or immature cells, either myeloid or lymphoid, that tend to have a proliferative advantage opposed to the normal counterpart [2].

Chemicals that have been implicated in these diseases include organochlorines and phenoxyacetic acids that are commonly found in pesticides and herbicides [3-6]. For these compounds, in addition to occupational exposure there is a risk of consumption of contaminated food and drinking water [7]. Among environmental exposures, high-level benzene exposure is accepted as a cause of chromosome damage and acute leukemia (AL) [8-10]. Benzene's toxicity is related to cumulative dosage, and the risk of AL and myelodysplastic syndromes (MDS) was high before current occupational safety standards [11, 12].

In what concerns lifestyle-related exposures, cigarette smoking was linked to a small increase in risk for acute lymphoblastic leukemia (ALL) among adults [13]. In other two

reports, smoking was found to be a risk factor for acute myeloid leukemia (AML) and MDS [14, 15]. In addition, there are epidemiologic studies that implicate indoor tanning in the development of non-Hodgkin Lymphomas (NHL) [16, 17], however, this association was refuted by others [18, 19].

In the literature, specific jobs and hobbies that are related with an increased risk for the development of AML include those manufacturing or exposed to paint or hair dyes [13]. A number of other factors have been mentioned, including ionizing radiation, electromagnetic fields, or alcohol, to name a few, but the data is weak to support an association of any of these factors with an increased risk of hematologic neoplasms [20-23].

Although the evidence suggests an association between chemical exposures and hematologic malignancies, data is dispersed in the literature and many studies are focused on single risk factors, in individual diseases or a specific group of diseases. Here, to assess potential associations between exposure to a variety of environmental factors and the risk of developing hematologic neoplasms, we performed a meta-analysis.

Methods and Statistical analysis

Literature search

A literature search was performed in PubMed on the 16th of May 2019, with the keywords “risk factor and cancer and hematologic and (chemical OR pollution OR air OR water OR environmental) NOT childhood” with the filter language=“English” activated, and 592 abstracts were retrieved. The same search was repeated in May 2020, and 73 additional abstracts were screened to determine the suitability of each publication.

Of the total 665 works, 595 were excluded because they focused on secondary cancers or mentioned consequences and not causes of the cancer, such as

microbiological infections in cancer patients; others had no environmental risk factors associated or were not about cancer but rather about hematologic alterations in other diseases; some were performed in animal models, referred to solid cancers, to the paediatric population, or were reviews. For the remaining 70 works, the full-text articles were considered, and further 35 were excluded because there were no suitable data (either no cases, controls, or environmental data) (Figure 1).

Study selection

Studies included in this meta-analysis [3-6, 9, 10, 12-14, 18-43] had to meet all the following criteria: (a) the exposures of interest were chemical (benzene, other solvents), agricultural (pesticide, herbicide) and lifestyle (smoking, paint, indoor tanning); (b) the outcomes of interest were incidence of hematologic malignancies; (c) a cohort design or case-control design; (d) provide the risk and corresponding 95% confidence intervals (CIs) or data to calculate these. If there were multiple publications from the same study or overlapping study populations, the most recent and detailed study was eligible for inclusion in the meta-analysis. Details of the selected studies are provided in Table 1.

Data extraction

Data were collected independently by two authors using a predefined data collection form. The following data were extracted from each study and included in the final analysis: the study name (the first author's name and year of publication), country of origin, gender, age, study design, source of patients, number of cases/controls, risk factor assessment, matching covariates, and adjusted covariates. When necessary, the corresponding authors of the primary studies were contacted to obtain missing or insufficient data, and group consensus was used to resolve discrepancies.

Statistical analysis

When present, all within-study effect sizes were aggregated with agg function from MAD package (agg: Aggregate Dependent Effect Sizes,

https://rdrr.io/cran/MAd/man/agg.html), while considering the correlations among the within-study outcomes).

To determine whether to use the fixed- or random-effects model, we measured statistical heterogeneity. A fixed-effects model was used to calculate a pooled odds ratio (OR) with 95% CI when there was no heterogeneity. Otherwise, we calculated pooled ORs and confidence intervals assuming a random-effects model. The heterogeneity of ORs across individual studies was quantified by the Q statistic and the I2 score. P>0.1 for the Q-test was considered as a lack of heterogeneity among the studies. The I2 values of 25%, 50%, and 75% represented mild, moderate, and severe heterogeneity, respectively [44].

Potential publication bias was assessed by using Begg's funnel plots (rank correlation method where an asymmetrical plot suggested possible publication bias) [45] and Begg's bias test (a strong correlation implies publication bias P<0.05 indicated the presence of statistically significant publication bias) [46] and by calculating the 'fail-safe N', the number of additional 'negative' studies (studies in which the intervention effect was zero) that would be needed to increase the P value for the meta-analysis to above 0.05.

Sensitivity analysis was conducted, in which the meta-analysis estimates were calculated by sequential omission of every study in turn, so as to reflect the influence of the data from individual studies on the pooled ORs and evaluate the stability of the results. Subset analyses were performed by cell lineage type. All the statistical analyses were performed using software R version 3.6.1 © 2019, in RStudio environment Version 1.2.1578© 2009-2019 R Studio, Inc., where P<0.05 was considered statistically significant.

Results

A total of 35 case-control and cohort studies were included in the present work, on the association of agriculture, chemical and lifestyle exposures with the incidence of hematologic malignancies. These studies were published between 1990 and 2020 and were conducted in Europe, Asia and in the United States.

Risk estimation

Our analyses demonstrated a significant adverse association between agriculture and chemical exposures (exposed vs. non-exposed status) and incidence of hematologic malignancies. The results for agriculture exposure (OR = 1.48, 95%CI 1.26–1.74) are shown in Figure 2, and for chemical exposure (OR = 1.75, 95%CI 1.15–2.28) are presented in Figure 3. A statistically significant heterogeneity across studies was observed, for agriculture exposure (I2 = 85%, P<0.01) and for chemical exposure (I2 = 80%, P<0.01), and the summary OR were estimated using the random effects model.

Stratified analysis

We pooled the OR estimates of hematologic malignancies according to the cell type (lymphoid and myeloid lineage) and for each group of exposure (agriculture, chemical and lifestyle exposures). In this subset analyses, a statistically significant adverse effect of agriculture exposure on hematologic malignancies was observed for both lymphoid (OR = 1.38, 95%CI 1.11-1.72) and myeloid (OR = 1.79, 95%CI 1.28-2.50) disease groups. For the chemical exposure, a statistically significant adverse effect was observed for the myeloid diseases (OR = 2.15, 95%CI 1.63-2.85). In the lifestyle exposure group, a significant adverse effect was observed between smoking and incidence of myeloid diseases (OR = 2.45, 95%CI 1.61-3.73), which was not observed in paint and indoor tanning exposures (Table 2).

Publication bias

As reflected by the funnel plot (not shown), Begg's test, no asymmetry was discovered for agriculture (Begg's test, P = 0.175), chemical (Begg's test, P = 0.272), smoking (Begg's test, P = 0.188), paint (Begg's test, P = 0.09), or indoor tanning (Begg's test, P = 0.051).

Sensitivity analysis

We also carried out sensitivity analysis by sequentially excluding one study at a time to detect the influence of a single study on the overall estimate. The results demonstrated that no study disproportionately affected the summary risk estimates in this meta-analysis. The study-specific ORs were 1.34 (95%CI 1.27-1.40) for agriculture, 1.15 (95%CI 1.02-1.30) for chemical, 1.03 (95%CI 0.91-1.18) for smoking, 1.12 (95%CI 0.98-1.27) for paint and 1.01 (95%CI 0.80-1.27) for indoor tanning.

Discussion

Indoor and outdoor pollution has been associated with both acute and chronic human health conditions, including cancer [7]. We attempted to clarify the possible relationship between exposure to chemicals and the risk of developing hematologic malignancies, through a meta-analysis of case-control and cohort studies.

The results showed a significant adverse effect of the exposure to chemical compounds used in agriculture and hematologic malignancies. We also demonstrated a significant adverse association between exposure to benzene and other organic solvents. Regarding lifestyle exposures, the effect was observed in smoking but not in paint and indoor tanning groups. Our results are consistent with previous findings [19, 47, 48] but should be interpreted with caution, as there are some limitations in the present study. Since we have considered several studies within a timeframe of 30 years (1990-2020), it can be speculated that enforcement of regulations involving occupational exposures has altered the occupational risk profile. On the other hand, we

also considered studies with small sample size. By doing this meta-analysis we increased sample size and validated our findings with diverse populations.

Finally, one can argue that there is probably a lack of data consistency, which could compromise the ability to pool data in a standardized form. The designations of the different hematologic diseases, as well as their diagnosis, have changed through time, and some authors do not specify which disease is considered in each study. In order to overcome that, we have included several diseases in the same group, according to the cell lineage from which they are originated (either lymphoid or myeloid). The use of data from distinct geographical regions may also contribute to heterogeneity, and the fact that we could observe associations between environmental risk factors and hematologic malignancies, in spite these limitations, strengthens the approach and the results obtained.

As discussed previously, the great majority of the epidemiologic studies here considered are observational ones. This prevents the establishment of causal mechanisms between exposure variables and responses of interest.

Epidemiologic studies are often flawed because of small sample size and retrospective nature. In fact, there is a clear lack of carefully designed prospective epidemiologic studies, with large cohorts and prolonged follow-up, able to determine the validity of an association between a factor and a specific hematologic malignancy. As such, prospective planning of epidemiologic studies prior to any data collection is crucial to study accuracy. It would be interesting to perform a prospective national occupational survey and identify exposure–response relationships. This would allow to 1) better understand the underlying disease mechanisms triggered by the environment and, ultimately, 2) diminish their occurrence in the first place.

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Author contributions:

Conceptualization: GF, VA, RMS. Data curation: GF, AI, RMS. Formal analysis: VA, AI. Methodology: VA, AI, RMS. Project administration: VA, RMS. Visualization: AI. Writing – original draft: GF, AI. Writing – review & editing: GF, VA, AI, RMS.

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387 Table 1 – Main characteristics of studies evaluating the association between exposure and haematological disorders.

Study	Haematologic cell lineage	Country	Gender	Age	Study design	Number of cases	Number of controls
Agriculture							
Benavente (2018)[39]	Lymphoid	Spain	M/F	>18	Case-Control	560	1845
Brown (1990)[17]	Lymphoid	USA	M	>30	Case-Control	260	1245
Brown (1990)[17]	Myeloid	USA	M	>30	Case-Control	257	1245
Brown (1990)[17]	Not specified	USA	M	>30	Case-Control	578	1245
Ciccone (1993)[12]	Myeloid	Italy	M/F	15-74	Case-Control	86	246
Costas (2015)[35]	Lymphoid	Europe	M/F	>18	Case-Control	2178	2457
Fan (2012)[30]	Lymphoid	China	M/F	>18	Case-Control	147	294
Goldberg (1990)[18]	Myeloid	USA	-	28-88	Case-Control	52	52
Kokouva (2011)[13]	Lymphoid	Greece	M/F	27-73	Case-Control	133	455
Kokouva (2011)[13]	Myeloid	Greece	M/F	27-73	Case-Control	147	455
Kokouva (2011)[13]	Not specified	Greece	M/F	27-73	Case-Control	428	455
LV (2011)[14]	Myeloid	China	M/F	20-88	Case-Control	403	806
Mele (1994)[16]	Lymphoid	Italy	M/F	>15	Case-Control	100	1161
Mele (1994)[16]	Myeloid	Italy	M/F	>15	Case-Control	519	1161
Morton (2014)[34]	Lymphoid	Europe/North America/Australia	M/F	>18	Case-Control	17471	23096
Nisse (2001)[10]	Myeloid	France	M/F	>18	Case-Control	204	204
Pekmezovic (2006)[8]	Myeloid	Serbia Montenegro	M/F	18-85	Case-Control	80	160
Poynter (2017)[38]	Myeloid	USA	M/F	20-79	Case-Control	405	1348
Rigolin (1998)[11]	Myeloid	Italy	M/F	17-85	Case-Control	178	178

Slager (2014)[31]	Lymphoid	Europe/North America/Australia	M/F	>18	Case-Control	1595	11602
Smedby (2014)[33]	Lymphoid	Europe/North America/Australia	M/F	>18	Case-Control	331	9720
Strom (2005)[9]	Myeloid	USA	M/F	24-89	Case-Control	354	452
Wang (2014)[32]	Lymphoid	Europe/North America/Australia	M/F	>18	Case-Control	499	11490
West (1995)[15]	Myeloid	UK	M/F	>18	Case-Control	400	400
Zhang (2019)[41]	Lymphoid	China	M/F	>18	Case-Control	169	421
Chemical							
Costas (2015)[35]	Lymphoid	Europe	M/F	>18	Case-Control	2178	2457
Fan (2012)[30]	Lymphoid	China	M/F	>18	Case-Control	147	294
Hayes (1997)[29]	Lymphoid	China	M/F	>18	Cohort	90	1078
Hayes (1997)[29]	Myeloid	China	M/F	>18	Cohort	57	1078
Hayes (1997)[29]	Not specified	China	M/F	>18	Cohort	47	1078
Heavner (2015)[37]	Myeloid	USA	M/F	>42	Case-Control	54	472
Poynter (2017)[38]	Myeloid	USA	M/F	20-79	Case-Control	403	1344
Stenehjem (2015)[36]	Lymphoid	Norway	M/F	>18	Cohort	147	1661
Stenehjem (2015)[36]	Myeloid	Norway	M/F	>18	Cohort	31	1661
Stenehjem (2015)[36]	Not specified	Norway	M/F	>18	Cohort	112	1661
Zhang (2019)[41]	Lymphoid	China	M/F	>18	Case-Control	169	421
Teras (2019)[9]	Not specified	USA	M/F	>18	Cohort	2595	-
Indoor tanning							
Boffetta (2008)[24]	Lymphoid	Europe	M/F	>18	Case-Control	2028	2124
Grandin (2008)[23]	Lymphoid	France	M/F	>18	Case-Control	813	748

Hartge (2006)[27]	Lymphoid	USA	M/F	>18	Case-Control	551	462
Kelly (2010)[21]	Lymphoid	USA	M/F	>18	Case-Control	140	139
Smedby (2005)[28]	Lymphoid	Sweden and Denmark	M/F	>18	Case-Control	3740	3178
Smedby (2005)[28]	Not specified	Sweden and Denmark	M/F	>18	Case-Control	3740	3178
Veierod (2010)[22]	Lymphoid	Norway	F	>18	Cohort	158	104953
Wang (2017)[19]	Lymphoid	USA	F	20-79	Case-Control	1006	1038
Weihkopf (2007)[26]	Lymphoid	Germany	M/F	>18	Case-Control	710	710
Zhang (2007)[25]	Lymphoid	USA	F	>18	Cohort	601	717
Zhang (2013)[20]	Lymphoid	USA	F	>18	Cohort	4271	73358
Paint							
Mele (1994)[16]	Lymphoid	Italy	M/F	>15	Case-Control	100	1161
Mele (1994)[16]	Myeloid	Italy	M/F	>15	Case-Control	519	1161
Morton (2014)[34]	Lymphoid	Europe/North America/Australia	M/F	>18	Case-Control	17471	23096
Smedby (2014)[33]	Lymphoid	Europe/North America/Australia	M/F	>18	Case-Control	286	8150
Wang (2014)[32]	Lymphoid	Europe/North America/Australia	M/F	>18	Case-Control	454	9921
Zhang (2019)[41]	Lymphoid	China	M/F	>18	Case-Control	169	421
Smoking							
Benavente (2018)[39]	Lymphoid	Spain	M/F	>18	Case-Control	560	1845
Ben-Eli (2019)[42]	Lymphoid	Spain	M/F	>18	Case-Control	280	211
Fan (2012)[30]	Lymphoid	China	M/F	>18	Case-Control	147	294
Mele (1994)[16]	Lymphoid	Italy	M/F	>15	Case-Control	28	467
Mele (1994)[16]	Myeloid	Italy	M/F	>15	Case-Control	249	467

Zhang (2019)[41]	Lymphoid	China	M/F	>18	Case-Control	169	421

(-) Not referred.

Table 2 - Stratified pooled odds ratios of the relationship between agriculture, chemical and lifestyle exposures, and risk by cell-lineage type. The number of studies in each group is indicated. Note that some studies contribute with detailed information for more than one subgroup.

Exposure type/Cell-Lineage	No. studies	Effect size	CI low	CI high	I^2	P-value Cochran
Agriculture	**20**	**OR 1.48**	**1.26**	**1.74**	**85%**	**< 0.01**
Lymphoid	11	OR 1.38	1.11	1.72	91%	< 0.01
Myeloid	12	OR 1.79	1.28	2.50	78%	< 0.01
Haematological disorders not specified	2	OR 1.33	0.82	2.15	75%	= 0.05
Chemical	**8**	**OR 1.62**	**1.15**	**2.28**	**80%**	**< 0.01**
Lymphoid	5	OR 1.54	0.81	2.92	78%	< 0.01
Myeloid	4	OR 2.15	1.63	2.85	0%	< 0.53
Haematological disorders not specified	3	OR 1.40	0.90	2.16	61%	= 0.07
Lifestyle exposures						
Smoking	**5**	**OR 1.14**	**0.82**	**1.59**	**80%**	**< 0.01**
Lymphoid	5	OR 0.97	0.78	1.20	48%	= 0.11
Myeloid	1	OR 2.45	1.61	3.73	-	-
Paint	**5**	**OR 1.12**	**0.99**	**1.27**	**0%**	**= 0.61**
Lymphoid	5	OR 1.11	0.98	1.26	0%	= 0.51
Myeloid	1	OR 1.38	0.61	3.11	-	-
Indoor tanning	**10**	**RR 1.01**	**0.80**	**1.27**	**0%**	**= 1.00**
Lymphoid	10	RR 1.00	0.78	1.28	0%	= 0.29
Haematological disorders not specified	1	RR 1.09	0.61	1.95	-	-

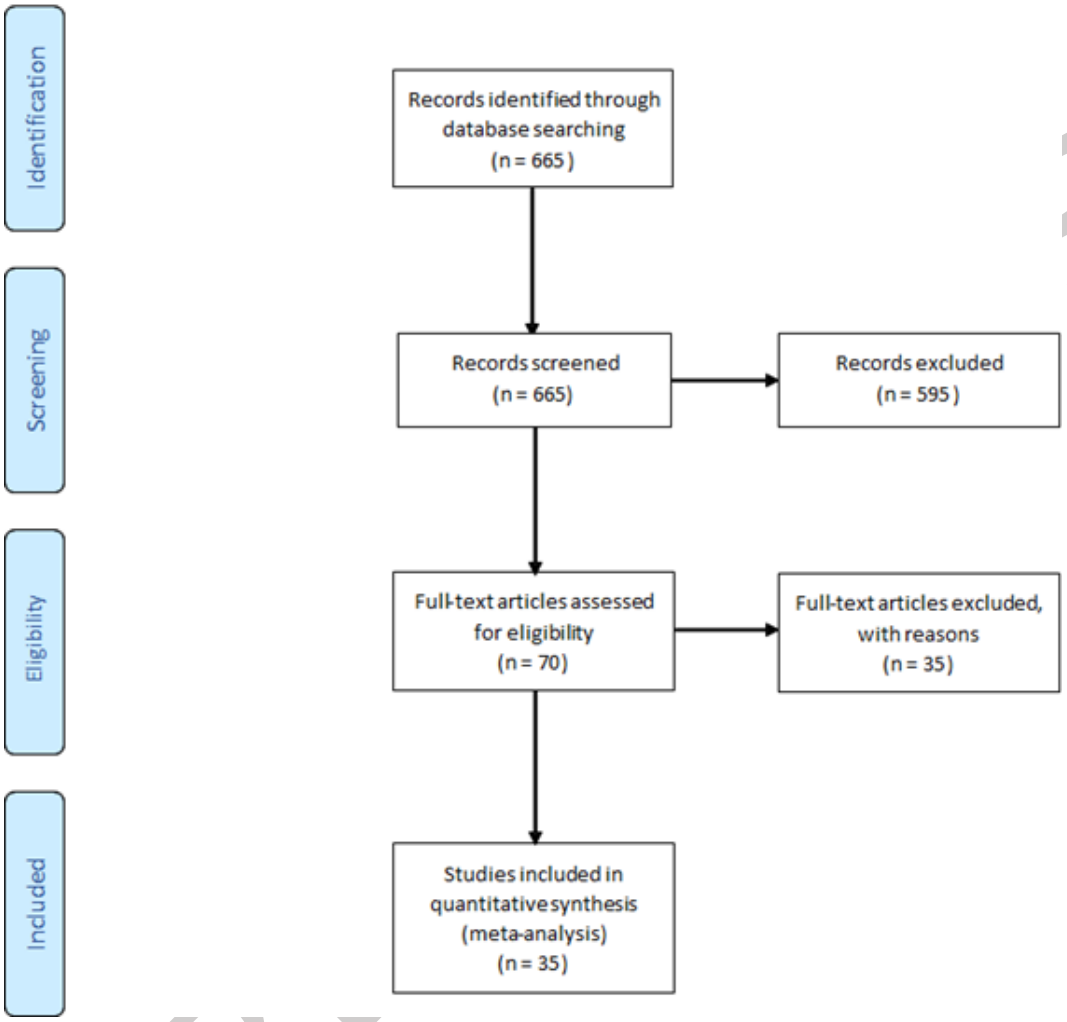

Figure 1- Study selection procedure. Of the 665 abstracts retrieved from the PubMed searches, 595 were excluded. Most had no environmental risk factors or were focused on secondary cancers and non-hematologic cancers. From the 70 full-text articles considered, 35 works had no suitable data and only the remaining 35 were included in the meta-analysis.

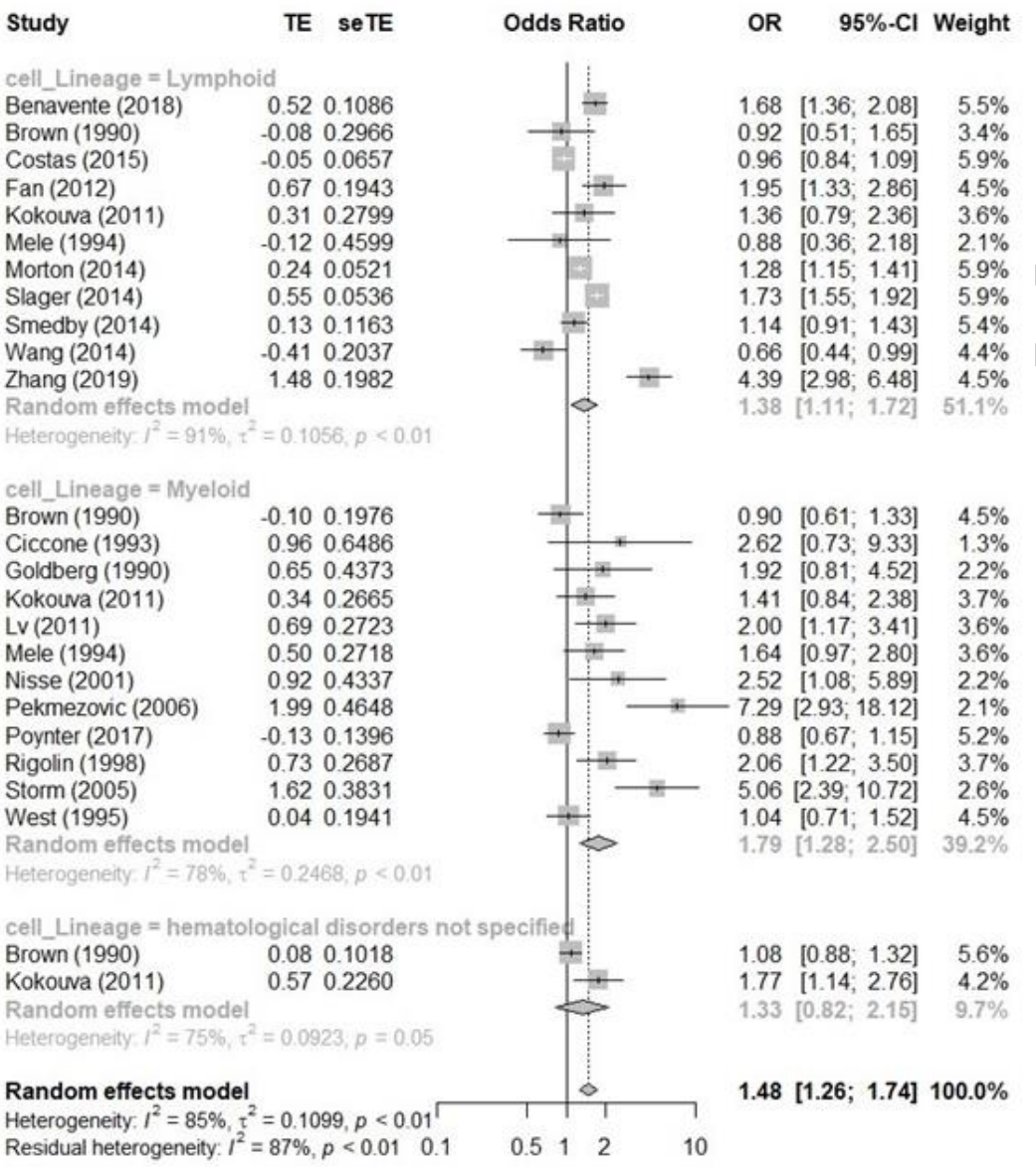

Figure 2 - A forest plot illustrating risk estimates from studies included in the analysis of agriculture exposure and the risk of development of lymphoid/myeloid malignancies.

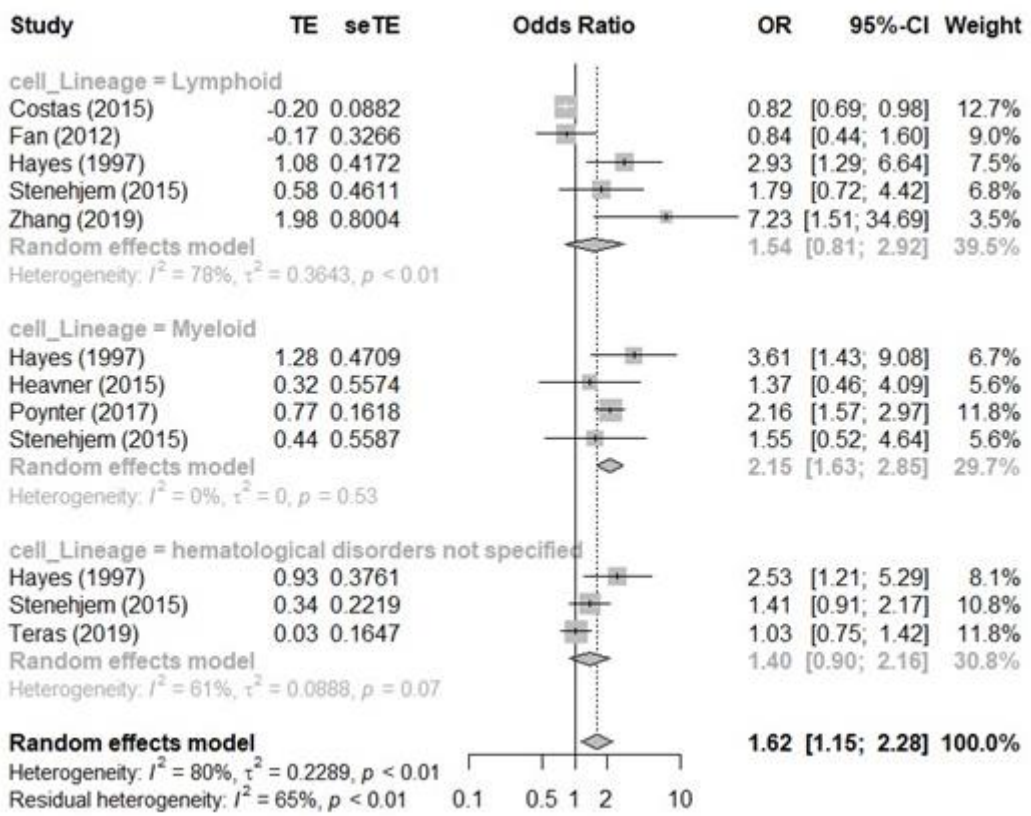

Figure 3 - A forest plot illustrating risk estimates from studies included in the analysis of chemical exposure and the risk of development of lymphoid/myeloid malignancies.