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The Impact of Chronic Exposure to Organophosphate Pesticides on the Incidence of Primary Brain Tumors in Farmers: A Narrative Review

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ABSTRACT

Introduction: Primary brain tumors have high mortality and morbidity rates. Its causes and risk factors have not been explored further. Several studies indicate that exposure to pesticides can be one of the main triggering factors. Organophosphate insecticide is one of the most common pesticides used by farmers. Chronic exposure to organophosphates is known to trigger an imbalance of reactive oxygen species (ROS) in the body by suppressing the acetylcholinesterase enzyme. **Objective:** This study aimed to determine the impact of chronic exposure to organophosphates in terms of the types of organophosphates used by farmers, frequency of usage, and duration of exposure, using a narrative review method. **Methods:** A literature search was conducted with multiple electronic databases, such as PubMed, ScienceDirect, Cochrane Library, and Springer. The keywords will be searched using the boolean operator method, while synonyms will be found in the Medical Subject Heading (MeSH) database. Articles were assessed using the Newcastle-Ottawa Scale (NOS) Questionnaire. **Results:** There were 1071 articles found, but only 14 were selected for review. The studies showed that there was a relationship between the type, frequency, and duration of organophosphate usage and the incidence and risk factors for primary brain tumors. **Conclusion:** Chronic exposure to organophosphate pesticides, either directly or indirectly, can increase the incidence of primary brain tumors in farmers. The influencing factors include the type, frequency, and duration of pesticide exposure. The most influential factor is the duration of chronic pesticide exposure by farmers. Pesticide reduction exposure is beneficial in preventing the incidence of primary brain tumors in farmers.

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INTRODUCTION

Primary brain tumors (PBT) are tumors that originate in the brain parenchyma and its surrounding structures. Although the incidence is low, they have high mortality and morbidity rates.[1] Furthermore, the causes and risk factors of the disease remain unclear. Pesticide exposure has been identified as a risk factor.[2] Farmers commonly use organophosphate insecticides (OPEs). It has a strong killing power, with an immediate and obvious effect on the plants.[3] In addition, this pesticide is widely recommended in agriculture because it decomposes easily in nature compared to other types, such as dichlorodiphenyltrichloroethane (DDT). Chronic exposure to organophosphates can cause the body to increase the production of reactive oxygen species (ROS) through inactivation of the acetylcholinesterase (AChE) enzyme is found in chronic exposure to organophosphates.[4,5,6] Cancer can develop through a variety of mechanisms, including the ability of cells to replicate indefinitely, the occurrence of continuous angiogenesis, the avoidance of growth suppression and destruction of the body's immune system, the avoidance of apoptosis, autonomous regulation of cell energy requirements, invasion and metastasis activation, and genome instability.[7] One type of organophosphate, chlorpyrifos (CPF), is known to mediate oxidative stress in neutrophils through reactive oxygen species (ROS). This raises the levels of RIPK1/RIPK3/MLKL expression and inhibits the levels of caspase-8 expression, which then leads to cell necrosis.[8]

Several studies in agricultural areas, both in developing and developed countries, have found a significant increase in incidences of primary brain tumors associated with pesticide exposure, especially organophospates. However, existing research has not summarized in detail the characteristics of organophosphate exposure obtained by farmers with PBT. For example, a case-control study in southwestern France showed that occupational pesticide exposure increased the incidence of brain tumors.[9] Meanwhile, a study in Brazil showed that there was a tendency to increase mortality from brain cancer in agricultural areas.[10] This data shows that people, especially farmers in agricultural areas, have a higher incidence and mortality rate in comparison to people who are not exposed to pesticides. Thus far, no article has examined the current incidence of primary brain tumors and the characteristics of organophosphate pesticide exposure in agricultural areas. This lack of research encouraged the authors to conduct a narrative review on the impact of organophosphate pesticide exposure on the incidence of primary brain tumors among farmers.

OBJECTIVE

This study was to determine the impact of chronic organophosphate exposure from several aspects, i.e., the type of organophosphate used by farmers, frequency of use, and duration of exposure, through a narrative review.

METHODS

This study used a narrative review study design. The study selection was carried out in April 2021, with data retrieved between April and August 2021. Databases used in this study are the PubMed database, Cochrane Library, Springer, ScienceDirect, and other reliable sources. The technique of searching for research articles was through bibliographic searching and manual hand searching. The article search method used the PICO (population/patients, indicators, comparison, outcome) method through keywords and free text. Keyword synonyms were searched using the aid of Medical Subject Headings (MeSH). Articles found were evaluated using the NOS questionnaire, and only those that had a good or fair category were included.

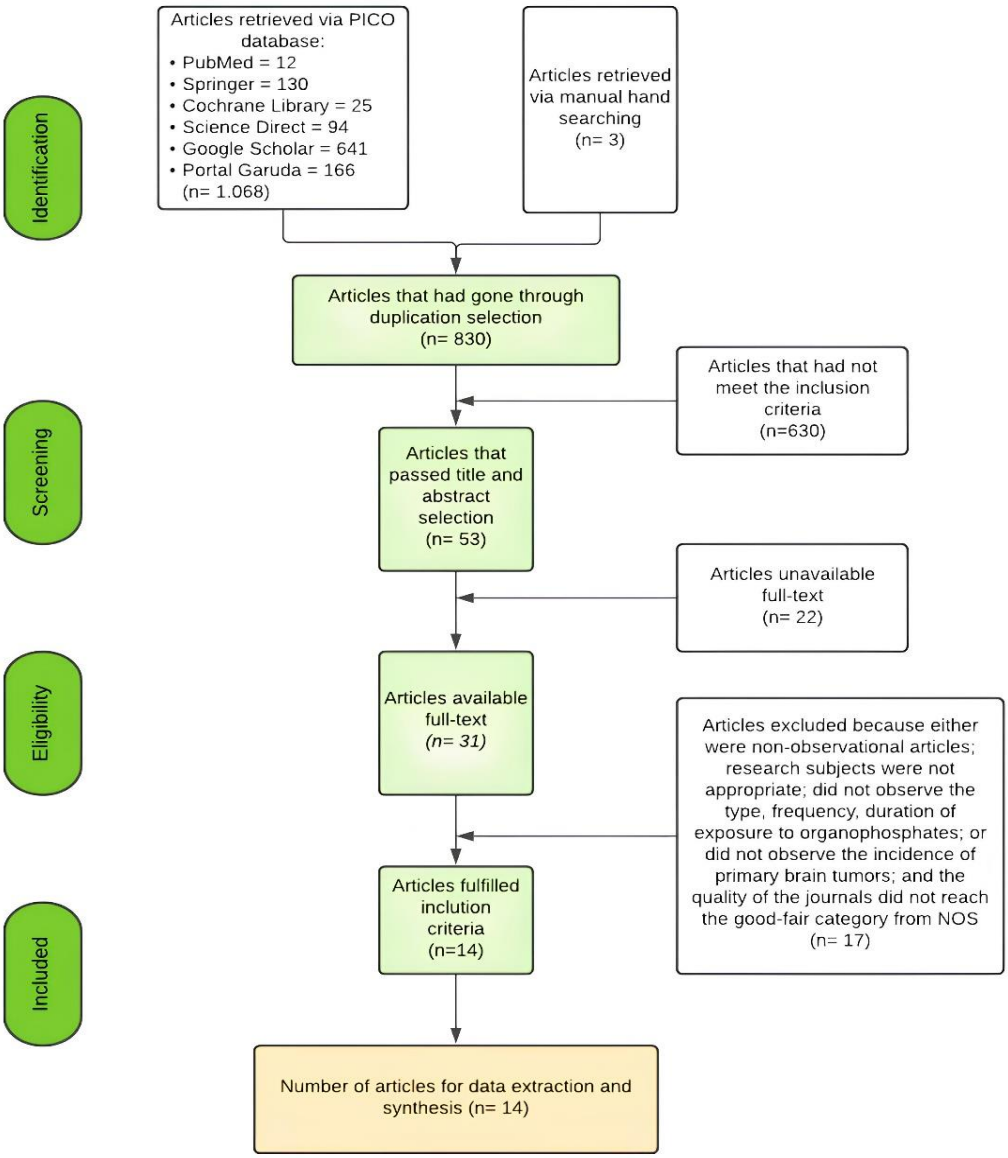

Figure 1. PRISMA of study selection

RESULTS

The article search was conducted in April 2021; therefore, it included research published between 2012 and 2021. Studies retrieved using the PICO keywords were downloaded into Mendeley albums. The publications found were 1071 research articles. The duplication selection showed that there were 189 duplicate journals. There were 830 articles left after the duplication merger. Articles were manually sorted by title and research abstract. There were 53 articles that met the exclusion criteria; however, only 31 of them are available in full text or in English. The remaining articles were then reviewed, and journals with research subjects were unsuitable or did not observe any of the variables of this study (type, frequency, duration of exposure to organophosphates, incidence of primary brain tumors, or article quality less than good or fair in the NOS questionnaire), were excluded. After reviewing the journal's quality, 14 articles were selected for final inclusion criteria. The PRISMA diagram can be seen in Figure 1.

The pesticide exposure studied in this journal is the type, frequency, and duration of exposure to subject groups (farmers). The characteristics of the articles found are shown in Figure 2. The types of pesticides listed in the journal are organophosphates of the chlorpyrifos, terbuphos, methamidophos, carbofuran, malathion, diazinon, and prophenophos groups. The average farmer did not only use one type of pesticide while working in the agricultural sector and often combined other types of pesticides (e.g., carbamates). There were also articles that did not list the specific types of pesticides used by farmers.

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However, organophosphates were consistently used by farmers in journals that did not include pesticide groups as research variables.

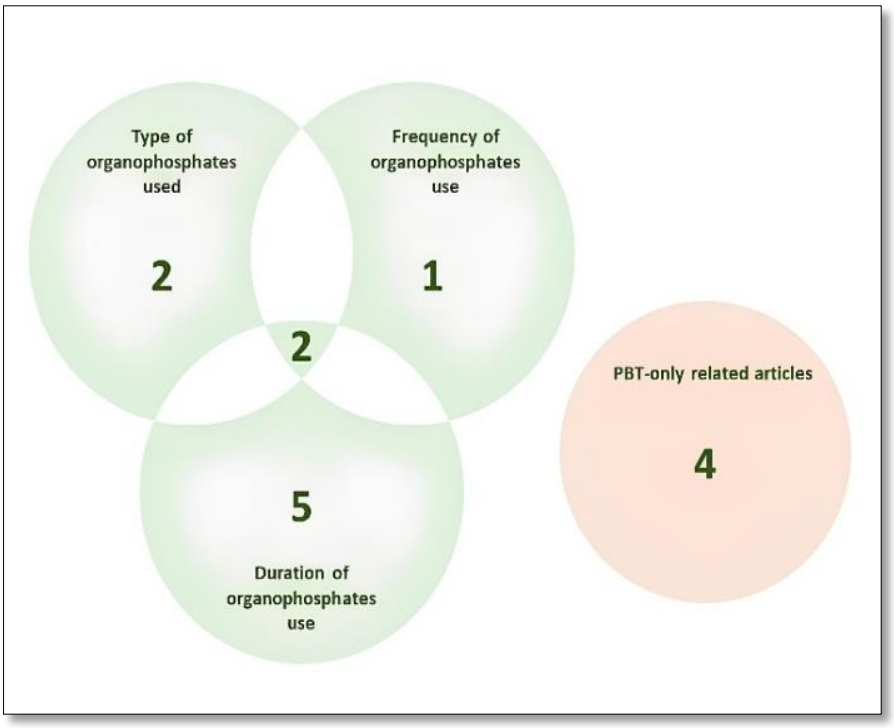

Figure 2. Number of studies based on variable used in this research

Type and frequency of organophosphates

Five articles looked into the type and frequency of organophosphate exposure, as well as the onset and risk factors for primary brain tumors.[11–15] Several studies have clearly stated which types of organophosphates influence research results. The most widely used types are chlorpyrifos or malathion. Articles on frequency of use used calculations ranging from day per week to day per month to the number of days of pesticide exposure throughout a lifetime. According to the journal, farmers typically use one spray each week or month. Table 1 contains details about this variable.

Table 1. Impact of type and frequency of OPEs on the incidence of PBT

Researcher Name (Year) and Location	Study Design	Organophosphates Exposure			
		Type	Impactful	Frequency of use	Impactful
Starks *et al*. (2012), USA	Cohort	- Malathion (77%) - Chlorpyriphos (60%) - Terbuphos (51%) - Diazinon (43%)	Yes	-	-
Parrón *et al*. (2014), Spain	Case-control	-	-	High intensity uses of pesticides	Yes
Manyilizu *et al*. (2016), Tanzania	Cohort	- Prephonophos - Chlorpyriphos	Yes	On average, 1 spraying in one week, or 38 weeks in one year	Yes
Yiin *et al*. (2012), USA	Case-control	Organophosphates (OPEs) in general	Insignificant (OR 1.00; 95% Ci 0.98-1.01)	-	-
Payán-Rentería *et al*. (2012), Mexico	Cohort	- Chlorpyriphos - Terbuphos - Methamidophos - Carbofuran	Yes	On average 4-5 times spraying in 5 months	Yes

Duration of Exposure to Organophosphates

A total of seven articles discussed the impact of the duration of organophosphate use on the incidence or risk factors for primary brain tumors.[13,15–20] The study's subjects pesticide exposure ranged from three years to a lifetime. This exposure could take the form of direct or indirect contact. All articles that analyzed the varied duration of organophosphate usage showed that the duration of pesticide use (supported by direct contact with this substance) had an impact on farmers, as shown in Table 2.

Table 2. Impact of exposure duration of OPEs on the incidence of PBT

Researcher Name (Year) and Location	Study Design	Organophosphates Exposure		
		Duration	Impactful	Exposure Type
Piel *et al*. (2017), France	Cohort	A minimum of 3 years of exposure for a lifetime, especially for farmers who use pesticides	Yes	chronic, direct contact
Payán-Rentería *et al*. (2012), Mexico	Cohort	Average 19 years of exposure (April–August [5 months] high-intensity exposure)	Yes	chronic, direct contact
Miranda Filho *et al*. (2014), Brazil	Cohort	Exposure to high levels of chronic pesticides over the past 30 years has affected farmers and communities in the Serrion agricultural area.	Yes	chronic, direct contact, indirect contact
Baldi *et al*. (2021), France	Case-control	Exposure every day for life; grapes average 15 years, rice fields 21 years, and vegetable gardens 12 years	Yes	chronic, direct contact, indirect contact
Madani *et al*. (2016), Algeria	Cohort	Exposure for more than 6 years	Yes	chronic, direct contact
Manyillizu *et al*. (2016), Tanzania	Cohort	Chronic exposure on average 12 years	Yes	chronic, direct contact
Camille *et al*. (2017), France	Case-control	-	-	direct contact, indirect contact

Impact of Organophosphates Exposure on the Incidence of Primary Brain Tumors

Research articles that studied the type, frequency, and duration of use of organophosphates were four, three, and seven articles, respectively. While articles that discuss primary brain tumor-related topics were only in four journals.[16,18,19,20] A summary of these three variables is listed in Table 3, while the incidence of primary brain tumors can be seen in Table 4. All research articles showed a relationship between the type and frequency of pesticide use, except the study by Yiin *et al.*[14] These studies also showed significant results for the relationship between duration of exposure to incidence and risk factors for primary brain tumors. Therefore, it was concluded that chronic exposure to organophosphate pesticides has an impact on the incidence of primary brain tumors in farmers.

Table 3. The range of reasearch studied

Variable	Number of Studies	Research Name and Year	Range: Farmer's amount of OPEs used, frequency, and duration
Organophosphates Type			
Malathion	1	Starks *et al*. (2012)	77%
Chlorpyriphos	3	- Payán-Rentería *et al*. (2012) - Starks *et al*. (2012) - Manyilizu *et al*. (2016)	60%
Terbuphos	2	- Payán-Rentería *et al*. (2012) - Starks *et al*. (2012)	51%
Diazinon	1	Starks *et al*. (2012)	43%
Prophenophos	1	Manyilizu *et al*. (2016)	Unavailable
Carbofuran	2	- Payán-Rentería *et al*. (2012) - Starks *et al*. (2012)	Unavailable

Table 3. The range of reasearch studied

Variable	Number of Studies	Research Name and Year	Range: Farmer's amount of OPEs used, frequency, and duration*
Organophosphates Frequency of Use			
Weekly use	1	Manyilizu *et al*. (2016)	± once a week
Monthly use	1	Payán-Rentería *et al*. (2012)	± once a month
High-intensity use	1	Parrón *et al*. (2014)	8883.74 ton of pesticides annually
Organophosphates Duration of Use			
Chronic use	1	Piel *et al.* (2017)	3 years-lifetime use
	1	Payán-Reteria *et al*. (2012)	Average 19 years exposure
	1	Miranda Filho *et al.* (2014)	Average 30 years exposure
	1	Baldi *et al.* (2021)	- Vine farmers: average 15 years of exposure. - Fields farmers: average 21 years of exposure. - Fruit and vegetable farmers: average 12 years of exposure.
	1	Madani *et al.* (2016)	≥6 years
	1	Manyilizu *et al.* (2016)	Average 12 years exposure
Organophosphates Exposure Type			
Direct exposure	7	- Payán-Rentería *et al*. (2012) - Miranda Filho *et al*. (2014) - Madani *et al* (2016) - Manyilizu *et al*. (2016) - Camile *et al*. (2017) - Piel *et al*. (2017) - Baldi *et al.* (2021)	- Without adequate PPE - Incorrect personal hygiene
Indirect exposure	3	- Miranda Filho *et al*. (2014) - Camile *et al*. (2017) - Baldi *et al.* (2021)	- Storage inside the house - Post spraying clothes left unattended inside the house

*This data was processed from the extraction results of 14 articles in April–August 2021. The variables found in the studies had different values because the indicators used in each research article vary.

Table 4. Incidence of PBT in research articles

Researcher Name, Year, and Location	PBT incidences
Piel *et al*. (2017), France	273 cases in 5.3 years of research
Starks *et al*. (2012), USA	-
Kachuri *et al.* (2017), Canada	<5 cases
Parrón *et al.* (2014), Spain	916 cases of total 1.832.053
Lerro *et al.* (2019), USA	93 primary brain tumors of 8.700 cancer cases
Filho *et al.* (2014), Brazil	5.734 brain tumors death in research
Baldi *et al.* (2021), France	1.788 primary brain tumors
Madani *et al.* (2016), Algeria	-
Manyizilu *et al.* (2016), Tanzania	-
Yiin *et al.* (2012), USA	1.873 cases
Rezaianzadeh *et al.* (2020), Iran	1.043 malignant brain neoplasm case
Camille *et al*. (2017), France	1.788 glioma and meningioma cases
Payán-Renteria *et al*. (2012), Mexico	-
Salerno *et al.* (2016), Italy	6 of 1.000 farmers had primary brain tumors

DISCUSSION

The increase in the incidence and mortality ration of brain cancer over the last decade might be related to the improved diagnostic capacity due to the use of CT scans and MRIs. Aging has an impact because it is a significant risk factor for brain cancer.

Filho *et al*. found that the Serrana area, a small

agricultural city in Brazil, has a higher incidence and mortality ratio than the country's metropolitan cities, which have better access to medical care.[18]

The aging factor must also be considered, as the Serrana area has a higher ratio of sufferers than the elderly population in big cities. Therefore, the most common cause is environmental exposure, which includes various pesticides. One study found that farmers who used pesticides had an increased risk of developing primary brain tumors.[21] Other studies have shown an increased risk of primary brain tumors for farmers and their families who live in agricultural areas.[16,19] This statement aligns with the Agricultural Health Study in the United States, which found a four-fold increase in glioma cases among farmers exposed to chlorpyrifos.[22] Although studies on organophosphate exposure used a variety of instruments, the majority of them showed the impact of chronic exposure to organophosphate pesticides on primary brain tumors among farmers.

Kachuri *et al*., Lerro *et al*., and Salerno et al. did not specifically examine primary brain tumors but rather reported the number of cases that subjects had.[23,24,25] Kachuri *et al*. found that there was an increased risk of cancer, but the incidence of primary brain tumors was only <5 cases out of 70,057 study subjects.[23] Meanwhile, Lerro *et al*. showed that there were 93 cases of primary brain tumors among the 8,700 cancers studied. Similar to the two previous journals, Salerno *et al*. reported that six out of 1,000 farmer subjects had primary brain tumors.[24,25] The average incidence of primary brain tumor in these three journals was 0.58%. This value indicates that the incidence of primary brain tumors in farmers is not significant when compared to other tumors. However, it should be noted that Central Nervous System tumors do not exhibit detectable in situ or premalignant stages, unlike other carcinomas. Low-grade lesions can spread across the brain, create significant clinical impairments, cannot be resected, and have a poor prognosis. In addition, the anatomic location of brain neoplasms can predispose to serious complications (e.g., benign meningiomas can cause cardiac, vascular, or respiratory arrest).

Organophosphates are known to cause the inactivation of acetylcholinesterase (AChE). Inhibition of AChE in the blood can initiate cellular dysfunction, which then leads to increased activity of free radicals and reactive oxygen species (ROS) in erythrocytes.[26] This causes cellular oxidative stress due to an imbalance between antioxidants and oxidants, causing changes in the structure of cell formation.[27] Elevated levels of ROS, as well as downregulation of ROS and antioxidants, have been associated with nucleic acid, protein, and lipid breakdown. The effect can lead to chromosomal instability, mutations, loss of cell organelle function, membrane damage, and other stages of the carcinogenesis process.[28] The mind map of this study can be seen in Figure 3.

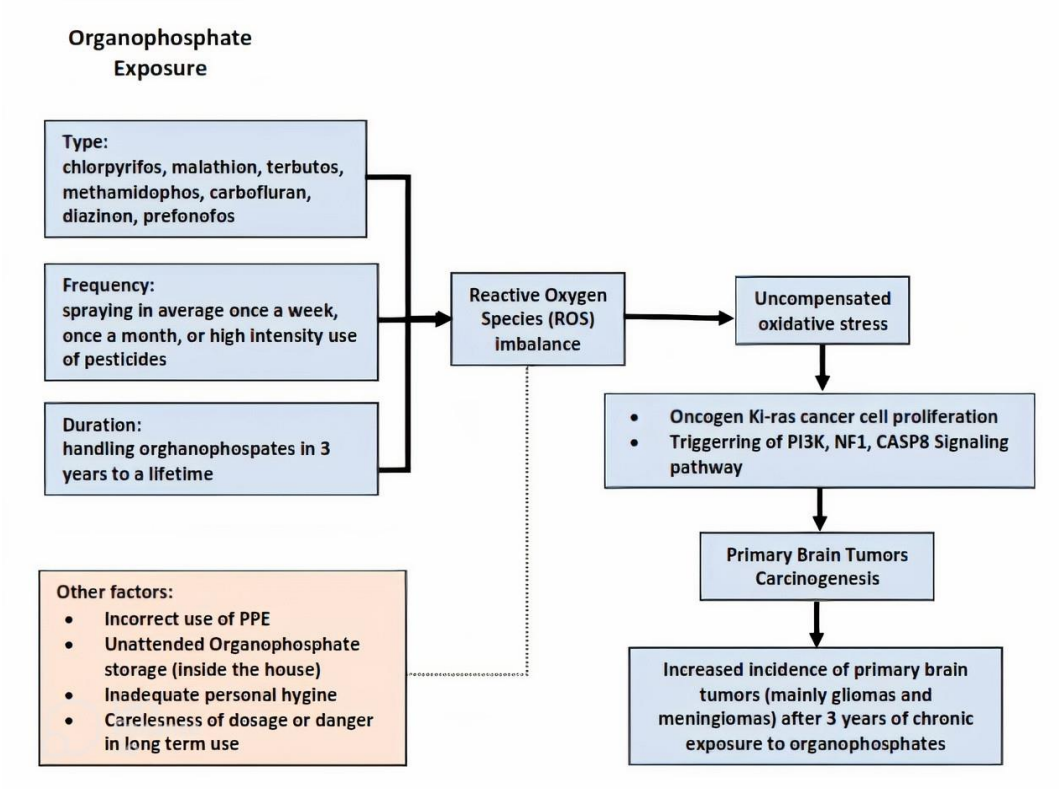

Figure 3. Mind map of the impact of chronic OPEs exposure on PBT's incidence

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Articles that discuss the risk of primary brain tumors associated with organophosphates are still limited. Countries that have undertaken studies are still unable to answer with precision how many pesticides were used in their area, which can affect the number of cases of primary brain tumors. Therefore, this study was unable to conclude the dose of organophosphate exposure toxicity required to cause primary brain tumors. Some studies do not specify the pesticides used by farmers, the frequency and duration of use, or the types of neoplasms or specific neurological dysfunctions caused by exposure.

Based on the explanation above, it has been proven that the use of pesticides poses a significant risk to the health of farmers and their families, especially with the increase in the incidence of brain tumors. The government is expected to pay more attention to farmers by educating them about the duration of pesticide exposure and the importance of using and storing personal protective equipment (PPE) correctly to avoid contaminating individuals or the surrounding environment. It is vital to explore transitioning away from pesticide use and toward organic farming, which is safer for farmers and consumers of agricultural products.

CONCLUSION

It can be concluded that chronic organophosphate exposure can be one of the main triggering factors for primary brain tumors in farmers. The duration of chronic pesticide exposure by farmers is a significant factor in the incidence of primary brain tumors. Other factors that must be considered are the type and frequency of pesticide use.

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Author Contribution
AP contributes to conceptualization, drafting, editing, and administration. JT and JF perform all data processing, editing, review, and monitoring. All authors read and approved the final draft.

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