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REVIEW ARTICLE

The association between pesticide use and cutaneous melanoma: a systematic review and meta-analysis

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Abstract

Background The incidence of cutaneous melanoma (CM), the deadliest form of skin cancer, has gradually increased in the last decades among populations of European origin. Epidemiological studies suggested that farmers and agricultural workers are at an increased risk of CM because they were exposed to pesticides. However, little is known about the relationship between pesticides and CM.

Objectives To investigate the association between exposure to pesticides and CM by systematically reviewing the literature. Secondary aim was to determine the categories of pesticides mainly involved in CM development.

Methods A systematic review of the literature was performed up to September 2018 using MEDLINE, Embase and Web of Science. Studies assessing CM risk in licensed pesticide applicators were considered. Strict criteria were established to select independent studies and risk estimates; random effect models, taking into account heterogeneity, were applied. A pooled risk estimate for CM was calculated for the use of each type of pesticide and type of exposure. Between-study and estimate heterogeneity was assessed and publication bias investigated.

Results A total of nine studies (two case–controls and seven cohorts) comprising 184 389 unique subjects were included. The summary relative risks for the categories 'herbicides – ever exposure', 'insecticides – ever exposure', 'any pesticide – ever exposure' and 'any pesticide – high exposure' resulted 1.85 [95% confidence interval (CI): 1.01, 3.36], 1.57 (95% CI: 0.58, 4.25), 1.31 (95% CI: 0.85, 2.04) and 2.17 (95% CI: 0.45, 10.36), respectively. Herbicides and insecticides had no between-study heterogeneity ($I^2 = 0\%$), while a significant heterogeneity ($I^2 > 50\%$) was detected for the high exposure to any pesticide. No indication for publication bias was found.

Conclusions Individuals exposed to herbicides are at an increased risk of CM. Future properly designed observational studies are required to confirm this finding.

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Conflicts of interest

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Introduction

The Food and Agriculture Organization of the United Nations described the pesticides as 'any substance, or mixture of substances, or micro-organisms including viruses, intended for repelling, destroying or controlling any pest, including vectors of human or animal disease, nuisance pests, unwanted species of plants or animals causing harm during or otherwise interfering with the production, processing, storage, transport, or marketing of food, agricultural commodities, wood and wood products or animal feeding stuffs, or which may be administered to animals for the control of insects, arachnids or other pests in or on their bodies'.[1] The term includes substances intended for use as insect or plant growth regulators, defoliants, desiccants, agents for setting, thinning or preventing the premature fall of fruit, and substances applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport. In fact, the pesticides are considered ubiquitous and, although agriculture is the main user, these compounds are also sprayed on urban lawns and gardens, as well as in home.

Based on the target, pesticides are mainly grouped into herbicides, insecticides, fungicides, bactericides, rodenticides and fumigants (Table 1).[2]

In the last few years, the International Agency for Research on Cancer has listed some pesticides as carcinogens and a linkage between these compounds and different human cancers has been established in various epidemiologic studies (Table 2).[3–20] The mechanisms by which pesticides may be linked to cancers in humans are unclear, and carcinogenic properties of pesticides can be influenced by a series of complex factors comprising age, sex, individual susceptibility, duration of exposure and simultaneous contact to other tumour-causing agents.[21,22] Potential mechanisms include oxidative stress, DNA damage, chromosome aberration, mutation induction, immune response abnormality and chronic inflammation.[22]

Individuals may be exposed to pesticides by direct (during the preparation and application of pesticides) and/or indirect (through inhalation of residual air concentrations or exposure to residues found on surfaces, clothing, bedding, food, dust, discarded pesticide containers or application equipment) routes.[23]

In the last 30 years, several studies have reported possible associations between cutaneous melanoma (CM) and the environmental or professional exposure to a variety of elements and chemicals. A review published in 2008 highlighted the presence of a higher risk of developing CM in people employed in petroleum factories, graphic laboratories, electrics and electronics, who had contact with polychlorinated polycyclic aromatic hydrocarbons, benzene and/or polychlorinated biphenyls.[24] Moreover, biomedical research personnel and people employed in the clothing, metal and chemical industries seemed also at risk, due to the possible contact with trichloroethylene, as well as the paper and polyvinyl chloride workers who are commonly exposed to dioxin.[24] In addition, a recent meta-analysis suggested a slightly augmented risk of developing CM among oil/petroleum workers and an increased mortality among people employed in the oil/petroleum and chemical industry.[25] Hence, we performed a systematic review and meta-analysis to investigate the possible association between pesticide exposure and CM.

Methods

Reporting

This report followed the Meta-analysis of Observational Studies in Epidemiology guidelines.[26]

Information sources and search strategy

MEDLINE, Embase and Web of Science were searched by two independent authors (SG and MBDF) who selected the studies

Table 1 Categories of commonly used pesticides

Type of pesticide	Chemicals
Herbicide	Chlorophenoxy (dichlorprop, mecoprop, 2-methyl-4-chlorophenoxyacetic acid, 2,4-dichlorophenoxyacetic acid, 2,4,5-trichlorophenoxyacetic acid and dicamba), triazines (atrazine), amides (propanil), bipyridines (paraquat and diquat), thiocarbamates (*S*-ethyl-*N*,*N*-dipropylthiocarbamate and butylate), chloroacetanilides (alachlor, acetochlor and metolachlor), imidazolinones (imazethapyr), dinitroanilines (pendimethalin) and phosphonoglycines (glyphosate)
Insecticide	Organochlorines [dichlorodiphenylethanes (dichlorodiphenyldichloroethane, dichlorodiphenyltrichloroethane and dicofol), benzenes (lindane and hexachlorobenzene) chlorinated cyclohexanes, cyclodienes (aldrin, dieldrin, endosulfan, chlordane, heptachlor and toxaphene) and chlordecone (mirex)], organophosphates (chlorpyrifos, diazinon, fonofos, parathion and malathion), carbamates (carbaryl, aldicarb and aminocarb), pyrethroids (pyrethrins, permethrin, deltamethrin and cypermethrin), rotenone and microbiologicals (*Bacillus thuringiensis*)
Fungicide	Dithiocarbamates (maneb and mancozeb), benzimidazoles (benomyl), captan, captafol, pentachlorophenol, iprodione and sulphur
Bactericide	Chlorine, chlorine-releasing agents, dichloronitrobenzene and triazine-S-triones
Rodenticide	Anticoagulants (bromadiolone, chlorophacinone, difethialone, diphacinone, brodifacoum and warfarin), zinc phosphide, sodium fluoroacetate, bromethalin, cholecalciferol and strychnine
Fumigant	Methyl bromide and phosphine gas (magnesium phosphide and aluminium phosphide)

Table 2 Pesticides associated with elevated incidence of cancer in epidemiological studies

Type of cancer	Type of pesticide	Authors (Year) [Reference]
Leukaemia	Chlordane and heptachlor	Purdue *et al.* (2007)[3]
	Chlorpyrifos	Lee *et al.* (2004)[4]
	Diazinon	Beane Freeman *et al.* (2005)[5]
	S-ethyl-*N*,*N*-dipropylthiocarbamate	van Bemmel *et al.* (2008)[6]
	Fonofos	Mahajan *et al.* (2006)[7]
Non-Hodgkin's lymphoma	Lindane	Purdue *et al.* (2007)[3]
	Oxychlordane and chlordane	Spinelli *et al.* (2007)[8]
Multiple myeloma	Permethrin	Rusiecki *et al.* (2009)[9]
Brain cancer	Chlorpyrifos	Lee *et al.* (2004)[4]
Prostate cancer	Fonofos	Mahajan *et al.* (2006)[7]
	Methyl bromide	Alavanja *et al.* (2005)[10]
	Butylate	Lynch *et al.* (2009)[11]
	Chlordecone	Multigner *et al.* (2010)[12]
	Dichlorodiphenyltrichloroethane, lindane and simazine	Band *et al.* (2011)[13]
Colon cancer	Aldicarb	Lee *et al.* (2007)[14]
	Dicamba	Samanic *et al.* (2006)[15]
	S-ethyl-*N*,*N*-dipropylthiocarbamate	van Bemmel *et al.* (2008)[6]
	Imazethapyr	Koutros *et al.* (2009)[16]
Rectum cancer	Chlordane	Purdue *et al.* (2007)[3]
	Chlorpyrifos	Lee *et al.* (2004)[4]
	Aldicarb	Lee *et al.* (2007)[14]
	Pendimethalin	Hou *et al.* (2006)[17]
Pancreatic cancer	*S*-ethyl-*N*,*N*-dipropylthiocarbamate and pendimethalin	Andreotti *et al.* (2009)[18]
	Dichlorodiphenyltrichloroethane	Garabrant *et al.* (1992)[19]
Lung cancer	Chlorpyrifos	Lee *et al.* (2004)[4]
	Diazinon	Beane Freeman *et al.* (2005)[5]
	Dicamba	Samanic *et al.* (2006)[15]
	Dieldrin	Purdue *et al.* (2007)[3]
	Metolachlor and pendimethalin	Alavanja *et al.* (2004)[20]
	Pendimethalin	Hou *et al.* (2006)[17]
Bladder cancer	Imazethapyr	Koutros *et al.* (2009)[16]

and extracted relevant data. Disagreements were resolved by discussion between these two reviewers. Search strategy adopted was similar across the databases, and it was developed using the keywords: 'pesticides' [Medical Subject Headings (MeSH) terms] OR 'pesticides' [All Fields] OR 'pesticides' [Text Word] AND 'melanoma' [MeSH Terms] OR 'melanoma' [All Fields] OR 'melanoma' [Text Word]. To identify any additional studies, relevant reference lists of articles were also screened. The search was conducted for the period from 1 January 1964 through 30 September 2018.

Study selection

The search was limited to human studies, and there was no language restriction. After suppressing duplicate publications, ecological studies, case reports, editorials and studies regarding one specific subtype of CM such as acral melanoma were not included. Review articles not reporting original data were also excluded but checked for references.

Titles and abstracts were screened for the evaluation of a possible association between pesticide exposure and CM. If the abstract content was relevant, full copies of articles were retrieved and fully read by at least two authors.

In order to reduce between-study heterogeneity in terms of types of exposure, substances and populations, the analysis was conducted considering only the licensed pesticide applicators, while the pesticide users without licence or only potentially exposed were excluded from the study. Licensed pesticide applicators are classified by the United States Environmental Protection Agency as either private (individual who uses or supervises the use of any pesticide that is classified for restricted use for purposes of producing any agricultural commodity on property owned or rented by him or his employer) or commercial (any person who has completed the requirements for certification to use or supervise the use of any pesticide for any purpose or on any property other than as provided in the definition of private applicator; information available from https://www.epa.gov/

pesticide-worker-safety/federal-certification-standards-pesticide-applicators). In the European Union (EU), pesticides are only sold to professional pesticide users (any person who uses pesticides in the course of their professional activities, including operators, technicians, employers and self-employed people, both in the farming and other sectors), distributors and advisors, all of whom receive proper training in handling these substances and possess a certificate proving appropriate professional knowledge (information available from https://ec.europa.eu/food/plant/pesticides/sustainable_use_pesticides_en). Only specifically authorized products in the EU will be available for sale to non-professional users.

The inclusion criteria were as follows:

1 Studies providing sufficient information to obtain a risk estimate and 95% confidence interval (CI) for the association between pesticide use/contact and melanoma incidence [odds ratio (OR), risk ratio, rate ratio, standardized incidence ratio (SIR) or crude data and corresponding standard errors, variance, CI or *P*-value of the significance of the estimates].
2 Studies had to be independent and not duplicate results published in another article. When several articles concerned the same cohort, we chose the study to be included following these criteria:
   a The one with the largest sample of subjects/events.
   b The one with the longest follow-up.
   c The one with fully adjusted estimates.

If no estimates for 'any pesticide' were presented, we included one estimate concerning a specific pesticide. Criteria to select estimates to be included when more estimates were presented from the same study were as follows:

1 The one with the largest sample of subjects/events.
2 The one with estimates separated by gender (to investigate differences by gender when possible).
3 The one of commercial applicators.

Data extraction

A standardized data-collection protocol was used for gathering the relevant data from each selected article. Data extraction was done in a predefined database. For each study selected for this meta-analysis, we pulled out information on authors, journal and year of publication, country, types of exposure, type of pesticide, source of controls (hospital or population), number of cases and controls and confounders considered in the analysis.

Outcome

The outcome of this meta-analysis was the evaluation of the relationship between pesticide use and CM. Our analyses addressed two questions:

1 Is there a significant association between use of pesticides and melanoma risk?
2 Is one or more categories of pesticides mainly involved?

Quality assessment

Two authors (VDM and IS) independently assessed the methodological quality of the included studies using the Newcastle Ottawa scale (NOS, available from http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). A maximum of 10 and 9 points was given for case–control (four for the selection of cases and controls, two for the comparability, and four for the ascertainment of exposure) and cohort studies (four for the selection of the exposed cohort, two for the comparability, and three for the ascertainment of outcome), respectively.

Statistical analysis

Since melanoma is a relatively rare disease, the distinction between the various risk estimates (i.e. OR, rate ratio, risk ratio and SIR) was ignored and all measures were interpreted as relative risk. Every measure of association, adjusted for the maximum number of confounding variables, and corresponding CIs were transformed into log relative risks, and the corresponding variance was calculated using the formula proposed by Greenland.[27] When no estimates were given, crude estimates were calculated from tabular data. Woolf's formula was used in order to evaluate the standard error of the log relative risk.

The summary relative risk (SSR) was estimated by pooling the study-specific estimates with random effects models.[28] CIs were computed assuming an underlying t-distribution.

The homogeneity of the effects across studies was assessed using the large sample test based on the chi-square statistic. Since the chi-square test has limited power, we considered statistically significant heterogeneity at the $P = 0.10$ level of association. A further measure of heterogeneity (I^2) has been considered in order to compare between-study heterogeneity for different numbers of pooled studies. It can be interpreted as the percentage of total variation across several studies that is attributable to heterogeneity: larger values of I^2 indicate greater heterogeneity.[29] A threshold of I^2 below 50% is generally considered an acceptable level of variability.

The SRRs were presented separately for each type of pesticide and type of exposure (ever use and high use vs. none). Moreover, forest plots including both the study-specific and the pooled risk estimates were produced.

Heterogeneity was investigated through meta-regression, subgroup analyses and sensitivity analyses looking at gender, study design and latitude, adjustments for confounders as proxy of sun exposure.

Publication bias was evaluated graphically with a funnel plot, and the Macaskill test was conducted,[30] which is more powerful when <20 estimates are included in the analysis.

All the statistical analyses were performed using SAS® software version 9.2 (SAS Institute, Cary NC, USA) and R software version 2.12.2 (http://www.r-project.org).

Results

Study selection

The literature search retrieved 42 articles after duplicate publications were removed. We reviewed the bibliography of all these articles, and 47 additional articles were included. Therefore, a total of 89 full-text articles were assessed and, as reported in the flow chart of the study selection (Fig. 1), 59 full-text articles were excluded. The remaining 30 articles were considered eligible for the analysis estimates comparing 'exposed' vs. 'unexposed' subjects, independently of type of pesticide.[3–7,9–11,15–17,31–49] The major features of these studies are summarized in Table 3.

Finally, 21 full-text articles were excluded due to the overlapping populations and a total of nine studies (two case–controls and seven cohorts) were therefore included in the meta-analysis.[10,31–33,36,41,43,46,49]

The quality score of these studies assessed using the NOS ranged from 6 to 9 (Table 4). All selected studies had a NOS score ≥6 and were considered medium/high quality.

Study characteristics

The nine included studies comprised 184 389 unique subjects. Characteristics of the studies included in the meta-analysis are summarized in the Table 4.

Alavanja *et al.*[10] conducted a cohort study [Agricultural Health Study (AHS)] of 89 658 individuals including 52 395 private applicators (farmers or nursery workers) from Iowa and North Carolina, 4916 commercial applicators (people employed by pest control companies or businesses that use pesticide applications) from Iowa, and the 32 347 spouses of private applicators. Cancer incidence was ascertained by linking the cohort to the population-based cancer registries in Iowa and North Carolina. CM resulted significantly elevated among the spouses of the private applicators (SIR: 1.64, 95% CI: 1.27–2.09) but not among the private or commercial applicators. However, the spouses were not considered in the present study because they did not hold pesticide application licences and they reported a personal use of pesticides far less than the private or commercial applicators (only 9% of the spouses used pesticides >10 days/year).

Zhong and Rafnsson[31] performed a cohort study of 2449 Icelandic workers in the agricultural sphere comprising 1860 males and 589 females but, due to the lack of women's risk estimate for CM, only the men who were ever exposed to any pesticides were included in our study. The cohort was followed-up in the Icelandic Cancer Registry from the date individuals became licensed pesticide users, and the observed number of cancers was compared with expected values calculated on the basis of cancer incidence in Iceland.

Lynge[32] conducted a cohort study of 2119 Danish certified pesticide users including 940 individuals employed in the chlorophenoxy herbicide manufacturing and packaging departments and 1179 in manual service function. The main products

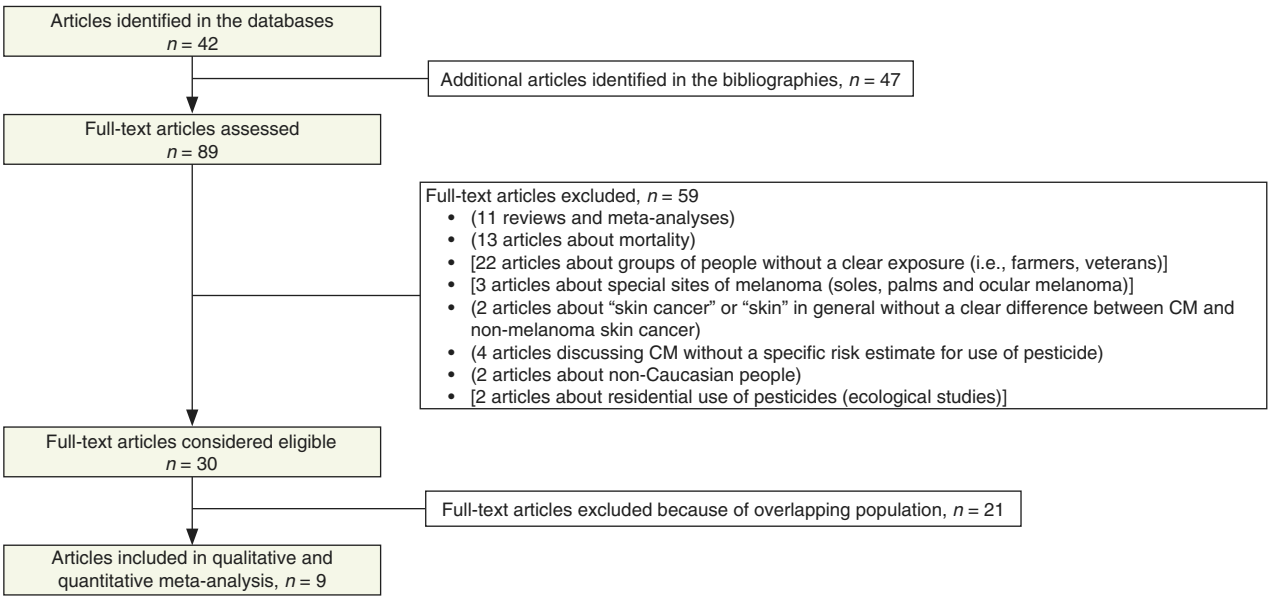

Figure 1 Flow chart showing selection of studies for meta-analysis.

Table 3 Risk estimate and 95% confidence interval (CI) for the 30 selected articles

Authors (Year) [Reference]	Gender	Pesticide	Exposure	Risk estimate (95% CI)	Adjustment
Purdue *et al.* (2007)[3]	M	Any pesticide	Ever use	Rate ratio 0.8 (0.5–1.2)	Adjusted for age, state, sex, education level, smoking history, alcohol consumption, family history of cancer and lifetime days of total pesticide application
	M	Aldrin (I)	Ever use	Rate ratio 1.1 (0.7–2)	
	M	Chlordane (I)	Ever use	Rate ratio 1.0 (0.6–1.7)	
	M	DDT (I)	Ever use	Rate ratio 1.0 (0.6–1.6)	
	M	Dieldrin (I)	Ever use	Rate ratio 1.4 (0.7–2.9)	
	M	Heptachlor (I)	Ever use	Rate ratio 1.6 (0.9–2.8)	
	M	Lindane (I)	Ever use	Rate ratio 1.3 (0.7–2.2)	
	M	Toxaphene (I)	Ever use	Rate ratio 1.3 (0.7–2.3)	
	M	Toxaphene (I)	LED	Rate ratio 2.9 (1.1–8.1)	
	M	Toxaphene (I)	IWLD	Rate ratio 1.8 (0.7–5.1)	
	M	Organochlorine (I)	LED	Rate ratio 1.3 (0.5–3.1)	
	M	Organochlorine (I)	IWLD	Rate ratio 1.0 (0.4–2.5)	
Lee *et al.* (2004)[4]	M	Chlorpyrifos (I)	Ever use	Rate ratio 1.11 (0.65–1.88)	Adjusted for age, year of enrolment, state, sex, education level, smoking history, alcohol consumption, family history of cancer and exposure to the four pesticides most highly correlated with Chlorpyrifos (Alachlor, Carbofuran, Fonofos and Trifluralin)
Beane Freeman *et al.* (2005)[5]	M	Diazinon (I)	LED	Rate ratio 0.71 (0.16–3.04)	Adjusted for age, state, education level, smoking history, family history of cancer and lifetime days of any pesticide application
	M	Diazinon (I)	IWLD	Rate ratio 0.62 (0.14–2.67)	
van Bemmel *et al.* (2008)[6]	M	EPTC (H)	LED	Rate ratio 0.79 (0.31–2.02)	Adjusted for age, state, race, smoking history, alcohol consumption, family history of cancer, applicator type and lifetime days of total pesticide application
	M	EPTC (H)	IWLD	Rate ratio 1.35 (0.71–2.55)	
Mahajan *et al.* (2006)[7]	M	Fonofos (I)	IWLD	Rate ratio 1.17 (0.48–2.83)	Adjusted for age, state, smoking history and exposure to the four pesticides most highly correlated with Fonofos (Carbofuran, EPTC, Trichlorofon and Imazethapyr)
Rusiecki *et al.* (2009)[9]	M	Permethrin (I)	LED	Rate ratio 0.79 (0.35–1.83)	Adjusted for age, year of enrolment, state, sex, race, smoking history, family history of cancer and lifetime days of total pesticide application
	M	Permethrin (I)	IWLD	Rate ratio 0.84 (0.37–1.93)	
Alavanja *et al.* (2005)[10]	M and F	Any pesticides (private applicators)	Ever use	SIR 0.95 (0.78–1.16)	Not adjusted
	M and F	Any pesticides (commercial applicators)	Ever use	SIR 1.05 (0.42–2.17)	
Lynch *et al.* (2009)[11]	M	Butylate (H)	LED	Rate ratio 1.75 (0.81–3.78)	Adjusted for age, sex, race, education level, smoking history and family history of cancer
	M	Butylate (H)	IWLD	Rate ratio 1.19 (0.5–2.85)	
Samanic *et al.* (2006)[15]	M	Dicamba (H)	LED	Rate ratio 0.83 (0.33–2.13)	Adjusted for age, state, education level, smoking history, family history of cancer and lifetime days of total pesticide application
	M	Dicamba (H)	IWLD	Rate ratio 0.77 (0.28–2.07)	
Koutros *et al.* (2009)[16]	M	Imazethapyr (H)	IWLD	Rate ratio 1.08 (0.49–2.37)	Adjusted for age, year of enrolment, race and family history of cancer
Hou *et al.* (2006)[17]	M	Pendimethalin (H)	LED	Rate ratio 1.3 (0.4–3.8)	Adjusted for age, year of enrolment, state, sex, education level, smoking history, alcohol consumption, family history of cancer and exposure to the five pesticides most highly correlated

Table 3 *Continued*

Authors (Year) [Reference]	Gender	Pesticide	Exposure	Risk estimate (95% CI)	Adjustment
					with Pendimethalin (Ziram, Dieldrin, Butylate, Chlorimuron ethyl and Metribuzin)
Zhong and Rafnsson (1996)[31]	M	Any pesticides	Ever use	SIR 1.15 (0.02–6.4)	Not adjusted
Lynge (1998)[32]	M	Dichlorprop (H), Mecoprop (H) and MCPA (H)	Ever use	SIR 1.23 (0.4–2.9)	Not adjusted
Acquavella *et al.* (2004)[33]	M and F	Alachlor (H)	Ever use	SIR 2.78 (1.02–6.06)	Adjusted for age, sex, race and calendar period
	M and F	Alachlor (H)	High exposure	SIR 2.29 (0.62–5.87)	
Lee *et al.* (2004)[34]	M	Alachlor (H)	Ever use	Rate ratio 1.59 (0.83–3.05)	Adjusted for age, year of enrolment, state, sex, education level, smoking history, alcohol consumption, family history of cancer and exposure to the five pesticides most highly correlated with Alachlor (Metolachlor, Atrazine, Cyanazine, Trifluralin and 2,4-D)
	M	Alachlor (H)	Ever use	SIR 1 (0.7–1.37)	
De Roos *et al.* (2005) [35]	M	Glyphosate (H)	Ever use	Rate ratio 1.6 (0.8–3)	Adjusted for age, year of enrolment, state, education level, smoking history, alcohol consumption, family history of cancer, the five pesticides for which cumulative exposure-day variables were most highly associated with Glyphosate cumulative exposure-days (Alachlor, 2,4-D, Atrazine, Metolachlor and Trifluralin) and the five pesticides most highly associated with ever use of Glyphosate (Benomyl, Maneb, Paraquat, Carbaryl, Diazinon)
	M	Glyphosate (H)	LED	Rate ratio 0.9 (0.5–1.8)	
	M	Glyphosate (H)	IWLD	Rate ratio 0.7 (0.2–1.2)	
Kennedy *et al.* (2005)[36]	M	Any pesticides	Low exposure	OR 1.2 (0.5–2.6)	Adjusted for age, skin type and smoking history
	M	Any pesticides	High exposure	OR 0.5 (0.2–1.5)	
	M	Insecticides	Ever use	OR 1.1 (0.5–2.6)	
	M	DDT (I)	Ever use	OR 0.8 (0.3–2.4)	
	M	Parathion (I)	Ever use	OR 0.9 (0.2–3.4)	
Bonner *et al.* (2007)[37]	M	Malathion (I)	LED	Rate ratio 0.48 (0.17–1.30)	Adjusted for age, year of enrolment, state, sex, education level, smoking history, alcohol consumption and family history of cancer
	M	Malathion (I)	IWLD	Rate ratio 0.47 (0.17–1.28)	
	M	Malathion (I)	Frequency (<5 days of use per year)	Rate ratio 0.94 (0.46–1.94)	
	M	Malathion (I)	Frequency (≥5 days of use per year)	Rate ratio 0.66 (0.27–1.62)	
	M	Malathion (I)	Duration (≤10 years)	Rate ratio 0.84 (0.41–1.72)	
	M	Malathion (I)	Duration (>10 years)	Rate ratio 0.86 (0.34–2.18)	
Mahajan *et al.* (2007)[38]	M and F	Carbaryl (I)	LED	Rate ratio 4.11 (1.33–12.75)	Adjusted for age, state, sex, smoking history and exposure to the four pesticides most highly correlated with Carbaryl (Diazinon, Chlordane, Malathion and Dieldrin)
	M and F	Carbaryl (I)	Frequency (1–4 days of use per year)	Rate ratio 2.00 (0.99–4.05)	
	M and F	Carbaryl (I)	Frequency (5–9 days of use per year)	Rate ratio 3.02 (1.23–7.39)	
	M and F	Carbaryl (I)	Frequency (≥10 days of use per year)	Rate ratio 5.50 (2.19–13.84)	
	M and F	Carbaryl (I)	Duration (≤10 years)	Rate ratio 2.34 (1.22–4.50)	
	M and F	Carbaryl (I)	Duration (>10 years)	Rate ratio 3.19 (1.28–7.92)	
Bonner *et al.* (2010)[39]	M and F	Terbufos (I)	IWLD	Rate ratio 0.88 (0.46–1.68)	Adjusted for age, year of enrolment, state, sex, education level, smoking history, alcohol consumption, family

Table 3 *Continued*

Authors (Year) [Reference]	Gender	Pesticide	Exposure	Risk estimate (95% CI)	Adjustment
					history of cancer and the five pesticides most highly correlated with Terbufos (Atrazine, Fonofos, Carbofuran, 2,4-D and Phorate)
Koutros *et al.* (2010)[40]	M and F	Any pesticides (private applicators)	Ever use	SIR 0.89 (0.76–1.03)	Not adjusted
	M and F	Any pesticides (commercial applicators)	Ever use	SIR 1.09 (0.58–1.86)	
Dennis *et al.* (2010)[41]	M and F	Benomyl (F)	IWLD (<133 exposure-days)	OR 1 (0.4–2.2)	Adjusted for age, sex, tendency to burn, red hair, sun exposure (≤2 h/day, ≥3 h/day) and BMI at 20 years of age
	M and F	Benomyl (F)	IWLD (≥133 exposure-days)	OR 2.8 (1.2–6.5)	
	M and F	Benomyl (F)	Ever use	OR 1.2 (0.7–2.1)	Adjusted for age and sex using IWLD
	M and F	Benomyl (F)	Ever use (not exposed to lead arsenate)	OR 0.7 (0.3–1.6)	
	M and F	Benomyl (F)	Ever use (exposed to lead arsenate)	OR 6.7 (1.6–27)	
	M and F	Carbaryl (I)	IWLD (<56 exposure-days)	OR 1.3 (0.9–2.1)	Adjusted for age, sex, tendency to burn, red hair, sun exposure (≤2 h/day, ≥3 h/day) and BMI at 20 years of age
	M and F	Carbaryl (I)	IWLD (≥56 exposure-days)	OR 1.7 (1.1–2.5)	
	M and F	Carbaryl (I)	Ever use	OR 1.5 (1–2)	Adjusted for age and sex using IWLD
	M and F	Carbaryl (I)	Ever use (not exposed to lead arsenate)	OR 1.4 (1–2)	
	M and F	Carbaryl (I)	Ever use (exposed to lead arsenate)	OR 1.8 (0.2–14.4)	
	M and F	Maneb/Mancozeb (F)	IWLD (<63 exposure-days)	OR 1.6 (0.8–3.4)	Adjusted for age, sex, tendency to burn, red hair, sun exposure (≤2 h/day, ≥3 h/day) and BMI at 20 years of age
	M and F	Maneb/Mancozeb (F)	IWLD (≥63 exposure-days)	OR 2.4 (1.2–4.9)	
	M and F	Maneb/Mancozeb (F)	Ever use	OR 1.5 (0.09–2.5)	Adjusted for age and sex using IWLD
	M and F	Maneb/Mancozeb (F)	Ever use (not exposed to lead arsenate)	OR 0.9 (0.5–1.8)	
	M and F	Maneb/Mancozeb (F)	Ever use (exposed to lead arsenate)	OR 10.8 (2.3–51.3)	
	M and F	Parathion (I)	IWLD (<56 exposure-days)	OR 1.6 (0.8–3.1)	Adjusted for age, sex, tendency to burn, red hair, sun exposure (≤2 h/day, ≥3 h/day) and BMI at 20 years of age
	M and F	Parathion (I)	IWLD (≥56 exposure-days)	OR 2.4 (1.3–4.4)	
	M and F	Parathion (I)	Ever use	OR 1.9 (1.2–3)	Adjusted for age and sex using IWLD
	M and F	Parathion (I)	Ever use (not exposed to lead arsenate)	OR 1.5 (0.8–2.7)	
	M and F	Parathion (I)	Ever use (exposed to lead arsenate)	OR 7.3 (1.5–34.6)	
Freeman *et al.* (2011)[42]	M and F	Atrazine (H)	LED	Rate ratio 1.15 (0.71–1.87)	Adjusted for age, state, sex, education level, smoking history, alcohol consumption, family history of cancer, applicator type and exposure to the five pesticides most highly correlated with
	M and F	Atrazine (H)	IWLD	Rate ratio 0.85 (0.51–1.42)	

Table 3 *Continued*

Authors (Year) [Reference]	Gender	Pesticide	Exposure	Risk estimate (95% CI)	Adjustment
					Atrazine (Dicamba, Cyanazine, Metolachlor, Trifluralin, 2,4-D)
Frost *et al.* (2011)[43]	M	Any pesticides	Ever use	SIR 0.94 (0.73–1.21)	Not adjusted
	F	Any pesticides	Ever use	SIR 1.06 (0.44–2.56)	
Barry *et al.* (2012)[44]	M and F	Methyl Bromide (Fumigant)	IWLD	Rate ratio 0.36 (0.14–0.94)	Adjusted for age, year of enrolment, state, sex, race, education level, smoking history, alcohol consumption, family history of cancer, applicator type and the five pesticides most highly correlated with Methyl Bromide (Metalaxyl, Ethylene Dibromide, Carbaryl, Aldicarb and Maneb/ Mancozeb)
Jones *et al.* (2015)[45]	M	Diazinon (I)	LED	Rate ratio 0.58 (0.24–1.45)	Adjusted for age, state, education level, smoking history, alcohol consumption and family history of cancer
	M	Diazinon (I)	IWLD	Rate ratio 1 (0.49–2.02)	
Lerro *et al.* (2015)[46]	M	Acetochlor (H)	Ever use	Relative risk 1.61 (0.98–2.66)	Adjusted for age, state, race, education level, smoking history, alcohol consumption, family history of cancer, BMI, use of an enclosed cab, applicator type and correlated/ associated pesticide use
	M	Acetochlor (H)	Days of use per year (low)	Relative risk 1.41 (0.67–2.97)	
	M	Acetochlor (H)	Days of use per year (high)	Relative risk 1.78 (0.9–3.52)	
	M	Acetochlor (H)	IWLD (low)	Relative risk 1.79 (0.93–3.45)	
	M	Acetochlor (H)	IWLD (high)	Relative risk 1.38 (0.64–2.99)	
Segatto *et al.* (2015)[47]	M and F	Organochlorines (I), Organo-phosphates (I), Pyrethroids (I) and Carbamates (I)	Ever use (general)	OR 1.62 (1.17–6.34)	Adjusted for age, sex, centre, education level, skin photo type, hair colour, eye colour, skin colour, sunburn episodes in childhood, occupational sun exposure, use of sunscreen in adulthood, family history of skin cancer, number of nevi, presence of freckles, actinic keratosis/non-melanoma skin cancer and solar lentigines
	M and F	Organochlorines (I), Organo-phosphates (I), Pyrethroids (I) and Carbamates (I)	Ever use (residential outdoor)	OR 1.95 (0.82–3.06)	
	M and F	Organochlorines (I), Organo-phosphates (I), Pyrethroids (I) and Carbamates (I)	Ever use (residential indoor)	OR 1.74 (0.91–2.94)	
	M and F	Organochlorines (I), Organo-phosphates (I), Pyrethroids (I) and Carbamates (I)	Ever use (occupational)	OR 4.23 (1.94–6.31)	
	M and F	Organochlorines (I), Organo-phosphates (I), Pyrethroids (I) and Carbamates (I)	Frequency of use (times/year; general)	OR 0.91 (0.43–1.94)	
	M and F	Organochlorines (I), Organo-phosphates (I), Pyrethroids (I) and Carbamates (I)	Frequency of use (times/year; residential outdoor)	OR 0.84 (0.42–3.66)	

Table 3 *Continued*

Authors (Year) [Reference]	Gender	Pesticide	Exposure	Risk estimate (95% CI)	Adjustment
	M and F	Organochlorines (I), Organophosphates (I), Pyrethroids (I) and Carbamates (I)	Frequency of use (times/year; residential indoor)	OR 1.44 (1.11–3.49)	
	M and F	Organochlorines (I), Organophosphates (I), Pyrethroids (I) and Carbamates (I)	Frequency of use (times/year; occupational)	OR 1.22 (0.87–3.77)	
	M and F	Organochlorines (I), Organophosphates (I), Pyrethroids (I) and Carbamates (I)	Duration of exposure (general)	OR 1.69 (0.82–4.02)	
	M and F	Organochlorines (I), Organophosphates (I), Pyrethroids (I) and Carbamates (I)	Duration of exposure (residential outdoor)	OR 0.74 (0.22–3.22)	
	M and F	Organochlorines (I), Organophosphates (I), Pyrethroids (I) and Carbamates (I)	Duration of exposure (residential indoor)	OR 2.84 (1.56–5.33)	
	M and F	Organochlorines (I), Organophosphates (I), Pyrethroids (I) and Carbamates (I)	Duration of exposure (occupational)	OR 1.17 (0.83–4.17)	
Silver *et al.* (2015)[48]	M and F	Metolachlor (H)	LED	Rate ratio 1.19 (0.65–2.18)	Adjusted for age, state, sex, race, education level, smoking history, alcohol consumption, family history of cancer, applicator type and the five pesticides most highly correlated with Metolachlor (Imazethapyr, Alachlor, Atrazine, Dicamba and Trifluralin)
	M and F	Metolachlor (H)	IWLD	Rate ratio 1.03 (0.55–1.93)	
Fortes *et al.* (2016)[49]	M and F	Any pesticide	Ever use	OR 2.58 (1.18–5.65)	Adjusted for age, sex, centre, education level, skin photo type, number of nevi, sunburn episodes in childhood and family history of skin cancer
	M and F	Carbamates (I)	Ever use	OR 4.15 (0.81–21.2)	
	M and F	Phosphonoglycines (H)	Ever use	OR 3.29 (0.72–15)	
	M and F	Organophosphates (I)	Ever use	OR 5.34 (1.06–26.8)	
	M and F	Inorganic compound	Ever use	OR 3.78 (0.67–21.2)	
	M and F	Herbicides	Ever use	OR 3.08 (1.06–8.97)	
	M and F	Insecticides	Ever use	OR 2.24 (0.88–5.7)	
	M and F	Fungicides	Ever use	OR 3.88 (1.17–12.9)	

Table 3 *Continued*

Authors (Year) [Reference]	Gender	Pesticide	Exposure	Risk estimate (95% CI)	Adjustment
	M and F	Only one type of pesticide	Ever use	OR 1.81 (0.66–4.99)	
	M and F	At least two types of pesticides	Ever use	OR 4.04 (1.20–13.6)	
	M and F	Any pesticides	Low frequency of use (times/month)	OR 2.29 (0.93–5.6)	
	M and F	Any pesticides	High frequency of use (times/month)	OR 2.86 (0.45–18.3)	
	M and F	Any pesticides	Duration (<10 years)	OR 1.26 (0.32–5)	
	M and F	Any pesticides	Duration (≥10 years)	OR 7.4 (1.91–28.7)	
	M and F	Any pesticides	Indoor or Indoor/ Outdoor	OR 1.32 (0.40–4.38)	
	M and F	Any pesticides	Outdoor	OR 4.68 (1.29–17)	

2,4-D, 2,4-dichlorophenoxyacetic acid; BMI, body mass index; DDT, dichlorodiphenyltrichloroethane; dichlorprop or 2,4-DP, 2-(2,4-dichlorophenoxy)propionic acid; EPTC, *S*-ethyl-*N*,*N*-dipropylthiocarbamate; F, fungicide; H, herbicide; I, insecticide; IWLD, intensity-weighted lifetime days; LED, lifetime exposure-days; MCPA, 2-methyl-4-chlorophenoxyacetic acid; mecoprop or MCPP, 2-(4-chloro-2-methylphenoxy)propanoic acid; OR, odds ratio; SIR, standardized incidence ratio.

were 2-(2,4-dichlorophenoxy)propionic acid, 2-(4-chloro-2-methylphenoxy)propanoic acid and 2-methyl-4-chlorophenoxyacetic acid. Among these workers potentially exposed to chlorophenoxy herbicides, only the 1651 males were considered in the present study, while the 468 females cannot be included because the women's risk estimate for CM is not reported. Cancer incidence was established by linking the cohort to the Danish Cancer Register, and the observed number of cancers was compared with expected values calculated on the basis of cancer incidence in the Danish population.

Acquavella *et al.*[33] performed a cohort study of 1153 workers from Iowa with potential alachlor exposure and at least 1 year of documented employment from plant start up. Of these, 700 individuals were judged to have a high alachlor exposure. Cancer incidence rates were compared to corresponding rates for the Iowa state general population. CM resulted more frequent than expected among all alachlor workers.

In the Netherlands, Kennedy *et al.*[36] conducted a case–control study of 966 individuals (466 males and 500 females): about 12% of controls and 9% of melanoma cases were exposed to pesticides, dichlorodiphenyltrichloroethane, parathion, polycyclic aromatic hydrocarbons, arsenic, coal, soot, pitch, tar, oils or asbestos and their relation to the risk of developing skin cancers. However, exposures resulted relatively rare among women and the risk estimates were calculated for men only.

Dennis *et al.*[41] examined dose–response relationships for 50 agricultural pesticides and CM incidence in the AHS cohort of 24 704 licensed pesticide applicators who completed the take-home questionnaire to allow for examination of potential confounding effects of melanoma risk factors [sun sensitivity factors (tendency to burn, hair and eye colour), sun exposure and obesity]. Incident cancer cases were obtained via linkage with the cancer registry files in Iowa and North Carolina. CM cases tended to be older in this cohort and had a higher body mass index based on weight at age 20, while sun exposure resulted not linearly related to this tumour. Among sun sensitivity factors, red hair had the strongest association with CM. Only four specific pesticides (benomyl, carbaryl, maneb/mancozeb and parathion) showed a dose–response association with CM between applicators. A significant effect modification was observed when benomyl and maneb/mancozeb users were also exposed to lead arsenate.

Frost *et al.*[43] performed a cohort study (Pesticide Users Health Study) of 62 960 British pesticide users (59 085 males and 3875 females) who have passed Certificates of Competence in applying agricultural pesticides since 1987. This study evaluated people exposed to ever use of any pesticide and compared to cancer risk of the Great Britain population. However, the database is restricted to the information provided at the time of application for the certificate and lacked information on potential confounding factors.

Lerro *et al.*[46] conducted a cohort study among AHS applicators who responded to the follow-up interview and due to the small number of females (n = 1006), the analyses were restricted to 33 484 licensed male pesticide applicators. Excluding individuals with missing days of use (n = 456) or intensity (n = 11), 33 028 and 33 017 applicators were, respectively, selected for the analyses that examined lifetime days and intensity-weighted days of acetochlor use. Incident cancer cases were obtained via linkage with Iowa and North Carolina state cancer registries. An association between CM and ever use of acetochlor was observed, though the exposure–response relationship resulted

Table 4 Characteristics of the included studies

Authors year [Reference]	Study type (Quality)	Period of enrolment	End of the follow-up	Country of study	Subjects (Females)	Pesticide	Type of exposure	Risk estimate (95% CI)	Adjustment
Alavanja *et al.* (2005)[10]	Cohort (NOS: 6)	1993–1997	31/12/2002	US (Iowa and North Carolina)	52 395 (1359)	Any pesticides (private applicators)	Ever use	SIR 0.95 (0.78–1.16)	Not adjusted
				US (Iowa)	4916 (204)	Any pesticides (commercial applicators)	Ever use	SIR 1.05 (0.42–2.17)	
Zhong and Rafnsson (1996)[31]	Cohort (NOS: 7)	1941–1993	01/12/1993	Iceland	1860 (0)	Any pesticide	Ever use	SIR 1.15 (0.02–6.4)	Not adjusted
Lynge (1998)[32]	Cohort (NOS: 7)	1947–1993	31/12/1993	Denmark	1651 (0)	Dichlorprop (H), Mecoprop (H) and MCPA (H)	Ever use	SIR 1.23 (0.4–2.9)	Not adjusted
Acquavella *et al.* (2004)[33]	Cohort (NOS: 7)	1968–1999	31/12/1999	US (Iowa)	1153 (227)	Alachlor (H)	Ever use	SIR 2.78 (1.02–6.06)	Adjusted for age, sex, race and calendar period
					700 (n/a)	Alachlor (H)	High exposure	SIR 2.29 (0.62–5.87)	
Kennedy *et al.* (2005)[36]	Case–control (NOS: 6)	n/a	n/a	Netherlands	466 (0)	Any pesticides	Low exposure	OR 1.2 (0.5–2.6)	Adjusted for age, skin type and smoking history
						Any pesticides	High exposure	OR 0.5 (0.2–1.5)	
						Insecticides	Ever use	OR 1.1 (0.5–2.6)	
						DDT (I)	Ever use	OR 0.8 (0.3–2.4)	
						Parathion (I)	Ever use	OR 0.9 (0.2–3.4)	
Dennis *et al.* (2010)[41]	Cohort (NOS: 9)	1993–1997	31/12/2005	US (Iowa and North Carolina)	24 704 (n/a)	Benomyl (F)	IWLD (<133 exposure-days)	OR 1 (0.4–2.2)	Adjusted for age, sex, tendency to burn, red hair, sun exposure (≤2 h/day, ≥3 h/day) and BMI at 20 years of age
						Benomyl (F)	IWLD (≥133 exposure-days)	OR 2.8 (1.2–6.5)	
						Benomyl (F)	Ever use	OR 1.2 (0.7–2.1)	Adjusted for age and sex using IWLD
						Benomyl (F)	Ever use (not exposed to lead arsenate)	OR 0.7 (0.3–1.6)	
						Benomyl (F)	Ever use (exposed to lead arsenate)	OR 6.7 (1.6–27)	
						Carbaryl (I)	IWLD (<56 exposure-days)	OR 1.3 (0.9–2.1)	Adjusted for age, sex, tendency to burn, red hair, sun exposure (≤2 h/day, ≥3 h/day) and BMI at 20 years of age
						Carbaryl (I)	IWLD (≥56 exposure-days)	OR 1.7 (1.1–2.5)	
						Carbaryl (I)	Ever use	OR 1.5 (1–2)	Adjusted for age and sex using IWLD
						Carbaryl (I)	Ever use (not exposed to lead arsenate)	OR 1.4 (1–2)	

Table 4 *Continued*

Authors year [Reference]	Study type (Quality)	Period of enrolment	End of the follow-up	Country of study	Subjects (Females)	Pesticide	Type of exposure	Risk estimate (95% CI)	Adjustment
						Carbaryl (I)	Ever use (exposed to lead arsenate)	OR 1.8 (0.2–14.4)	
						Maneb/Mancozeb (F)	IWLD (<63 exposure-days)	OR 1.6 (0.8–3.4)	Adjusted for age, sex, tendency to burn, red hair, sun exposure (≤2 h/day, ≥3 h/day) and BMI at 20 years of age
						Maneb/Mancozeb (F)	IWLD (≥63 exposure-days)	OR 2.4 (1.2–4.9)	
						Maneb/Mancozeb (F)	Ever use	OR 1.5 (0.09–2.5)	Adjusted for age and sex using IWLD
						Maneb/Mancozeb (F)	Ever use (not exposed to lead arsenate)	OR 0.9 (0.5–1.8)	
						Maneb/Mancozeb (F)	Ever use (exposed to lead arsenate)	OR 10.8 (2.3–51.3)	
						Parathion (I)	IWLD (<56 exposure-days)	OR 1.6 (0.8–3.1)	Adjusted for age, sex, tendency to burn, red hair, sun exposure (≤2 h/day, ≥3 h/day) and BMI at 20 years of age
						Parathion (I)	IWLD (≥56 exposure-days)	OR 2.4 (1.3–4.4)	
						Parathion (I)	Ever use	OR 1.9 (1.2–3)	Adjusted for age and sex using IWLD
						Parathion (I)	Ever use (not exposed to lead arsenate)	OR 1.5 (0.8–2.7)	
						Parathion (I)	Ever use (exposed to lead arsenate)	OR 7.3 (1.5–34.6)	
Frost *et al.* (2011)[43]	Cohort (NOS: 7)	1987–2003	31/12/2004	Great Britain	62 960 (3875)	Any pesticide	Ever use	SIR (males) 0.94 (0.73–1.21) SIR (females) 1.06 (0.44–2.56)	Not adjusted
Lerro *et al.* (2015)[46]	Cohort (NOS: 8)	1993–1997	31/12/2011	US (Iowa and North Carolina)	33 484 (0)	Alachlor (H)	Ever use	Relative risk 1.61 (0.98–2.66)	Adjusted for age, state, race, education level, smoking history, alcohol consumption, family history of cancer, BMI, use of an enclosed cab, applicator type and correlated/associated pesticide use
					33 028 (0)	Alachlor (H)	Days of use per year (low: 2–19 days)	Relative risk 1.41 (0.67–2.97)	
							Days of use per year (high: 20–1080 days)	Relative risk 1.78 (0.9–3.52)	
					33 017 (0)	Alachlor (H)	IWLD (low: 72–879 IW days)	Relative risk 1.79 (0.93–3.45)	
							IWLD (high: 880–47 520 IW days)	Relative risk 1.38 (0.64–2.99)	

Table 4 *Continued*

Authors year [Reference]	Study type (Quality)	Period of enrolment	End of the follow-up	Country of study	Subjects (Females)	Pesticide	Type of exposure	Risk estimate (95% CI)	Adjustment
Fortes *et al.* (2016)[49]	Case–control (NOS: 9)	2001–2003	01/05/2003	Italy (1 centre)	800 (437)	Any pesticide	Ever use	OR 2.58 (1.18–5.65)	Adjusted for age, sex, centre, education level, skin photo type, number of nevi, sunburn episodes in childhood, and family history of skin cancer
						Carbamates (I)	Ever use	OR 4.15 (0.81–21.2)	
						Phosphonoglycines (H)	Ever use	OR 3.29 (0.72–15)	
						Organophosphates (I)	Ever use	OR 5.34 (1.06–26.8)	
						Inorganic compound	Ever use	OR 3.78 (0.67–21.2)	
						Herbicides	Ever use	OR 3.08 (1.06–8.97)	
		2012–2013	01/09/2013	Brazil (3 centres)		Insecticides	Ever use	OR 2.24 (0.88–5.7)	
						Fungicides	Ever use	OR 3.88 (1.17–12.9)	
						Only one type of pesticide	Ever use	OR 1.81 (0.66–4.99)	
						At least two types of pesticides	Ever use	OR 4.04 (1.20–13.6)	
						Any pesticides	Low frequency of use (less than once a month)	OR 2.29 (0.93–5.6)	
						Any pesticides	High frequency of use (once a month or more)	OR 2.86 (0.45–18.3)	
						Any pesticides	Duration (<10 years)	OR 1.26 (0.32–5)	
						Any pesticides	Duration (≥10 years)	OR 7.4 (1.91–28.7)	
						Any pesticides	Occupational Sun Exposure (Indoor or Indoor/Outdoor)	OR 1.32 (0.40–4.38)	
						Any pesticides	Occupational Sun Exposure (Outdoor)	OR 4.68 (1.29–17)	

DDT, dichlorodiphenyltrichloroethane; dichlorprop or 2,4-DP, 2-(2,4-dichlorophenoxy)propionic acid; F, fungicide; H, herbicide; I, insecticide; IW days, intensity-weighted days; IWLD, intensity-weighted lifetime days; MCPA, 2-methyl-4-chlorophenoxyacetic acid; mecoprop or MCPP, 2-(4-chloro-2-methylphenoxy)propanoic acid; n/a, not available; NOS: Newcastle Ottawa Scale score; OR, odds ratio; SIR, standardized incidence ratio; US, United States.

not consistent for lifetime days and intensity-weighted days of use. Sun sensitivity and exposure characteristics were only available for about half of this cohort; however, the relationship between ever use of acetochlor and CM risk was strengthened (relative risk: 2.55, 95% CI: 1.45–4.48) after controlling for these two factors.

Fortes *et al.*[49] conducted a case–control study of 800 individuals (399 cases and 401 controls of whom 363 were males and 437 females), and 9% of cases and 3% of controls were exposed to ever use of any pesticide. Subjects were enrolled in four dermatological hospital centres, one Italian (IDI, Rome) and three Brazilians (UFCSPA, HCPA, PUC, Porto Alegre). This study observed an increased risk of CM among subjects with exposure to pesticides, especially among those exposed to sun at occupational level and for individuals using two or more types of pesticides.

Meta-analysis results

Results of the meta-analysis are presented in Fig. 2. A significant increase of CM risk following every herbicide use was found, with a SRR of 1.85 (95% CI: 1.01, 3.36). No indication for publication bias was found ($P = 0.43$). Conversely, it seemed that neither insecticides nor pesticides in general are significantly associated with CM risk, independently of level exposure. In detail, SRRs for the categories 'insecticides – ever exposure', 'any pesticide – ever exposure' and 'any pesticide – high exposure' resulted 1.57 (95% CI: 0.58, 4.25), 1.31 (95% CI: 0.85, 2.04) and 2.17 (95% CI: 0.45, 10.36), respectively.

Herbicides and insecticides had no between-study heterogeneity ($I^2 = 0\%$), while an acceptable level of variability ($I^2 = 32\%$) was observed for any pesticide. Instead, a significant heterogeneity ($I^2 = 72\%$) was found for the high exposure to any pesticide. We did not find any factor influencing significantly heterogeneity. We also carried out some sensitivity analyses excluding Lerro *et al.*[46] because the authors assessed the role of herbicide and consider as controls users of other pesticides and this could introduce a bias. Excluding this study, the summary risk estimate for herbicide is not any more significant: SRR = 2.21 (95% CI: 0.65, 7.58). We also calculated a summary estimate excluding Kennedy *et al.*[36] for high use of pesticide, because it is the smallest case–control study, and if we exclude this study, the heterogeneity becomes zero. Even excluding this study, the summary risk estimate does not show a significant increased risk: SRR = 3.57 (95% CI: 0.95, 13.41).

Discussion

The worldwide incidence of CM has risen rapidly over the course of the last 50 years, and it is greatest among fair-skinned populations and in regions of lower latitude. The major risk factors acknowledged nowadays are the phenotype (fair skin, blue and green eyes, blonde and red hair), sun sensitivity, high number of nevi, family history for skin cancer, the presence of some genetic mutations, and ultraviolet (UV) radiation that has been long recognized as the most important.[50,51] In contrast, it has been suggested that chronic exposure to UV radiation, as assessed through occupational exposure, appeared to reduce CM risk and this observation is consistent with the descriptive epidemiology of the condition, which shows lower risks in groups that work outdoors.[52] This inconsistency may be due to differences in the effects of chronic and intermittent sun exposure. However, the risk of CM does not increase with increasing sun exposure[53] and all the established melanoma risk factors do not seem sufficient to entirely explain CM cases. Therefore, given the high incidence and mortality of the disease, it is essential investigating new environmental risk factors to clarify this trend. Potential risk factors for CM that have been little explored are the pesticides.[24,54] Exposure to pesticides is very common worldwide, and these substances are widely used in agricultural and other settings, resulting in continuing human exposure.[55] Humans are exposed to pesticides though occupational or environmental exposure, and these substances can exert numerous effects on human health. Pesticides, due to their different chemical classes and active ingredients, may have different mutagenic, carcinogenic and/or immunotoxic properties. Some studies revealed that they induce malignant transformation of cells *in vitro* and *in vivo* by oxidative stress, DNA damage, chromosome aberration, mutation induction, immune response abnormality and chronic inflammation.[22,56] Pesticide formulations vary broadly in physicochemical properties and therefore their capacity to be absorbed through the skin.[57]

Dermal exposure to pesticides is the most important route of uptake for exposed individuals and can occur during mixing and loading, application and clean-up.[57,58] It can be influenced by amount and duration of exposure, presence of other material on the skin, temperature and humidity, and the use of personal protective equipment.[57]

While the main exposure of general population to pesticides is through eating and drinking contaminated food and water, substantial exposure occurs also when living close to a workplace using pesticides by inhaling residual air concentration and dust, or even using articles, such as clothing and bedding with residues.[59] Generally, the indirect exposure from pesticide residues in food, water and air involves low doses and is chronic (or semi-chronic).

Currently, there are no published studies that investigate whether there is a CM risk associated with environmental exposure to pesticides. Moreover, the evidence regarding associations between specific pesticides or chemicals and CM is still limited and the previous melanoma literature has mainly focused on host factors and sun exposure. However, it is challenging to capture with a questionnaire the sun exposure of some worker's categories such as farmers.[41] Agricultural workers tend to spend a greater number of hours outdoors than the general population, and so it is quite difficult to rule out sun exposure as a possible explanation for an increasing incidence of skin cancers.

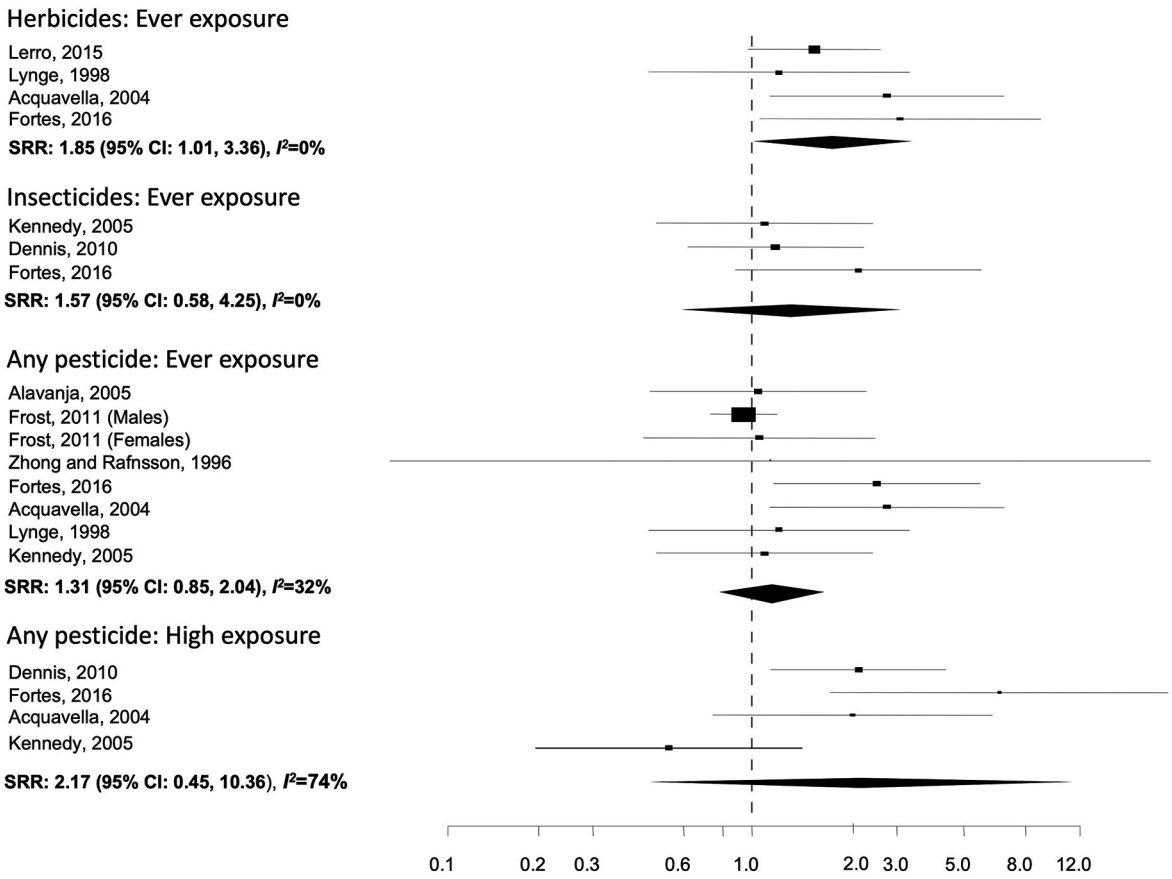

Figure 2 Forest plots of the cutaneous melanoma risk associated with pesticides.

Additionally, a questionnaire is not an objective measure and misclassification of sun exposure could be also a possible source of bias.

Data on CM in farmers are not consistent, and a significant excess of CM was reported by Blair *et al.*[60] as well as in the review from Fortes and de Vries,[24] but in contrast with the study in Nordic countries[61] and the meta-analysis from Acquavella *et al.*[62] This meta-analysis of 37 studies regarding the risk of development cancer among farmers found that lip cancer was the only tumour clearly elevated.[62]

The interaction between UV exposure and other possible environmental exposure such as pesticides remains to be clarified, and it might be advantageous adjusting evaluations for the major risk factors of CM. In our analysis, data were adjusted for potential confounders in five studies,[33,36,41,46,49] but only in two for sun exposure.[41,49] Dennis *et al.*[41] observed no effect modification of the association with pesticides by sun exposure. Instead, Fortes *et al.*[49] illustrated a possible synergistic effect between pesticides and sun exposure at occupational level, reinforcing the existence of a link between exposure to pesticides and the development of CM. Moreover, Lerro *et al.*[46] found in approximately half of study population that the relationship between ever use of acetochlor and CM risk was strengthened after controlling for sun sensitivity and exposure factors.

The effect modification by sun exposure may be explicated by the rise in temperature of the skin, caused by UV radiation, that increases blood flow and sweating facilitating transcutaneous absorption of pesticides.[63] A laboratory study of sunscreen found that those containing the physical UV absorbers titanium dioxide or zinc oxide enhance the transdermal absorption of parathion.[64] Therefore, another possibility of the increased risk seen among subjects exposed to both sun and pesticides is the use of sunscreen.

Fortes *et al.*[49] observed that the effect of pesticides exposure on CM was stronger for subjects using two or more types of pesticides. Epidemiologic studies usually examine pesticides either independently, or more often by chemical class, and little is known about the toxicology and potential carcinogenicity of pesticide mixtures. Future epidemiologic studies should consider the effects of pesticide mixtures, while toxicological studies

should attempt to understand whether exposure as a mixture influences genotoxicity and mutagenicity.

Our meta-analysis shows a significant increased risk of CM among herbicide users compared with not exposed subjects. Given the limited number of studies included and insufficient data regarding fungicides, this subgroup analysis was impossible to carry out.

Exposures resulted relatively rare among females, and the majority of the studies did not report women's risk estimates. Except for Alavanja *et al.*,[10] all other authors did not include spouses in their analysis because they had no information regarding frequency and duration of pesticide exposure and they did not control for potential confounders.

The elimination of carcinogenic exposure is important in the primary prevention of cancer, but this is not always possible. In these cases, steps should be taken either to reduce exposure to the lowest level or to activate a surveillance programme for high-risk categories.

There are still many differences among EU, the United States and developing countries, in the use of pesticides.[65] Many pesticides that have been banned or are being phased out in the EU, China and Brazil are still in large use in the United States. Currently, the strictly EU regulation is the most comprehensive and protective (information available from https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32009R1107).

Some limitations should be considered when interpreting our results. As with any meta-analysis, ours may be biased in part because of publication bias. Recall and selection bias were inevitable in the observational studies, especially for case–control studies. Moreover, inadequate adjustment for potential confounders, particularly sun exposure, may have attenuated the true association. In addition, adding results of future studies could modify our results.

Conclusions

This systematic review and meta-analysis reveal that individuals exposed to herbicide are at an increased risk of CM, but further properly designed observational studies are necessary to confirm this finding. More researches on chemicals and other environmental factors that may increase the risk of CM are also needed. A precautionary public health safety policy that includes preventive individual counselling and surveillance to workers exposed to pesticides may be advisable.

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