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REVIEW

Pesticide exposure and risk of Central Nervous System tumors in children: a systematic review with meta-analysis

Anne Lívia Cavalcante Mota (https://orcid.org/0000-0002-4701-5811) [1]
Isadora Marques Barbosa (https://orcid.org/0000-0002-3799-7882) [1]
Andrea Bezerra Rodrigues (https://orcid.org/0000-0002-2137-0663) [2]
Edna Maria Camelo Chaves (https://orcid.org/0000-0001-9658-0377) [1]
Paulo César de Almeida (https://orcid.org/0000-0002-2867-802X) [1]

Abstract *Central Nervous System (CNS) tumors represent more than half of all childhood malignant neoplasms. The aim of this study was to determine the relationship between environmental exposure to pesticides and the development of CNS tumors in children. We conducted a systematic review of the literature in the PubMed/MEDILINE, Embase, Web of Science, Scopus, and CINAHL databases. The inclusion criteria were cohort and case-control studies investigating the association between exposure to pesticides and CNS tumors (all histological types included in group III of the WHO Classification of Childhood Cancer) in children aged 0-14 years. The meta-analysis was performed using a random effects model and the Mantel-Haenszel method. Strength of association was measured using odds ratios (OR). The review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under identification number CRD42021209354. The search identified 1,158 studies, 14 of which were included in the review. There was evidence of an association between the development of astrocytomas and exposure to all classes of pesticides (OR 1.50; 95%CI 1.15-1.96; p=0.03). The synthesis of the evidence pointed to a relationship between exposure to pesticides and some histological types of CNS tumors in childhood.*

Key words *Central Nervous System neoplasms, Risk factors, Environmental exposure, Child*

[1] Programa de Pós-Graduação em Cuidados Clínicos em Enfermagem e Saúde, Universidade Estadual do Ceará (UECE). Av. Dr. Silas Munguba 1700, Campus do Itaperi. 60714-903 Fortaleza CE Brasil. aliviacante@gmail.com
[2] Departamento de Enfermagem, Universidade Federal do Ceará. Fortaleza CE Brasil.

Introduction

Childhood cancer has become a major cause of morbidity and mortality among children in both developed and developing countries in recent years. In the United States, the incidence rate of malignant and non-malignant brain and central nervous system (CNS) tumors among children and adolescents (0-19 years) between 2013 and 2017 was 6.14 per 100,000 population[1].

In Brazil, cancer is one of the leading causes of death in children and adolescents aged 1-19 years. The most common types of cancer are leukemia, lymphomas, and CNS tumors[2]. The latter is the most common cancer among children, accounting for 20% of all neoplasms, with incidence peaking between ages 1-4 years[3].

CNS tumors and leukemia combined account for more than half of all malignant tumors in children. Moreover, the former has the greatest variation of histological subtypes and metastatic capacity and highest infant mortality rate[4]. Subtypes include ependymomas, astrocytomas, primitive neuroectodermal tumors (PNET), gliomas, and specified and unspecified intracranial and intraspinal neoplasms[5].

The identification of risk factors associated with the development of CNS tumors in children has become an epidemiological imperative to guide prevention and treatment. Studies investigating direct exposure to pesticides (use for home pest control) and indirect exposure (related to parental occupation) conducted in recent years have shown a possible link between exposure and CNS tumors[6].

Pesticides include herbicides (weed killers), insecticides (used to control insects), ant killers, acaricides (used to control spider mites and animal ticks), larvicides (used to control insect larvae), fungicides (used against fungi), rodenticides (used to kill rodents, particularly mice and rats), and avicides (used to kill seed-eating birds)[7].

The National Cancer Institute (INCA)[8] underlines that occupational exposure to pesticides poses a risk not only to workers, but also other individuals, such as family members and residents living close to pesticide use sites. Other forms of exposure can contribute to poisoning among the general population, including eating pesticide residues in food, drinking contaminated water, and using insecticides in the home.

The investigation of environmental risk factors is therefore important to gain a deeper understanding of the possible relationship between the use of pesticides and CNS tumors and help shape health promotion and prevention policies.

The metanalyses available in the literature address these factors in an isolated manner, focus on adolescents and young adults, or were conducted more than five years ago[6,9-11]. A systematic review of the literature on the topic was therefore undertaken to consolidate knowledge on exposure to pesticides and CNS tumors in children. The latest INCA report on cancer incidence, morbidity, and mortality specifies the following age groups: children (0-14 years), adolescents (15-19 years), and young adults (20-29 years)[12]. The present study focused on CNS tumors in children (0-14 years) because the incidence rate in this group differs from that among adolescents and young adults.

The aim of this literature review is therefore to determine the relationship between environmental exposure to pesticides and the development of CNS tumors in children.

Method

We conducted a systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA-P) guidelines[13] and recommendations set out in the Cochrane Manual[14]. The review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO)[15] under identification number CRD42021209354.

Formulation of the research question

The research question was formulated using the PECOS acronym[16] (P: population; E: exposure; C: comparison; O: outcome; S: study design), recommended for observational studies, as follows:

- Population (participants): children aged 0-14 years.
- Exposure: environmental exposure to all pesticide classes.
- Comparison: control (without exposure to pesticides).
- Outcome: development of CNS tumors.
- Study design: observational studies (case-control and cohort studies).

Based on the above elements, the following research question was formulated: what environmental risk factors (environmental exposure to pesticides, including herbicides, insecticides, and others) may be related to the development of CNS tumors in children?

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Eligibility

The following studies were considered eligible for the review: 1) studies assessing the relationship between exposure to all types of pesticides (insecticides, herbicides, fungicides, and others) and the development of CNS tumors in children; 2) cohort and case-control studies. No restrictions were applied in relation to language and data of publication.

The following exclusion criteria were used: studies including histological types not included in group III (tumors of the central nervous system) of the World Health Organization Classification of Childhood Cancer[5].

Data sources and search strategies

Searches were performed of six major databases: PubMed (MEDLINE), Embase, Web of Science, Scopus, Engineering Village, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). We also searched the following grey literature sources: Google Scholar, OpenGrey, ProQuest Dissertations and Theses, and the periodicals platform of the Coordination for the Improvement of Higher Education Personnel (CAPES Periodicals).

The searches were performed using controlled Health Sciences Descriptors (DeCS), Medical Subjects Headings (MeSH), and Embase Subject Headings (Emtree) health vocabularies and one engineering controlled vocabulary (Engineering Village - Elsevier), specific to each database. We also used ordinary language terms (keywords) to complement the searches and increase the number of retrieved articles on the study topic[17,18]. The search strategy included specific terms for types of pesticides and general terms for environmental exposure factors (Chart 1).

Data collection

The review strategies were tested on each database by the systematic review team (reviewers and librarian) to identify inconsistencies and feasibility. The team was made up of professionals with knowledge of the topic and/or method, exploiting the specific skills and competencies of each member. The group was composed as follows:

- *First reviewer (R1)*: performed the search, screening, selection, and statistical and methodological analysis of the studies and wrote the review together with the second reviewer.
- *Segundo reviewer (R2)*: screened the articles and selected and performed the statistical and methodological analysis of the studies together with the first reviewer.
- *Third reviewer (R3)*: checked the work of the two reviewers (R1 and R2) and helped with biostatistics (planning and viability of the meta-analysis).
- *Other members*: librarian who helped design and test the search strategies.

The retrieved data were saved in a RIS file on the same day at one-hour intervals. The metadata file was then exported to the Mendeley reference manager to check for inconsistencies and correct errors. Duplicate references were excluded using the relevant reference manager and Microsoft Excel (2020 update) tools and by checking the article titles, since many author's names and titles were different on the databases. A blind pairwise comparison of the results was performed by the reviewers. The search and definitive extraction of data was performed in November 2021.

Study selection involved three stages: screening of the titles and abstracts of the studies included after excluding the duplicates; screening of the full version of the articles that met the eligibility criteria (exposure to pesticides in children aged 0-14 years and cohort and case-control studies); and reading of the references of the articles included in the previous stage to identify other studies that met the inclusion criteria.

Data analysis

The following study information was recorded: author name, country of origin, study design, age group, sample size (case-controls and cohorts), histological type of CNS tumors, type of environmental exposure, exposure setting, and main results.

The methodological quality of the individual studies was assessed using the Newcastle-Ottawa (NOS) Quality Assessment Scale for Case-Control and Cohort Studies, developed by the Ottawa Hospital Research Institute and used for assessing the quality of nonrandomized (observational) studies. The studies were scored based on the following three criteria: selection (0-4 points), comparability (0-2 points), outcome/exposure (0-3 points). Based on the overall score across the three criteria, the studies were classified as follows: high quality and low risk of bias (greater than or equal to 7 points), intermediate quality and risk of bias (6 points), and low quality and high risk of bias (less than or equal to 5 points)[19].

Chart 1. Search strategy focusing on environmental factors.

P (population)	(infant OR baby OR babies OR neonato OR newborn OR “newborn infant” OR child OR children OR childhood OR “preschool child” OR “preschool children” OR “human neonate” OR “newborn baby” OR “newborn child” OR “newborn infant” OR “newly born baby” OR “newly born child” OR “newly born infant”)
E (exposure)	(“environmental exposure” OR “environmental risk factor” OR "environmental risk” AND pesticide OR agrochemical OR agrichemical OR fertilizer OR chemicals OR herbicide OR algicide OR algaecide OR antibacterial OR antibiotic OR insecticide OR acaricide OR bacteriocide OR fungicide OR miticide OR “insecticidal agent” OR “insecticide agent” OR “fungicidal agent” OR “fungicide agent” OR “mite killer” OR “miticide agent” OR “agricultural chemical” OR “herbicidal agent” OR “herbicide agent” OR “phytotoxic agent” OR "anti-bacterial agente” OR “antiinfective agent” OR “antibacterial agent” OR “bacteriocidal agent” OR “anti-mycobacterial agent” OR “anti mycobacterial agent” OR “antimycobacterial agent”) AND (“chemical compound exposure” OR “pesticide exposure” OR “inhalation exposure” OR “occupational exposure” OR “exposure time” OR exposure)
C (comparison)	Identification by reading the abstract
O (Outcome)	(cerebroma OR glioma OR ganglioglioma OR glioblastoma OR glioblastomas OR glyoblastoma OR astrocytoma OR astroglioma OR oligoastrocytoma OR oligodendroglioma OR olegodendrocytoma OR olegodendroglioma OR oligodendrocytoma OR oligodendrocytosis OR oligodendroblastoma OR ependymoma OR medulloblastoma OR "ependymal glioma" OR “ependymal tumor” OR “ependymal tumour” OR "ependymoma myxopapillare" OR "myxopapillary ependymoma" OR “blastoma medullae” OR "medullo blastoma" OR “nervous system tumor” OR “nervous system neoplasms” OR “nervous system tumour” OR "brain neoplasms" OR "brain neoplasm" OR "brain tumor" OR "brain tumour" OR "cerebral tumor" OR "cerebral tumour" OR "cerebrum tumor" OR "cerebrum tumour" OR "intracerebral tumor" OR "intracerebral tumour" OR "intracranial neoplasm" OR "midline tumor" OR "midline tumour" OR "multiple brain tumor" OR "multiple brain tumour" OR "subtentorial tumor" OR "subtentorial tumour" OR "supratentorial brain tumor" OR "supratentorial brain tumour" OR "supratentorial neoplasms" OR "supratentorial tumor" OR "supratentorial tumour" OR "tumor cerebri" OR "tumour cerebri" OR "brain câncer" OR "brain carcinoma" OR "brain malignant tumor" OR "brain malignant tumour" OR "cerebral carcinoma" OR "cerebral neoplasm" OR "brain glioma" OR "cerebral glioma" OR "glia tumor" OR "glia tumour" OR "glial tumor" OR "glial tumour" OR "high grade glioma" OR "low grade glioma" OR "recurrent glioma" OR “glioblastoma multiforme” OR “glioblastoma multiforme” OR “malignant glioma” OR “anaplastic oligodendroglioma”)

Source: Authors.

The quality assessment was performed by reviewers 1, 2 and 3.

Heterogeneity was assessed using Cochran’s Q test (p-value) and inconsistency Index (I^2) and classified as follows: low (0-40%), moderate (30-60%), and high (50-90%)[14]. The meta-analysis included only outcomes with low heterogeneity and not classified as having a high risk of bias.

The meta-analysis was performed using a random effects model and the Mantel-Haenszel method[16]. Odds ratios (OR) were used to measure association, adopting a 95% confidence interval. The meta-analysis was performed using The Cochrane Collaboration’s Review Manager 5® (RevMan 5).

Ethical aspects

The study did not require ethical approval as it analyzed evidence from primary studies using secondary data.

Results

The searches identified 1,158 studies, 14 of which were found to be eligible for analysis after screening[20-33]. Figure 1 shows the study selection process.

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Epidemiological and clinical characteristics

The general study characteristics are presented in Chart 2. The selected articles were published between 1993 and 2018, with two studies being published in 2005[25,27] (studies 6 and 9) and 2009[29,31] (studies 12 and 14) and two (14%) annual publications. With regard country, most of the studies were conducted in the United States, accounting for nine (64%) publications[21,22,25,26-29,32,33]. All the studies were case-control studies[20-33]. The most investigated age group was 0-14 years, accounting for five (36%) studies[20,23,30,33]. The most commonly studied histological type was astrocytomas, present in eight (57%) of the studies[20-23,29,30,32,33] (Chart 2).

Features of environmental exposure

The environmental risk factor exposure to all pesticide classes was found in all the studies. The most common exposure setting was the home, identified in 10 (71%) of the articles[20-26,28-31] (Chart 3).

Only one study (7%) reported a possible association between exposure to pesticides the year before pregnancy and CNS tumors[24]. Exposure to pesticides during pregnancy was associated with an increased risk of cancer in four (28%) studies[20,24,25,28]. One study (7%) found a higher odds ratio for the outcome after birth[28].

Two studies (14%) reported an association between exposure to all groups of pesticides and astrocytomas[21,32]. One study (7%) found an elevated risk of astrocytoma for both maternal and paternal exposure to insecticides[33]. Two studies (14%) showed an increased chance of astrocytoma for exposure to herbicides/fungicides[29,33]. Increased risk of PNET was observed for exposure to all pesticides[32], especially herbicides[33].

One study (7%) observed an association between use of pesticides to control pests in the home, garden, or orchard and CNS tumors[22]. Another study examining the association between genetic polymorphisms and childhood brain tumors showed increased risk of tumors with exposure any time from 1 month before conception and birth[26]. Two specific pesticides (methyl bromide and chlorothalonil) showed an association with cancer in one (7%) of the studies[27].

Risk bias analysis (methodological quality)

Eight of the 14 studies scored seven points (high quality and low risk of bias)[20,25-27,32-34], five scored six (intermediate quality and risk of bias)[21,23,28,30,31], and one scored four (low quality and high risk of bias)[23].

Metanalysis

For the meta-analysis, the studies were divided into two subgroups based on histological type. First, an analysis was performed of all the tumor groups, resulting in high heterogeneity among studies (I^2=88%). We therefore analyzed the data for two groups of CNS tumors: astrocytomas and PNET.

The first analysis (exposure to pesticides and astrocytomas) included five studies[21,29,30,32,33], which showed low heterogeneity (I^2=26%). There was evidence of an association between exposure to all pesticide classes and astrocytomas (OR 1.50; 95%CI: 1.15-1.96; p=0.03) (Figure 2A).

The analysis of exposure to pesticides and PNET included four studies[21,29,32,33] without presence of heterogeneity (I^2=0). There was no evidence of an association between exposure to pesticides and development of PNET (OR 1.09; 95%CI: 0.82-1.44; p=0.55) (Figure 2B).

Discussion

Study synthesis

The individual findings of the studies included in this review point to an association between exposure to all pesticide classes and CNS tumors under certain circumstances, including exposure before and during pregnancy[20,24,25,28] and residential pesticide use[20-22,24-26,28]. Two meta-analyses showed increased risk for occupational exposure or maternal exposure during pregnancy in the home[12,34].

Pesticides are classified as potentially carcinogenic substances, particularly insecticides used for residential insect control[35]. Carbamates and organophosphates are able to cross the placental barrier and can therefore be readily transferred from the mother to fetus[36,37]. Fetuses and children are more vulnerable to exposure to these types of pesticides because they have an immature nervous system and their cells divide more rapidly[38]. The synthesized findings of this review showing that exposure before and especially during preg-

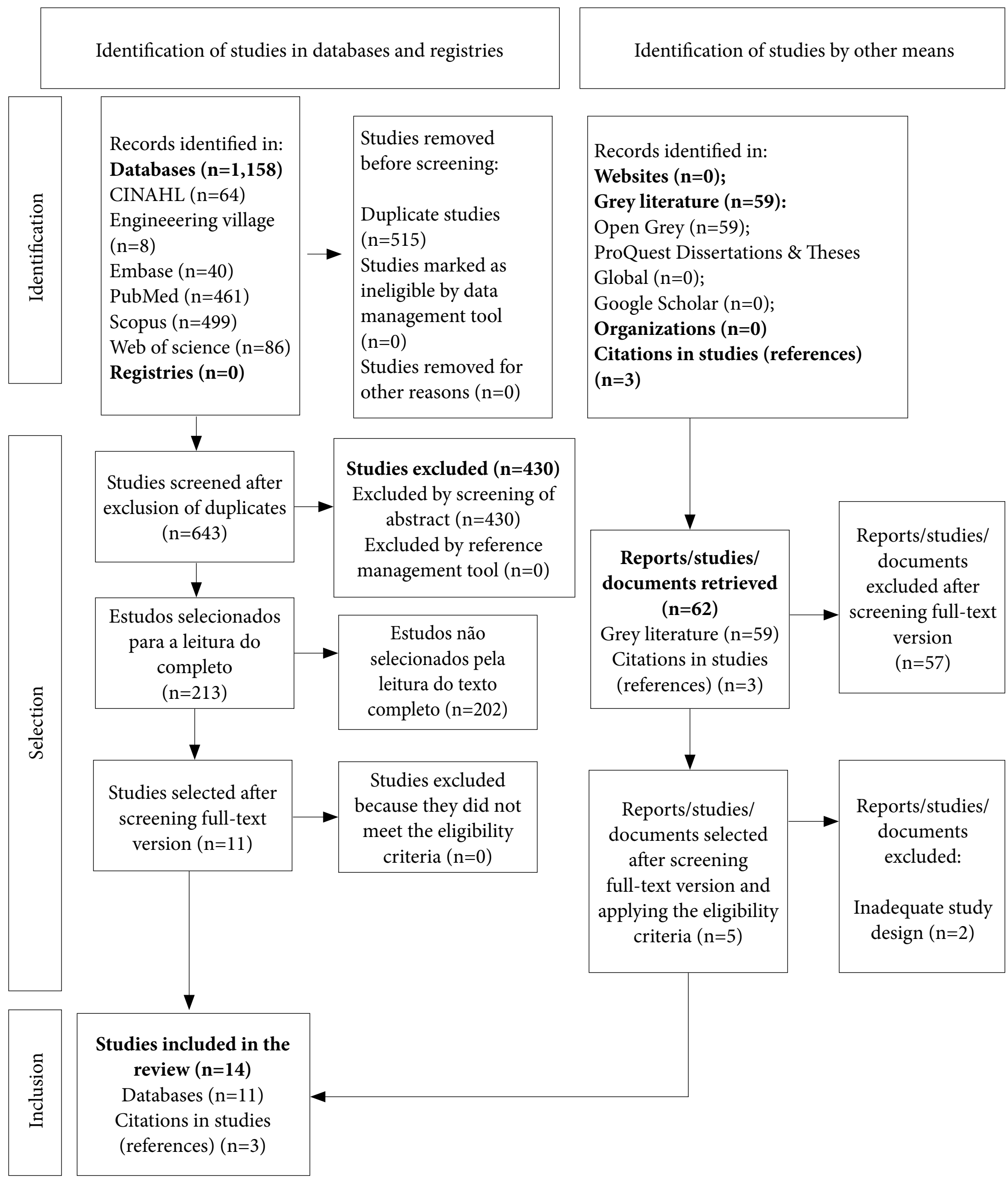

Figure 1. Flowchart of the study selection process adapted from PRISMA.

Source: Authors.

nancy increases risk of CNS tumors in children corroborate pathophysiological evidence of the carcinogenicity of these chemicals.

Some studies indicate that proximity to industrial sites and urban areas (exposure to chemical pollutants) can contribute to higher incidence of CNS tumors in children[39,40]. Other studies investigating the use of agrichemicals close to residential areas found differing results, reporting excess risk among children living within a 1 km radius of crops[41], but not in counties with harvested acreage of crops[42].

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Chart 2. Study clinical and epidemiological characteristics.

Reference/year	Country	N° of cases and controls	Age (years)	Type of tumor
Bagazgoïtia *et al.*, 2018[20]	France	437 cases/3,102 controls	0-14	Gliomas, astrocytomas, ependymomas and embryonic tumors
Bunin *et al.*, 1994[21]	United States	321 cases/321 controls	0-6	Astrocytomas and PNET
Davis *et al.*, 1993[22]	United States	45 cases/85 controls	0-10	Astrocytomas, medulloblastoma and embryonal tumors
Febvey *et al.*, 2016[23]	France, United Kingdom and Germany	1,361 cases/5,498 controls	0-14	Astrocytomas, ependymomas, embryonic tumors and others
Greenop *et al.*, 2013[24]	Australia	303 cases/941 controls	0-14	Gliomas, ependymomas and embryonal tumors
Nielsen *et al.*, 2005[25]	United States	65 cases/136 controls	0-10	Astroglias and PNET
Nielsen *et al.*, 2010[26]	United States	201 cases/285 controls	0-10	Astroglia, medulloblastoma, ependymoma and PNET
Reynolds *et al.*, 2005[27]	United States	352 cases/395 controls	0-4	CNS tumors
Rosso *et al.*, 2008[28]	United States	283 cases/262 controls	0-6	Medulloblastoma and PNET
Shim *et al.*, 2009[29]	United States	526 cases/526 controls	0-10	Astrocytoma, PNET and other tumors
Shutz *et al.*, 2001[30]	Germany	466 cases/2,458 controls	0-14	Medulloblastomas, astrocytoma and ependymomas
Spix *et al.*, 2009[31]	Germany	88 cases/204 controls	0-5	CNS tumors
Walker *et al.*, 2007[32]	United States	766 cases/3,487 controls	0-14	Astrocytomas and PNET
Wijngaarden *et al.*, 2003[33]	United States	604 cases/604 controls	0-6	Astrocytomas and PNET

Source: Authors.

Comparison with other literature reviews

The astrocytoma subgroup meta-analysis showed increased risk and moderate heterogeneity. Two of the studies that found elevated risk investigated the association between parental occupational exposure to pesticides and risk of CNS tumors. The odds ratios reported by these studies (2.26; 95%CI: 1.36-3.75 and 1.79; 95%CI: 1.08-2.95) show that exposure to pesticides may be an important factor in the etiology of childhood astrocytomas[29,33].

Studies investigating the association between exposure to all pesticide classes and PNET in groups with and without CNS tumors found similar results. Two studies observed a strong association (OR 1.32; 95%CI: 0.70-2.48 and OR 1.32; 95%CI: 0.81-2.14)[33,34], while one study suggested that exposure to pesticides was a protective factor for PNET[21].

The most recent meta-analyses investigating residential or occupational exposure to pesticides involved children and adolescents (0-19 year) and young adults (<25 years). One found a significantly increased effect of 1.34 (95%CI 1.15-1.56) for exposure to pesticides during childhood with moderate heterogeneity (I^2=60%)[10]. These results suggest that increased risk of astrocytomas and PNET with exposure to pesticides may be similar across all age groups up to young adults (<25 years). However, it is worth highlighting that the two histological types were part of the same subgroup, unlike our meta-analysis.

Heterogeneity among the studies included in this review hampered the analyses of all the histological type and exposure subgroups. We considered presenting results with moderate to low heterogeneity to make the findings representative of reality. Observational studies already incur considerable risk of bias and it is therefore

Chart 3. Study environmental exposure characteristics.

Reference/Year	Place and type of exposure	Odds Ratio (95%CI)
Bagazgoïtia *et al.*, 2018[20]	The home - Pesticides	Pesticidas (inseticidas) durante a gravidez OR 1,4 (1,2-1,8)
Bunin *et al.*, 1994[21]	The home - Pesticides	Pesticidas e astrocitoma OR 1,5 (0,8-2,7) Pesticidas e PNET OR 0,7 (0,4-1,4)
Davis *et al.*, 1993[22]	The home - Pesticides Herbicides Insecticides	Pesticidas e pragas OR 3,4 (1,1-0,6) Inseticidas no pomar OR 2,6 (1,1-5,9) Herbicidas no quintal OR 3,4 (1,2-9,3)
Febvey *et al.*, 2016[23]	Work - Pesticides	Exposição materna durante a gravidez OR 0,76 (0,41-1,41) Exposição paterna durante a gravidez OR 0,71 (0,53-0,95)
Greenop *et al.*, 2013[24]	The home - Pesticides	Pesticidas no ano anterior a gravidez OR 1,54 (1,07-2,22) Pesticidas durante a gravidez OR 1,52 (0,99-2,34) Pesticidas após o nascimento OR 1,04 (0,75-1,43)
Nielsen *et al.*, 2005[25]	The home - Pesticides	Pesticidas (por alelo PON1-108T) durante a gravidez ou infância OR 2,6 (1,2-5,5)
Nielsen *et al.*, 2010[26]	The home - Pesticides	Exposição a pesticidas por (alelo PON1-108T) OR 1,8 (1,1–3,0) Exposição a pesticidas por (alelo FMO1–9536) OR 2,7 (1,2–5,9)
Reynolds *et al.*, 2005[27]	Agricultural site - Pesticides	Pesticidas (brometo de metila) OR 1,59 (0,87-2,89) Pesticidas (clorotalonil) OR 1,18 (0,58-2,38)
Rosso *et al.*, 2008[28]	The home - Pesticides	Pesticidas durante a gravidez OR 1,6 (1,0–2,4) Pesticidas após o nascimento OR 1,7, (1,1–2,6)
Shim *et al.*, 2009[29]	The home - Pesticides (herbicides)	Astrocitoma e exposições a herbicidas de uso residencial OR 1,9 (1,2–3,0)
Shutz *et al.*, 2001[30]	The home and farm - Pesticides	Pesticidas nos jardins OR 0,94 (0,68-1,29) e nas fazendas OR 0,41 (0,18-0,93)
Spix *et al.*, 2009[31]	Agricultural site e the home - Pesticides	Exposição a pesticidas e herbicidas OR 0,39 (0,18 -0,83)
Walker *et al.*, 2007[32]	Agricultural site - Pesticides	Pesticidas e tumores do SNC OR 1,3 (0,9-1,8) Pesticidas e astrocitomas OR 1,4 (0,8-2,2) Pesticidas e PNET OR 1,3 (0,7-2,5)
Wijngaarden *et al.*, 2003[33]	Work - Pesticides	Astrocitoma e exposição paterna a inseticida OR 1,5 (0,9-2,4) Herbicida OR 1,6 (1,0-2,7) e fungicida OR 1,6 (1,0-2,6) PNET e exposição paterna para herbicidas OR 1,5 (0,9-2,6) Astrocitomas e exposição materna a inseticidas OR 1,9 (1,1-3,3) Herbicidas OR 1,3 (0,5-3,7) e fungicidas não agrícolas OR 1,6 (0,9-2,7)

Source: Authors.

important to consider these difficulties in the evidence summary.

One of the limitations of this review is therefore the heterogeneity of the observational studies included in the meta-analysis and the limited number of studies that met the inclusion criteria for statistical analysis, bearing in mind that Cochran's Q test should be used with caution when the number of studies is less than 20[43]. In addition, the odds ratios found in the present study may have been affected by publication bias, which can prevent the collection of all existing evidence and means that data published in the studies are often not fully representative of all outcomes (both positive and negative) related to exposure factors[44].

This review sought to ascertain whether there is an association between exposure to pesticides and living in industrial or rural areas and CNS tumors. We found a large amount of evidence in the literature for exposure to pesticides, with individual study findings pointing to a possible association with childhood CNS tumors. However, the synthesis of the evidence only included two histological types of tumors: astrocytomas and PNET. The results suggest an increased risk of

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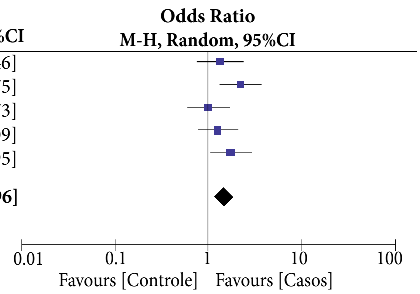
(A)

Study or Subgroup	Casos Events	Casos Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95%CI
BUNIN et al. (1994)	34	155	26	155	17.2%	1.39 [0.79, 2.46]
SHIM et al. (2009)	53	226	27	226	20.4%	2.26 [1.36, 3.75]
SHUTZ et al. (2001)	18	104	374	2208	19.6%	1.03 [0.61, 1.73]
WAlKER et al. (2007)	20	277	193	3414	22.2%	1.30 [0.81, 2.09]
WIJNGAARDEN et al. 2003	53	154	35	154	20.6%	1.78 [1.08, 2.95]
Total (95% CI)		**916**		**6157**	**100.0%**	**1.50[1.15, 1.96]**
Total events						

Heterogeneity: $Tau^2=0.02$; $Chi^2=5.43$, df=4 (P=0.25); $I^2=26\%$
Test for overall effect: Z=2.97 (P=0.003)



(B)

Study or Subgroup	Casos Events	Casos Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95%CI
BUNIN et al. (1994)	31	166	39	166	27.4%	0.75 [0.44, 1.27]
SHIM et al. (2009)	26	146	24	146	20.7%	1.10 [0.60, 2.03]
SHUTZ et al. (2001)	11	150	193	3414	19.3%	1.32 [0.70, 2.48]
WAlKER et al. (2007)	51	158	42	158	32.6%	1.32 [0.81, 2.14]
WIJNGAARDEN et al. 2003		**620**		**3884**	**100.0%**	**1.09[0.82, 1.44]**
Total events	119		298			

Heterogeneity: $Tau^2=0.00$; $Chi^2=2.88$, df=3 (P=0.41); $I^2=0\%$
Test for overall effect: Z=0.59 (P=0.55)

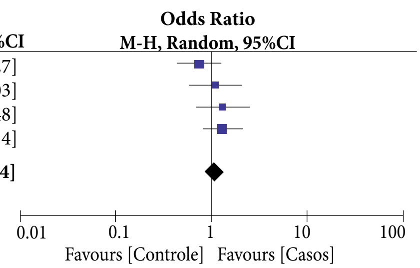


Figure 2. Forest plot of exposure to pesticides and astrocytomas (A) and PNET (B).

Source: Authors.

astrocytomas in children exposed to all pesticide classes.

Individual studies observed that place of residence was a factor in increased risk; however, it was not possible to synthesize the evidence due to the limited number of studies retrieved. Further research is therefore required to investigate this type of exposure.

To strengthen the body of evidence on exposure to pesticides, including exposure to industrial and agricultural activities, and CNS tumors, studies need to be more specific, especially in relation to histological type and the chemical substance. Associated studies are also required to investigate genetic and environmental aspects, both of which are key factors in the etiology of cancer.

The investigation of factors related to the risks of using pesticides is vital to inform environmental policy and curb the indiscriminate use of these substances in agriculture. In recent years, the Brazilian government has approved the use of more than 86 highly hazardous pesticides and their derivatives[45].

A package of measures are therefore required, including public policies, effective environmental protection, and educational initiatives in primary health care services. The latter should address the residential use of potentially harmful chemicals, encourage healthy eating based on the consumption of organic foods, promote the use of personal protective equipment by parents employed in agriculture, and provide guidance to avoid the use of pesticides in the home before and during pregnancy.

Collaborations

All authors read and approved the content of the manuscript, in addition to actively participating in the development of the study in the elaboration of the steps that follow: ALC Mota participated in the conception, data search, data analysis and writing of the article. IM Barbosa participated in the conception, search for data, data analysis and evaluation of the final writing. AB Rodrigues participated in the data analysis and critical evaluation of the final writing. EMC Chaves participated in the data analysis and critical evaluation of the final writing and PC Almeida participated in the design, data search, analysis of the data and evaluation of the final essay.

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