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Original Article

Effects of pesticide exposure on neurotoxicity: A bibliometric analysis and cross-sectional study in Indonesia's rural area, Jember

[Efectos de la exposición a pesticidas sobre la neurotoxicidad: Un análisis bibliométrico y un estudio transversal en la zona rural de Jember, Indonesia]

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Abstract

Context: Pesticide chemicals are commonly used by agricultural workers to eliminate pests, but their use has the potential to cause various neurotoxicity in humans.

Aims: To explore the research field related to pesticides and neurotoxicity from a bibliometric and cross-sectional perspective in a rural area of Indonesia, Jember.

Methods: Bibliometric analyses using data on pesticide and neurotoxicity-related research publications were obtained from the Scopus Web database and Vosviewer Software. The cross-sectional study was conducted in an agro-industrial area in Jember, Indonesia. It used a structured interview questionnaire regarding demographic data, clinical conditions of neuropathy, and risk factors for neuropathy due to pesticide exposure.

Results: A total of 469 publications on pesticides and neurotoxicity were included. The publications were mostly from the United States, India, and the United States. The highest publication affiliation was from INSERM, France. Besides "pesticide" and "neurotoxicity", the terms "oxidative stress", "Parkinson's disease", and "organophosphate" were also the most frequently used keywords. In the Indonesia rural area cross-sectional, there were 55 farmers: 24 (43.6%) farmers were highly exposed, and 31 (56.4%) were not exposed. Most of them (47%) complained of peripheral pain and headache. Based on this study, there was no significant difference between the exposed and non-exposed groups regarding cognitive impairment based on questionnaires Q18, neuropathy symptom score (NSS), and neuropathy deficit score (NDS).

Conclusions: This study provides a comprehensive perspective on the current research on pesticides and neurotoxicity. In addition, a cross-sectional study in Jember, Indonesia, showed that pesticide exposure has a cognitive impairment effect on farmers.

Keywords: bibliometrics; cross-sectional; neurotoxicity; pesticide.

Resumen

Contexto: Los trabajadores agrícolas suelen utilizar pesticidas químicos para eliminar plagas, pero su uso tiene el potencial de causar diversas neurotoxicidades en los seres humanos.

Objetivos: Explorar el campo de investigación relacionado con los pesticidas y la neurotoxicidad desde una perspectiva bibliométrica y transversal en una zona rural de Indonesia, Jember.

Métodos: Se obtuvieron análisis bibliométricos utilizando datos sobre publicaciones de investigación relacionadas con pesticidas y neurotoxicidad de la base de datos web Scopus y el software Vosviewer. El estudio transversal se realizó en una zona agroindustrial en Jember, Indonesia. Se utilizó un cuestionario de entrevista estructurada sobre datos demográficos, condiciones clínicas de neuropatía y factores de riesgo de neuropatía debido a la exposición a pesticidas.

Resultados: Se incluyeron un total de 469 publicaciones sobre pesticidas y neurotoxicidad. Las publicaciones eran en su mayoría de Estados Unidos, India y Estados Unidos. La afiliación de publicación más alta fue de INSERM, Francia. Además de "pesticida" y "neurotoxicidad", los términos "estrés oxidativo", "enfermedad de Parkinson" y "organofosforado" también fueron las palabras clave más utilizadas. En el estudio transversal del área rural de Indonesia, había 55 agricultores: 24 (43,6%) agricultores estaban muy expuestos y 31 (56,4%) no estaban expuestos. La mayoría de ellos (47%) se quejaban de dolor periférico y dolor de cabeza. Según este estudio, no hubo diferencias significativas entre los grupos expuestos y no expuestos con respecto al deterioro cognitivo según los cuestionarios Q18, puntuación de síntomas de neuropatía (NSS) y puntuación de déficit de neuropatía (NDS).

Conclusiones: Este estudio proporciona una perspectiva integral sobre la investigación actual sobre pesticidas y neurotoxicidad. Además, un estudio transversal en Jember, Indonesia, mostró que la exposición a pesticidas tiene un efecto de deterioro cognitivo en los agricultores.

Palabras Clave: bibliometría; transversal; neurotoxicidad; pesticida.

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INTRODUCTION

Pesticides are chemicals commonly used by agricultural workers to eliminate pests. The use of these compounds has played an important role in advancing agriculture, especially in the last century (Tudi et al., 2021). However, the use of pesticides turns out to be relatively dangerous for health because they are not specific to pests, but they also have negative effects on non-target organisms, including humans. One of the most frequently studied negative effects of pesticides on humans is neurological toxicity or neurotoxicity (Richardson et al., 2019). In the last few decades, the toxic role of pesticides in nervous system disorders has received much attention because it has been shown to have various pathogenesis pathways, such as triggering oxidative stress, neuroinflammation, and neurodegeneration. For example, a study found that farmers exposed to pesticides had an increase in oxidative stress biomarkers (Sidthilaw et al., 2022). This oxidative stress condition is also proven by experimental studies where pesticide exposure can increase neuroinflammatory conditions and impaired behaviour through INF-γ (Song et al., 2023). A meta-analysis study of 24 studies showed that pesticide exposure can increase neurodegenerative diseases, such as Parkinson's disease (Gunnarsson and Bodin, 2019). Another meta-analysis revealed that farmers affected by pesticide exposure had decreased cholinesterase and haemoglobin levels compared to healthy people (Nuryati et al., 2022). Thus, an alteration in the levels of certain biomarkers could potentially be an early diagnostic of pesticide-induced neurotoxicity (Nuryati et al., 2022).

Despite the progressive development of published literature on pesticides and neurotoxicity, accurate key information concerning the number of relevant publications, authors, affiliations, countries, journals, keywords, and sponsors most frequently used in research related to pesticides and neurotoxicity still needs to be improved. Bibliometrics is a recent approach used to examine academic publications. The existence of Scopus as a scientific database facilitates the development of bibliometric research due to quality assurance through strict content selection (Baas et al., 2020). Scopus is one of the databases with the greatest accuracy that includes various types of abstracts and citations ranging from scientific journals and conference proceedings to scientific books at both global and regional levels and is offered free of charge for selected scientific studies of the academic research community (Baas et al., 2020). Bibliometrics is a method that includes qualitative and quantitative analyses that can provide various data on publication elements, such as country identification, affiliations, sponsors, number of relevant publications, countries, journals, and most common keywords, as well as revealing related research fields (Song et al., 2019). This method provides new researchers insight into the development and boundaries of the research field they want to study. Several bibliometric studies have been conducted to investigate publication trends in pesticides or neurotoxicity separately (Ocmen et al., 2023; Pandey et al., 2023). A bibliometric study of 1,767 articles on Parkinson's disease published from 1986 to 2019 found that "pesticide" and "neurotoxicity" have been among the trending keywords in recent decades (Liu et al., 2020). However, other bibliometric analyses still need to provide a comprehensive overview of pesticide and neurotoxicity research development.

Indonesia, as an agricultural country, is one of the countries with a high amount of pesticide use, making various farmers working in the agro-industrial sector such as agriculture, plantations, forestry, and others at risk (Muller, 2020). According to data from the World Health Organization (WHO), there were 137,300 cases of death and 7,825,000 years of life lost due to disability-adjusted life years (DALY), which are implications of the use of pesticides (World Health Organization, 2016). Therefore, the use of pesticides must be regulated to guarantee the farmer's safety. However, the implementation and enforcement of legislation often need to be improved, especially in low-middle income countries. Most farmers and agricultural communities in Indonesia are low-educated (Yuantari et al, 2013). Therefore, pesticide knowledge, attitude, and practices are often insufficient, potentially leading to extremely high exposure profiles in farmers and farmworkers (Rahaman et al., 2018). Jember is one of the agro-industrial areas in East Java, Indonesia (113°15'47'' until 114°02'35'' East longitude and 7°58'06'' until 8°33'44'' South latitude). Almost half of the Jember area is forest, rice fields, and plantations area, and 40.13% of the population work in agro-industrial sectors involved in agriculture, forestry, hunting, and fishery (BPS, 2020). To date, no study has analysed the effect of pesticide exposure on farmers in Jember. To fill this gap, we built a comprehensive global map of scientific publications related to "pesticide" and "neurotoxicity" research. In this study, we also analysed the profile of pesticide exposure and neurological problems among farmers in Jember, Indonesia.

MATERIAL AND METHODS

Bibliometric analysis

This research uses quantitative descriptive methods with bibliometric analysis of publication data. Data search using the Scopus platform. Scopus is a database platform for scientific content abstracts and citations. In Scopus, content is selected and included in the database through a strict process by the Content Selection and Advisory Board (CSAB). This ensures Scopus has high-quality content and secure credibility. Besides that, in accepting content, Scopus has strict procedures which include agreements with publishers, existing technical infrastructure to obtain publication sources directly from the publishers themselves, and ensuring comprehensive, complete, and accurate coverage of serial content (Baas et al., 2020). Literature types, including regular and review articles, with no language limitation. Relevant articles were exported and stored as csv (including full records and cited references) for further analyses.

Bibliometrics used to scient metric quantitative research. This bibliometrics uses software called *VOSviewer*. *VOSviewer* is software for creating and exploring maps based on network data (Arruda et al., 2022). *VOSviewer* explores co-authorship, co-occurrence, and co-citation linking in network, overlay, and density visualisations. The overlay visualisation shows the colour density, namely from blue (lowest density) to red (highest density) (Hofmann and Chisholm, 2015). Network visualisation shows the relationships between research topics.

Data analysis was carried out on 469 documents using the "analyse search result" facility provided by the Scopus database. The results used are document by year, document by author, document by affiliation, document by country/territory, document by type, document by subject area, and document by funding sponsor. The results of the analysis are presented in the form of tables and diagrams. Keyword retrieval by downloading search results of 469 documents. Analyse keywords to find out bibliometric maps using the VOSviewer application. The author determines keywords used at least four times by the author or appearing in publications. Based on the 469 documents analysed, 1278 keywords were compiled by the author. Seventy-one keywords were used at least four times by the author. Based on these 71 keywords, they were analysed using Network Visualization in the VOSsviewer application.

Jember cross-sectional

Study design

This cross-sectional study was conducted in the agro-industrial area in Jenggawah district, Jember, Indonesia, from September to November 2022. Most societies were farmers, predominantly involved in paddy and tobacco production. This study was approved by the Medical and Health Research Ethics Commission of the Faculty of Medicine, Universitas Jember (1.68/H25.1.11/KE/2022), dated September 21st, 2022.

Data collection

This study used a structured interview questionnaire regarding demographic data, clinical conditions of neuropathy, and risk factors for neuropathy due to pesticide exposure. Assessment of exposure to pesticides was determined using a Pesticide Exposure Measurement (PEM) questionnaire (Dosemeci et al., 2002). The general algorithm of a quantitative approach for estimating pesticide exposure.

Intensity Level = (Mix + Appl + Repair) * PPE

Cumulative exposure = Intensity level * Duration * Frequency

Where Appl: Application method; PPE: Personal protective equipment use

The entire respondent got a medical examination by a certified general practitioner. The medical examination consisted of symptoms and history taking anamnesis for health problem profiling. There was a specific examination for neurological problems through structured and validated questionnaires Q18, neuropathy symptom score (NSS), and neuropathy deficit score (NDS).

Statistical analysis

The research data were analysed using IBM SPSS 24 Statistics for Windows (SPSS Inc., Chicago, IL, USA). The parametric data was tested for normality of data distribution with Kolmogorov-Smirnov. For the normal data ($p>0.05$), the comparison analysis used T-test (2 groups) and One-way ANOVA (>2 groups). In contrast, the abnormal data was tested using the Marun-Whitney test to assess the mean difference between each group. The data was considered significant if $p<0.05$.

RESULTS

Bibliometric analysis

Publication summary

In this bibliometric study, 469 publications on pesticides and neurotoxicity were included. Fig. 1A illustrates the number and trend of annual publications on pesticides and neurotoxicity. 435 publications were published in English, 9 in French, 7 in German, 6 in Spanish, 2 in Italian, Japanese, and Portuguese, and 1 in Russian, Romanian, Croatian, Persian, Turkish, and Hungarian. The first publication was published in 1969, with the progression of research per year slowly increasing to 7 publications per year by 1999, resulting in 56 publications. In the following ten years, by 2009, the number of articles per year had increased to 11, resulting in 140 publications. Furthermore, ten years later, in 2019, the growth of articles continued to almost double to 21 publications per year, resulting in 319 publications. Furthermore, in the remaining five years, the number of articles doubled again by the end of 2023, which was 42 publications. At the beginning of 2024, a total of 469 publications have been recorded about pesticides and neurotoxicity.

Various types of publication documents have discussed pesticides and neurotoxicity, including 61.4% in the form of articles, 25.4% reviews, 6.8% book chapters, 4.5% conference papers, 0.6% short surveys, 0.4% editorials, 0.4% notes, 0.2% data papers, and 0.2% letters. Fig. 1B illustrates the document types of publications on pesticides and neurotoxicity.

Analysis of the most productive countries

Fig. 2A illustrates the number of articles for this study in each country/region. The ten countries with the highest number of publications are the United States (n = 164), followed by India (n = 68), the United Kingdom (n = 30), Italy (n = 27), France (n = 26), China (n = 23), Germany (n= 16), Iran (n = 16), Egypt (n = 13), and Spain (n = 13). The United States collaborates extensively with the most research links (n = 73). European countries are the continents with the highest levels of collaboration, for example, the United Kingdom (n = 43), Italy (n = 37), and France (n = 27). The Asian and African countries with the most collaboration are India (n = 29) and South Africa (n = 22). Other countries have also collaborated with under 20 collaborations, including Nigeria, Switzerland, Kenya, Egypt, and Sweden.

Analysis of the most productive affiliation

There have been many institutions contributing to pesticides and neurotoxicity. Fig. 2B is a graph showing the ten most productive affiliations. The French National Institute for Health and Medical Research (INSERM) is the most productive with 14 publications. After INSERM, the National Institute of Environmental Health Sciences followed with 11 publications, then the Indian Institute of Toxicology Research with nine publications, and the Centers for Disease Control and Prevention with eight publications. The National Institutes of Health NIH, Oregon Health & Science University, and Menoufia University with seven publications each. Then, with seven publications each, the National Institute for Occupational Safety and Health, CNRS Centre National, and National Toxicology Program NTP.

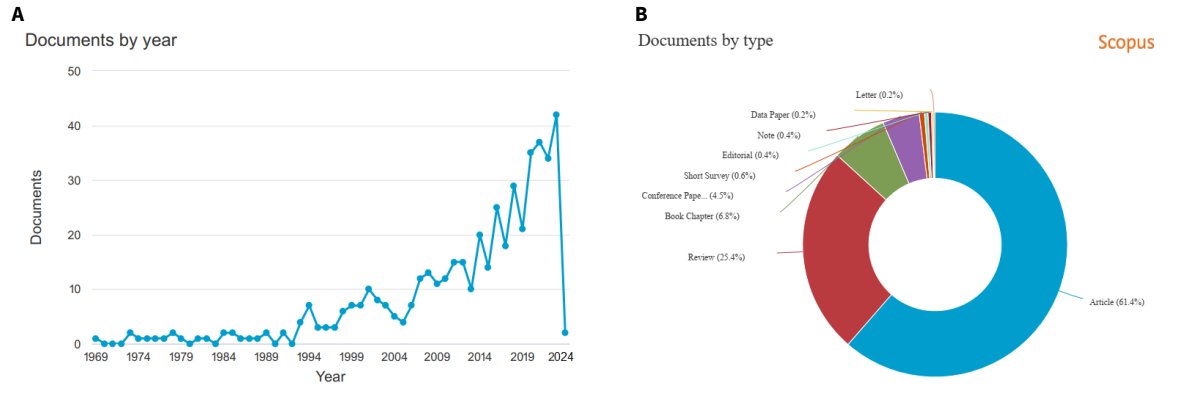

Figure 1. (A) Number of annual articles on pesticide and neurotoxicity by years. **(B)** Distribution of document types on pesticides and neurotoxicity.

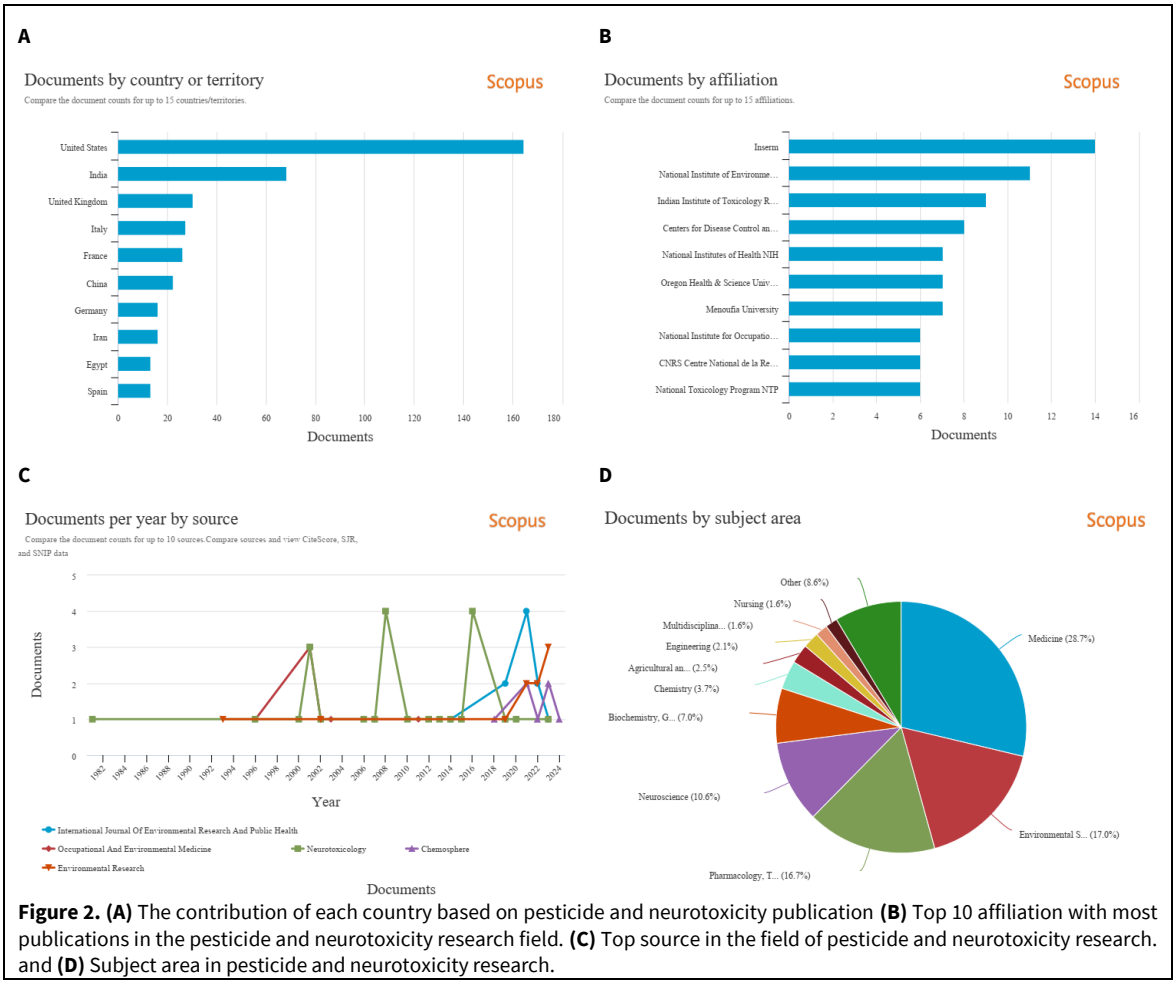

Figure 2. (A) The contribution of each country based on pesticide and neurotoxicity publication **(B)** Top 10 affiliation with most publications in the pesticide and neurotoxicity research field. **(C)** Top source in the field of pesticide and neurotoxicity research. and **(D)** Subject area in pesticide and neurotoxicity research.

Analysis of the source

Based on bibliometric results, it is known that 1393 organisations publish pesticides and neurological in the Scopus database. Most documents are published in the International Journal of Environmental Research and Public Health, Occupational and Environmental Medicine, Environmental Research, Neurotoxicology, and Chemosphere. The Source of Neurotoxicology was recorded as having two highest in 2008 and 2016 from 1994 to 2024 **(**Fig. 2C**)**. Besides that, the Source of Chemosphere was recorded as starting to produce documents in 2024.

Analysis of the subject area

Fig. 2D shows the subject areas that discuss pesticides and neurological problems in the Scopus database. The most common subject areas were medicine (28.7%), followed by environmental subject areas (17.0%), pharmacology (16.7%), neuroscience (10.6%), biochemistry (7.0%), chemistry (3.7%), and other subject area small percentage (8.6%).

Analysis of the authors

Based on bibliometric results, it is known that 2144 authors have published about pesticides and neurological in the Scopus database. Fig. 3A shows the ranking of 15 authors who discuss it. Ismail A.A. and Terry. A.V. was recorded as the author who produced the most documents, each one five documents, followed by Abdollahi, M. (4 documents), Baidi, I (4 documents), Dehande, L.S. (4 documents), Naughton, S.X. (4 documents), Rohlman, D.S. (4 documents), Stallones, L. (4 documents), Abou-Donia, M.B. (4 documents), and Altenkirch, H. (4 documents). Fig. 3B shows the collaboration of authors.

Analysis of the most funding sponsors

A wide range of global and local funding sponsors participated in research related to pesticides and neurotoxicity. The most funding sponsors were the National Institute of Environmental Health Sciences, with 41 funded publications, followed by the National Institutes of Health, with 27 funded publications. Other funding sponsors also participated in funding research in this field with 4 to 10 publications, as shown in Fig. 4.

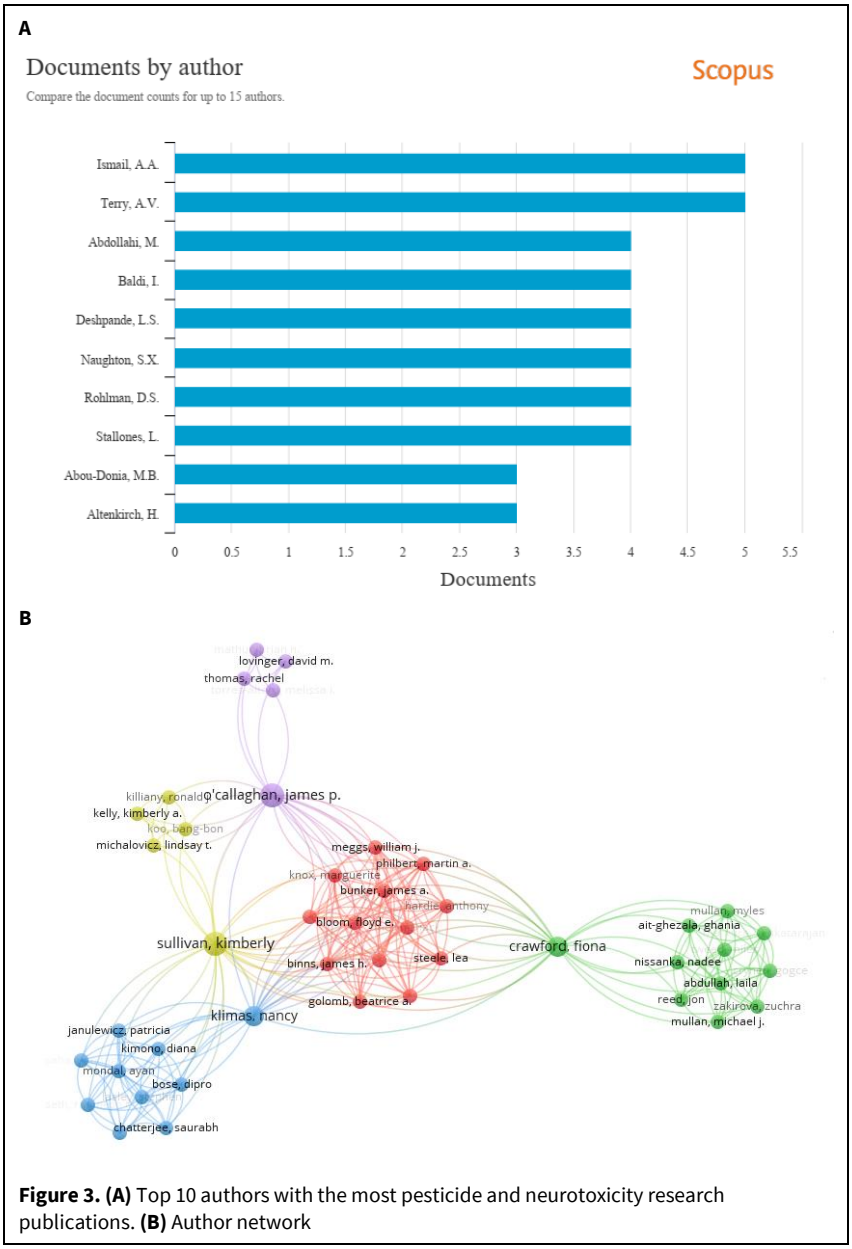

Figure 3. (A) Top 10 authors with the most pesticide and neurotoxicity research publications. **(B)** Author network

Analysis of the most frequently used keywords

Of the 1,728 keywords, with a minimum number of occurrences of 4, 71 keywords met the criteria for analysis. The visualisation of this keyword network is shown in Fig. 5A**.** The size of the nodes indicates the frequency with which the keywords are used, while the distance between nodes reflects the strength of the association between two words. There are several keywords that researchers often use; the three highest keywords are "pesticides" (n = 93), "pesticide" (n = 29), and "neurotoxicity" (n = 29). Some other keywords that were also frequently used by authors were "oxidative stress" (n = 21), "Parkinson's disease" (n = 20), "organophosphate" (n = 18), "organophosphates" (n = 16), "toxicity" (n = 14), "poisoning" (n = 13), "occupational exposure" (n = 12), "gulf war illness" (n = 12), "neurological disorder" (n = 11), "acetylcholinesterase" (n = 10), "epidemiology" (n = 10), "agriculture" (n = 10), and "neurodegeneration" (n = 10). Keywords such as "pesticide exposure", "heavy metals", "pyrethroids", "chlorpyrifos", and other keywords were also frequently used, but the number did not exceed 10.

The visualisation of the author keyword overlay is shown in Fig. 5B. The blue marks the keywords that appeared earlier, while the recent ones are coloured in yellow. The keywords that were the main topics in the early period included "organophosphate", "intoxication", "Alzheimer's disease," "suicide", and "seizure" were the topics. In contrast, keywords that have become popular topics recently are "neuroinflammation," "toxicity," "gut microbiota," "farmers," and "Parkinson's disease."

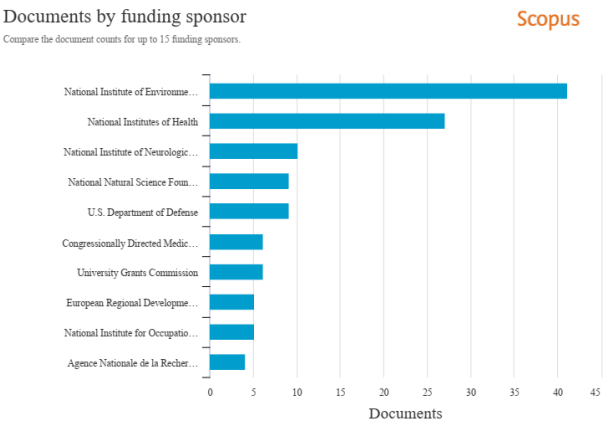

Figure 4. Top 10 funding sponsors in the field of pesticide and neurotoxicity research.

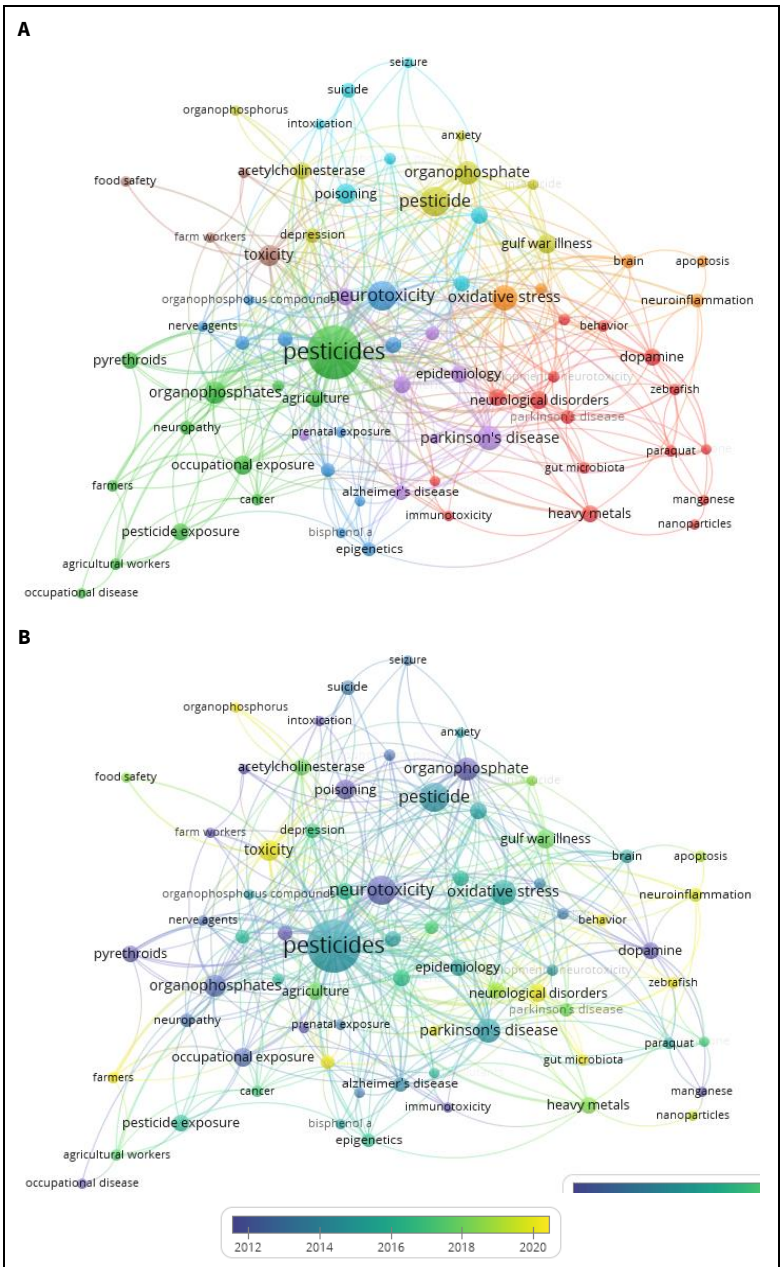

Figure 5. Analysis of the research hotspots on pesticide and neurotoxicity.
(A) network visualisation of author keywords. **(B)** Overlay visualisation of author keywords.

Table 1. Socio-demographic characteristics of farmers.

Characteristics		Frequency (%)
Sex	Male	17 (30.9)
	Female	38 (69.1)
Age (years)	≤25	1 (1.8)
	26-35	4 (7.3)
	36-45	10 (18.2)
	46-55	20 (36.4)
	56-65	13 (23.6)
	≥65	7 (12.7)
Education level	Not school	9 (16.36)
	Elementary school	28 (50.91)
	Junior high school	12 (21.82)
	Senior high school	4 (7.27)
	Undergraduate or higher	2 (3.64)
Time of working	Mean (years)	12.75

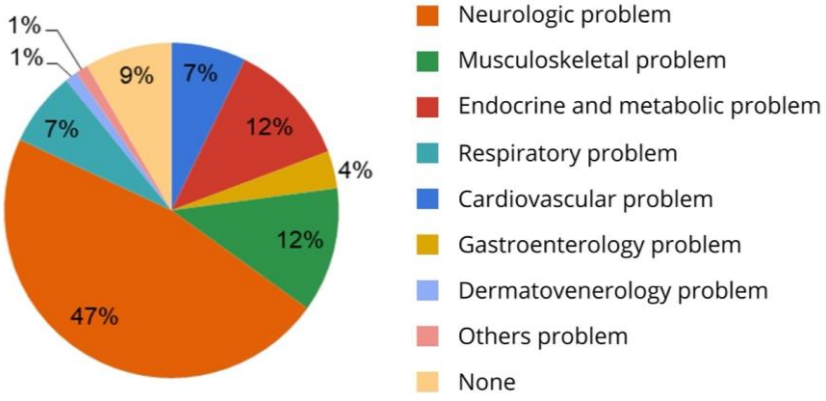

Figure 6. Health problem profile.

Jember cross-sectional

Socio-demographic of the study population

Fifty-five farmers participated in this survey. The socio-demographic profile is shown in Table 1. Most of the study participants were female (69.1%) and got an education until elementary school (50.91%), and the average age was 51.80 years.

Health problem profile

Based on the medical examination, most respondents (47%) complained about neurological symptoms such as peripheral pain and headache **(**Fig. 6). The other problems are musculoskeletal problems such as myalgia or low back pain and endocrine and metabolic problems.

Pesticide exposure measurement

The pesticide exposure measurement in this study uses the general algorithm of a quantitative approach for estimating pesticide exposure (Dosemeci et al., 2002). This algorithm consists of an item formula that measures intensity level, duration, and frequency of exposure. In this study, the result of the pesticide exposure measurement can be seen in Table 2. Based on this data, we also divided into two groups: 24 (43.6%) farmers were highly exposed, and 31 (56.4%) were not exposed.

Comparison of respondent characteristics and pesticide exposure

In this study, we compared the difference in pesticide exposure between each group of

Table 2. The pesticide exposure measurement.

Item Formula	Median (Min-Max)	p-value
Cumulative exposure	5280.60 (24.00 – 157680.00)	0.000*

*Normality test <0.05 indicates the data is not normal.

Table 3. Comparison between respondents' characteristics and pesticide exposure.

Characteristic	Statistical analytic (p-value)
Sex	0.049*
Age (years)	0.088
Education level	0.443

*p<0.05 significance different.

Table 4. Pesticide exposure and neurological problems.

Questionnaire	Pesticide exposure	Median (Min-Max)	p-value
Q18	Exposed	4444 (1111 – 8333)	0.227
	Not exposed	3889 (0 – 8333)	
NDS	Exposed	11 (0 – 16)	0.062
	Not exposed	7 (0 – 15)	
NSS	Exposed	0 (0 – 6)	0.501
	Not exposed	0 (0 – 9)	

*p<0.05 significance different.

respondents' characteristics. The result of the comparison of pesticide exposure measurement between each group can be seen in Table 3. Based on this data, there was only sex characteristic that has significant value for pesticide exposure difference. Both age and education level were not significantly different.

Pesticide exposure and neurological problems

This study compared the difference between pesticide exposure and neurological problems with several measurement methods. The analyses of pesticide exposure measurement and neurological problems in this study can be seen in Table 4.

DISCUSSION

This bibliometric review analyses the development of research on pesticides and neurotoxicity in the last 55 years. Publications on pesticides and neurotoxicity show a gradual increase recently, especially since 1999. Similar findings were also found in a previous bibliometric study on pesticides and one of the degenerative diseases, Parkinson's disease, where the upward trend mainly occurred after 1999 (Liu et al., 2020). Another bibliometric study on pesticides alone found the starting year of the substantial increase to be not far away: 2002 (Smith et al., 2021). The most likely reason for the progressive development of research on this topic may be the increased understanding of the role of pesticides in neurotoxicity. A total of 92.7% of publications were in English, with most publications being in the form of articles because most use articles or other publications in English. In addition, English is the most widely used global language, even in academic settings.

Most of the publications related to pesticides and neurotoxicity were from the United States (n = 164), followed by India (n = 68), the United Kingdom (n = 30), Italy (n = 27), France (n = 26), China (n = 23). This pattern almost resembles bibliometric studies in other fields, such as pesticide bioavailability and food (Andreo-Martínez et al., 2020), green pesticide (Smith et al., 2021), cancer and pesticide (Pedroso et al., 2022). Academic ability is generally affected by the economic status of an individual (Rahman et al., 2023) as well as a country (Kiraz, 2020; Kiraz and Demir, 2020). The government's funding for health can be one of the important indicators of studies and publications in the medical field. The United States spends the most on health per inhabitant, so it makes sense that the largest number of publications are in the United States. The United States is also a consistent collaboration Centre for Pesticide and Neurotoxicity Research. The total collaboration

between US researchers and other countries reached 73 links, which is very high compared to other countries. The UK is the next most collaborative country, ahead of India, which has more publications. Asian and African countries still have minimal collaboration, indicating the need for increased collaboration and studies in these regions.

Institutions in the United States, India, the United Kingdom, and France have published many articles on pesticides and neurotoxicity. Despite being ranked 5th in the most published countries, one French institution, INSERM, topped the list. Other institutions from the United States, India, and Egypt follow below. These institutions conduct general research, but some focus on environmental health and toxicology. Some examples of institutions focusing on toxicology, worker health, and environmental health include the Indian Institute of Toxicology Research, the National Institute for Occupational Safety and Health, and the National Toxicology Program NTP. This shows that toxicology-related research is the focus, including pesticides.

The National Institute of Environmental Health Sciences (NIEHS) sponsored the most publications, with a total output of 41 funded publications. In comparison, the National Institutes of Health (NIH) followed at number two with 27 funded publications. Both institutions are from the United States, demonstrating America's concern for environmental health. The NIEHS has come a long way in researching environmental health. Its research focuses on environmental health needs and issues. The National Institutes of Health, commonly referred to as NIH, is a US-based institute founded in the 1880s that focuses on biomedical research and public health and is now part of the United States Department of Health and Human Services.

The most productive published authors are Ismail, Laksmikan, Abdollahi, and Stallones, with four publications each. However, collaboration is only carried out between writers in the same community. Apart from that, from this data, it is known that Ismail Ahmed A wrote the most articles on the topic of pesticides and neurological because he is a "Pesticide Analyst". Therefore, his article focuses on this area. One of the articles is entitled "Monitoring of Organophosphorus Pesticide and Remediation Technologies of the Frequently Detected Compound (Chlorpyrifos) in Drinking Water". Apart from Ismail, Ahmed A., the author with the most articles is Deshpande; Laksmikan S. has expertise in the "Organophosphate toxicity" field. One of the articles is entitled "Repeated Low-Dose Organophosphate DFP Exposure Leads to the Developmental of Depression and Cognitive Impairment in a Rat Model of Gulf War Illness". The author of Despande, Laksmikan, comes from the country with the most publications, namely the United States.

From this data, it can also be seen that the authors of the most articles came from the organisation that published the most articles, namely Ahmed A. Ismail from the organisation "Community Medicine and Public Health Department, Faculty of Medicine, Menoufia University". One of the articles is entitled "Comparison of neurological health outcomes between two adolescent cohorts exposed to Pesticides in Egypt" (Phillips and Deshpande, 2016). Apart from that, some articles collaborate with organisations, such as the article "Longitudinal Assessment of Occupational Determinants of Chlorpyrifos Exposure in Adolescent Pesticide Workers in Egypt." (Fragomeni et al., 2018). The more frequently an organisation publishes with a focus on a particular topic, it means that this organisation is worthy of being used as a reference for further research on related topics.

Keywords are important instruments in scientific research because they indicate the core of a scientific paper. Analysis of the co-occurrence of keywords illustrates the relationship between research topics in scientific fields (Deng et al., 2020). In this study, other frequently used keywords besides "pesticide" and "neurotoxicity" generally focus on the potential mechanisms of pesticides in causing neurotoxicity. For example, "oxidative stress" is one of the main mechanisms of various disease pathogenesis, including neurological diseases. The oxidative stress mechanism is one of the main denominators that cause the death of neuronal cells, leading to degenerative diseases (Olufunmilayo et al., 2023). In line with this, degenerative diseases such as Alzheimer's and Parkinson's disease are also frequent keywords. Other high-frequency keywords are "organophosphate" and "acetylcholinesterase". Organophosphate is the most commonly used type of pesticide with many sample preparations, ranging from chlorpyrifos, fenthion, and parathion to diazinon (Ore et al., 2023). The main mechanism of organophosphate (OP) neurotoxicity is to inhibit and thus trigger hyperstimulation of muscarinic and nicotinic cholinergic receptors in the peripheral and central nervous system (Tsai and Lein, 2021). Inhibition of AChE by more than 60-70% triggers a 'cholinergic crisis', which is a clinical toxic syndrome characterised by muscle fasciculation and weakness, parasympathetic signs, depression of respiratory control centres in the brainstem, and seizures, all potentially leading to death (Richardson et al., 2019).

Of the 55 participants included in the Jember cross-sectional study, 24 participants (43.6%) were

exposed to pesticides based on pesticide exposure measurement score [Median (Min-Max) = 5280.60 (24.00–157680.00]. This means that pesticide exposure is still the main problem for almost half of Indonesian's farmer. In this study also if there was a significant difference between education levels. The current hypothesis was that Indonesian farmers have below-average education levels that influence the knowledge of pesticides used to prevent exposure. In Gaber and Abdel-Latif's study, it was concluded that higher levels of education were related to better knowledge and safer use of pesticides among Egyptian farmers (Gaber and Abdel-Latif, 2012). The Indonesian government should make an alternative strategy to protect the farmers from pesticide exposure, not only through education to increase knowledge but also through regulation for limiting pesticide use.

The main health problem of the farmers was neurological problems, including pain, headache and other symptoms. We tried to analyse objectively with several measurement methods. We found no significant difference between exposed and non-exposed farmers through Q18, NDS, and NSS. This means that our study group did not have any significant neurotoxicities. However, this non-significant result may be due to the uneven distribution of age and schooling level, causing a ceiling effect. In addition, the sensitivity and specificity of the questionnaire can also affect the results. Several studies have reported the correlation of chronic pesticide exposure with lower scores on neurological examinations. Based on the systematic reviews and meta-analysis, occupational exposure to pesticides and neurobehavioral effects found that there was a significant impact on cognitive function and exercise behaviour in most studies (Hernández et al., 2016). The other study showed that there was a correlation between Alzheimer's disease and pesticide exposure based on a meta-analysis of seven studies on Alzheimer's disease and pesticide exposure (Yan et al., 2016). However, the epidemiological evidence of pesticide exposure and cognitive impairment, or Alzheimer's disease, is still limited. There is still controversy about which pesticide substances are related to decreasing cognitive function. The current report suggested that organophosphate-type pesticides play an important role in neurobehavioral and neuropsychological disorders. Repetitive organophosphate pesticide exposures can affect attention, memory, and cognitive function impairment by "cholinergic crisis".

This study shows different results from a study in another location in Jember district, namely in Sukogidri Village, which found that there was a relationship between spraying frequency, spraying duration, tenure, and PPE use with neurobehavioral performance. However, pesticide type and spraying time were not associated with neurobehavioral performance (Pawestri and Sulistyaningsih, 2021).

CONCLUSION

The research on the role of pesticide effects on neurotoxicity has increased in recent decades. The substantial growth in publication indicates that this field is important for global health. The United States is the country with the most publications. The study also identified institutions and researchers frequently researching pesticides and neurotoxicity. INSERM from France is the most productive institution in this field of research. Acetylcholinesterase and oxidative stress are among the most frequently discussed topics, while gut microbiota and neuroinflammation will probably be the most frequently studied research topics. This analysis provides a comprehensive new perspective for new researchers in this field. There were 55 farmers: 24 (43.6%) were highly exposed, and 31 (56.4%) were not exposed. Most of them (47%) complained of peripheral pain and headache. However, there was no significant difference between the exposed and non-exposed groups regarding cognitive impairment based on Q18, NDS, and NSS.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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REFERENCES

Andreo-Martínez P, Ortiz-Martínez VM, García-Martínez N, López PP, Quesada-Medina J, Cámara MÁ, Oliva J (2020) A descriptive bibliometric study on bioavailability of pesticides in vegetables, food or wine research (1976–2018). Environ Toxicol Pharmacol 77: 103374. https://doi.org/10.1016/j.etap.2020.103374

Arruda H, Silva ER, Lessa M, Proença D Jr, Bartholo R (2022) VOSviewer and Bibliometrix. J Med Libr Assoc 110(3): 392–395. https://doi.org/10.5195/jmla.2022.1434

Baas J, Schotten M, Plume A, Côté G, Karimi R (2020) Scopus as a curated, high-quality bibliometric data source for academic research in quantitative science studies. Quant Sci Stud 1(1): 377–386. https://doi.org/10.1162/qss_a_00019

BPS (2020) Kabupaten Jember Dalam Angka 2020. Badan Pusat Statistik, Kabupaten Jember BPS-Statistics of Jember Regency. https://jemberkab.bps.go.id/publication/2020/05/20/c43569a520090bef8f9b8919/kabupaten-jember-dalam-angka-2020.html [Consulted 28 July, 2021].

Deng Z, Wang H, Chen Z, Wang T (2020) Bibliometric analysis of dendritic epidermal T cell (DETC) research from 1983 to 2019. Front Immunol 11: 259. https://doi.org/10.3389/fimmu.2020.00259

Dosemeci M, Alavanja MC, Rowland AS, Mage D, Zahm SH, Rothman N, Lubin JH, Hoppin JA, Sandler DP, Blair A (2002) A quantitative approach for estimating exposure to pesticides in the Agricultural Health Study. Ann Occup Hyg 46(2): 245-260. https://doi.org/10.1093/annhyg/mef011

Fragomeni SM, Sciallis A, Jeruss JS (2018) Molecular subtypes and local-regional control of breast cancer. Surg Oncol Clin N Am 27(1): 95–120. https://doi.org/10.1016/j.soc.2017.08.005

Gaber S, Abdel-Latif SH (2012) Effect of education and health locus of control on safe use of pesticides: A cross sectional random study. J Occup Med Toxicol 7: 3. https://doi.org/10.1186/1745-6673-7-3

Gunnarsson LG, Bodin L (2019) Occupational exposures and neurodegenerative diseases—A systematic literature review and meta-analyses. Int J Environ Res Public Health 16(3): 337. https://doi.org/10.3390/ijerph16030337

Hernández AF, González-Alzaga B, López-Flores I, Lacasaña M (2016) Systematic reviews on neurodevelopmental and neurodegenerative disorders linked to pesticide exposure: Methodological features and impact on risk assessment. Environ Int 92–93: 657–679. https://doi.org/10.1016/j.envint.2016.01.020

Hofmann M, Chisholm A (2015). Text Mining and Visualization. Case Studies Using Open-Source Tools, 1st Ed. New York: Chapman and Hall/CRC, 337 p. https://doi.org/10.1201/b19007

Kiraz M (2020) A Holistic investigation of global outputs of Covid-19 publications in Neurology and Neurosurgery. Euras J Med Invest 4(4): 506–512. https://doi.org/10.14744/ejmi.2020.36601

Kiraz M, Demir E (2020) A bibliometric analysis of publications on spinal cord injury during 1980–2018. World Neurosurg 136: e504–e513. https://doi.org/10.1016/j.wneu.2020.01.064

Liu C, Liu Z, Zhang Z, Li Y, Fang R, Li F, Zhang J (2020) A scientometric analysis and visualization of research on Parkinson's disease associated with pesticide exposure. Front Public Health 8: 91. https://doi.org/10.3389/fpubh.2020.00091

Muller (2020) Volume of Pesticides Used in Indonesia. https://www.statista.com/statistics/1101117/indonesia-pesticide-use-volume/ [Consulted 28 July, 2021].

Nuryati A, Rahardjo SS, Murti B (2022) Pesticide exposure and its correlation with hemoglobin and cholinesterase in farmers who used pesticide. J Epidemiol Public Health 7(3): 380–396. https://doi.org/10.26911/jepublichealth.2022.07.03.10

Ocmen E, Erdost HA, Hanci V (2023) The bibliometric analysis of most cited 100 papers in anesthesia-induced neurotoxicity. Medicine 102(48): e36508. https://doi.org/10.1097/MD.0000000000036508

Olufunmilayo EO, Gerke-Duncan MB, Holsinger RMD (2023) Oxidative stress and antioxidants in neurodegenerative disorders. Antioxidants 12(2): 517. https://doi.org/10.3390/antiox12020517

Ore OT, Adeola AO, Bayode AA, Adedipe DT, Nomngongo PN (2023) Organophosphate pesticide residues in environmental and biological matrices: Occurrence, distribution and potential remedial approaches. Environ Chem Ecotoxicol 5: 9–23. https://doi.org/10.1016/j.enceco.2022.10.004

Pandey P, Chakole S, Wanjari MB, Prasad R (2023) A bibliometric analysis of scientific research publications related to pesticide poisoning in the South Asian countries. Cureus 15(4): e38134. https://doi.org/10.7759/cureus.38134

Pawestri IN, Sulistyaningsih E (2021) Neurobehavioral performance of Indonesian farmers and its association with pesticide exposure: A cross-sectional study. Clin Epidemiol Glob Health 11: 100754. https://doi.org/10.1016/j.cegh.2021.100754

Pedroso TMA, Benvindo-Souza M, de Araújo Nascimento F, Woch J, Dos Reis FG, de Melo E Silva D (2022) Cancer and occupational exposure to pesticides: A bibliometric study of the past 10 years. Environ Sci Pollut Res Int 29(12): 17464–17475. https://doi.org/10.1007/s11356-021-17031-2

Phillips KF, Deshpande LS (2016) Repeated low-dose organophosphate DFP exposure leads to the development of depression and cognitive impairment in a rat model of Gulf War Illness. NeuroToxicology 52: 127–133. https://doi.org/10.1016/j.neuro.2015.11.014

Rahaman MM, Islam KS, Jahan M (2018) Rice Farmers' knowledge of the risks of pesticide use in Bangladesh. J Health Pollut 8(20): 181203. https://doi.org/10.5696/2156-9614-8.20.181203

Rahman S, Munam AM, Hossain A, Hossain ASMD, Bhuiya RA (2023) Socio-economic factors affecting the academic performance of private university students in Bangladesh: A cross-sectional bivariate and multivariate analysis. SN Soc Sci 3(2): 26. https://doi.org/10.1007/s43545-023-00614-w

Richardson JR, Fitsanakis V, Westerink RHS, Kanthasamy AG (2019) Neurotoxicity of pesticides. Acta Neuropathol 138(3): 343–362. https://doi.org/10.1007/s00401-019-02033-9

Sidthilaw S, Sapbamrer R, Pothirat C, Wunnapuk K, Khacha-Ananda S (2022) Effects of exposure to glyphosate on oxidative stress, inflammation, and lung function in maize farmers, Northern Thailand. BMC Public Health 22(1): 1343. https://doi.org/10.1186/s12889-022-13696-7

Smith HH, Idris OA, Maboeta MS (2021) Global trends of green pesticide research from 1994 to 2019: A bibliometric analysis. J Toxicol 2021: 6637516. https://doi.org/10.1155/2021/6637516

Song L, He X, Wang M, Li L, Liu J, Li G, Yang J (2023) IFN-γ mediated neuroinflammation and behaviour abnormality after maternal exposure to low dose mixture of food additives and pesticides. Food Agric Immunol 34(1): 2226841. https://doi.org/10.1080/09540105.2023.2226841

Song Y, Chen X, Hao T, Liu Z, Lan Z (2019) Exploring two decades of research on classroom dialogue by using bibliometric analysis. Comput Educ 137: 12–31. https://doi.org/10.1016/j.compedu.2019.04.002

Tsai YH, Lein PJ (2021). Mechanisms of organophosphate neurotoxicity. Curr Opin Toxicol 26: 49–60. https://doi.org/10.1016/j.cotox.2021.04.002

Tudi M, Daniel Ruan H, Wang L, Lyu J, Sadler R, Connell D, Chu C, Phung DT (2021) Agriculture development, pesticide application and its impact on the environment. Int J Environ Res Public Health 18(3): 1112. https://doi.org/10.3390/ijerph18031112

World Health Organization (2016) The Public Health Impact of Chemicals. Geneva: WHO Document Production Service.

Yan D, Zhang Y, Liu L, Yan H (2016) Pesticide exposure and risk of Alzheimer's disease: a systematic review and meta-analysis. Sci Rep 6: 32222. https://doi.org/10.1038/srep32222

Yuantari MGC, Widiarnako B, Sunoko HR (2013) Tingkat Pengetahuan Petani dalam Menggunakan Pestisida (Studi Kasus di Desa Curut Kecamatan Penawangan Kabupaten Grobogan). Seminar Nasional Pengelolaan Sumberdaya Alam Dan Lingkungan 2013: 142–148.

AUTHOR CONTRIBUTION:

Contribution	Supangat S	Sakinah EN	Nugraha MY	Tohari AI	Hidayat MRF	Athoillah N	Imtiyazfauz S	Isbach GP	Wiyono N
Concepts or ideas	x	x							x
Design	x	x	x	x					x
Definition of intellectual content	x	x	x	x					
Literature search			x	x	x	x	x	x	
Clinical trial			x	x		x	x	x	
Experimental studies			x	x		x	x	x	
Data acquisition				x					
Data analysis				x					
Statistical analysis						x		x	
Manuscript preparation	x		x			x		x	
Manuscript editing					x	x		x	
Manuscript review	x	x	x	x	x	x	x	x	x

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