A Bibliometric and Hot Topics Analysis of Organophosphate Non-Cholinergic Toxicity Based on Web of Science

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Abstract: The toxicity of most organophosphorus compounds cannot be explained only by cholinergic toxicity mechanism, indicating that non-cholinergic toxicity of organophosphorus compounds has a great impact on their comprehensive toxicity. Bibliometric analysis related to non-cholinergic toxicity of organophosphorus can provide data reference for researchers to understand key research directions and explore hot topics. This paper selected the web of science core collection database to obtain and sort out the documents data related to non-cholinergic toxicity of organophosphorus compounds in the recent 30 years. CiteSpace 5.8 R3 and origin 2019b software were utilized to analyze the annual publication amount and annual citation amount, countries, journals, authors and documents co-citation analysis and burst documents. It was found that the annual publication amount in this field was increasing, and the annual citation amount was increasing exponentially. The United States was the country with the largest number of documents published, and the US military attached great importance to the research on the non-cholinergic treatment of organophosphorus compounds poisoning. "PESTIC BIOCHEM PHYS" magazine ranked No. 1 in the number of documents published. The most influential authors were ELLMAN GL and VAN DER VEEN I. The research mainly covered the effects of organophosphorus pesticides and organophosphorus flame retardants on life. The effect of organophosphorus flame retardants on gene expression and non-cholinergic prevention and treatment of organophosphorus pesticide poisoning may be the future research hotspots.

1 INTRODUCTION

Organophosphorus compounds (OP) are ubiquitous in the environment (WANG, 2020). In agriculture, it has been used worldwide in insecticides, herbicides and mosquito repellents (KAUSHAL J, 2021). In industry, it is used as flame retardants and plasticizers for various materials in daily life (FARKHONDEH T, 2020). People are exposed to OP by a variety of routes (CHEN, 2020), causing acute effects (such as headache, dizziness, nausea, etc.) and chronic effects (such as cancer, asthma, diabetes, etc.) (JI, 2021; HUSSAIN T, 2021). The current studies on the toxicity of organophosphorus compounds mainly focus on the inhibition of acetylcholinesterase in the nerve center, which cannot fully explain all the adverse biological effects of OP. It is worth researching the potential non-cholinergic toxicity of organophosphorus compounds. With the deepening and expansion of the research, it is difficult for researchers to clarify the implied complex relationship between the various research directions. Bibliometrics is a way to analyze the research dynamics and development trends in the field, which can quickly explore the research directions and hotspots (YAO, 2020). To fully understand the research status of non-cholinergic toxicity of OP, this paper used the bibliometric method to analyze the documents related, to provide data reference for researchers to understand this field.

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2 MATERIALS & METHODS

2.1 Data Collection and Processing

Documents on non-cholinergic toxicity of OP between 1990 and 2021 were collected from the Web of Science Core Collection (WOSCC) Database, which is regarded as the most frequently used and most authoritative scientific database in many research fields. Boolean operation terms included the following: TS (Topic Search)=((organophosphate OR organophosphorus) AND ((toxicity of non-cholinergic) OR (toxicity of metabolic) OR (toxicity of immune)OR (toxicity of neurodevelopment) OR (toxicity of antioxidant system))) AND Language: (English). A total of 575 published documents were retrieved for initial screening, and saved as text files in the format of "abstract, full record (including cited references)", completed on December 11, 2021. To prevent the deviation of results, we presented an analysis of 491 articles only. All document types and proportions are shown in Figure 1.

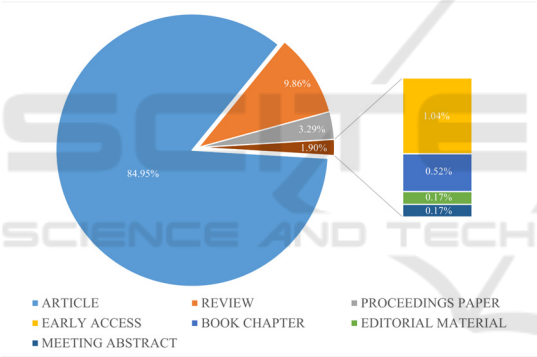

Figure 1: Document type and proportion.

2.2 Bibliometrics Analysis Methods

CiteSpace is one of the bibliometric analysis tools used for knowledge mapping and bibliometric research, developed by Dr. Chaomei Chen (CHEN, 2006). The nodes of the knowledge map represent one item such as journals, authors and articles, and the connecting lines of these nodes show their co-citation or co-occurrence. A series of tree rings in different colors are used to depict each node, where gray indicates the oldest and red indicates the newest. The warmer the color means the closer to the current time. The same applies to the color representation of the connecting lines. In this paper, CiteSpace 5.8 R3 software was utilized for all publication characteristics, including journals, authors, literature co-citation cluster analysis and burst literature analysis. Origin 2019b software was utilized to process data such as annual publication amount and annual citation amount. The process of bibliometric analysis is shown in Figure 2.

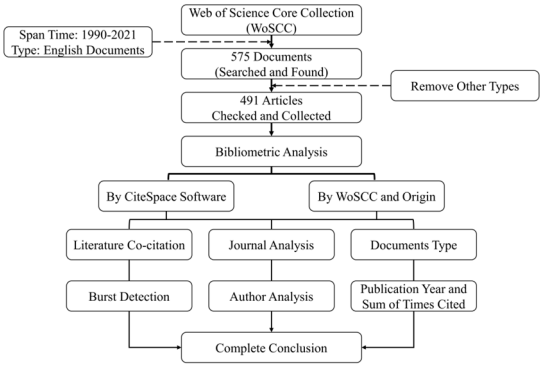

Figure 2: Flowchart of bibliometric analysis.

3 RESULTS

The annual publication amount, annual citation amount (1990-2021) and its trend are shown in Figure 3. In the past five years, more than 38% of the total number of documents has been published, and the largest number of documents (47 articles) published in 2021. The annual citation amount increased exponentially (R2=0.9687), indicating that researchers have paid great attention to this field in recent years.

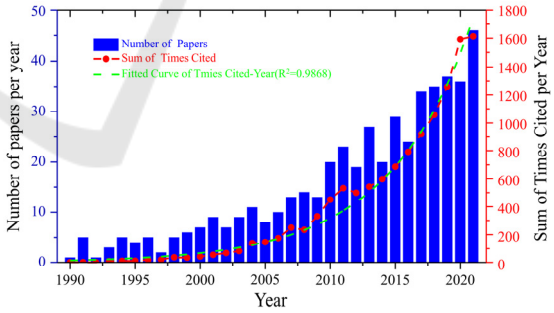

Figure 3: The annual publication amount, annual citation amount and its trend (1990-2021).

3.1 Contributed Countries and Institutions

The document data in this field were further analyzed using Citespace based on the contributed countries and institutions. A total of 59 countries weere involved in the non-cholinergic toxicity research of organophosphate. The United States, China and India have the largest number of published articles in this

field, with 141(28.7%), 77(15.7%) and 57(11.6%) respectively. The top 10 countries with the largest number of published articles are shown in Table S1.

A total of 713 scientific research institutions were involved in this field. Duke University, the Chinese Academy of Sciences, and UC Berkeley have the largest number of published articles, with 14(2.95%), 12(2.44%) and 8(2.04%) respectively. There are six scientific research institutions in America, two in China, one in Turkey and one in Iran. The top 10 institutes with the largest number of published articles are shown in Table S2.

The number of articles funded by the institute is positively correlated with the degree of its attention. The American Department of Health's Institute of Human Services, the National Institutes of Health, and the National Institutes of Health Sciences has the largest number of funded articles, with 74(15.07%), 68(13.85%) and 55(11.20%). There are five funding institutes in the United States, two in China, and one in India, the European Union and Brazil. The top 10 institutes with the largest number of funded articles are shown in Table S3.

3.2 The Amount of Articles Published and Co-Citation In Journals

A total of 199 journals were involved in this field. “Pesticide Biochemistry and Physiology” and “Chemosphere” published the largest amount of articles, with 26 (5.27%) and 20 (4.05%) respectively. The top 10 journals with the largest number of published articles are shown in Table S4.

The journal co-citation reflects the quality and the influence of the journals. “Toxicology and Applied Pharmacology”, “Toxicology” and “Pesticide Biochemistry and Physiology” had the largest number of co-citations, 240 times, 234 times and 195 times respectively. The top 10 journals with the largest number of co-citations are shown in Table S5. We imported all the document data into CiteSpace, and selected the "Cited Journal" module to analyze the journal co-citation. The results were obtained by using the Minimum Spanning Tree (MST) algorithm and described in a journal co-cited graph composed of 595 nodes and 1762 lines, as shown in Figure 4.

3.3 The Amount of Articles Published and Co-Citation of Authors

A total of 2196 authors involved in the field of organophosphate non-cholinergic toxicity. Seidler FJ and Slotkin TA have the largest number of published articles, both of which are 10 (2.04%). The top 5 authors with the largest number of published articles are shown in Table S6.

The author co-citation relationship reflects the influence of the author in this field. Ellman GL, Lowry OH and Costa LG were cited the most times, 109 times, 59 times and 42 times respectively. The top 5 authors with the largest number of co-citations are shown in Table S7.

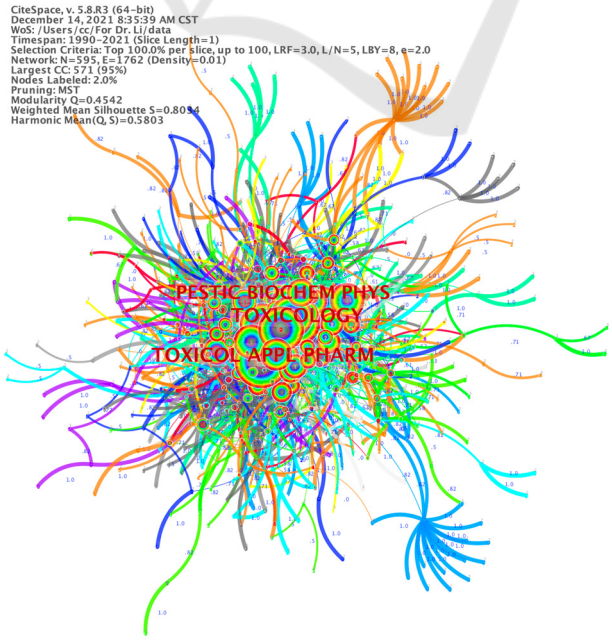

Figure 4: The journal co-cited map.

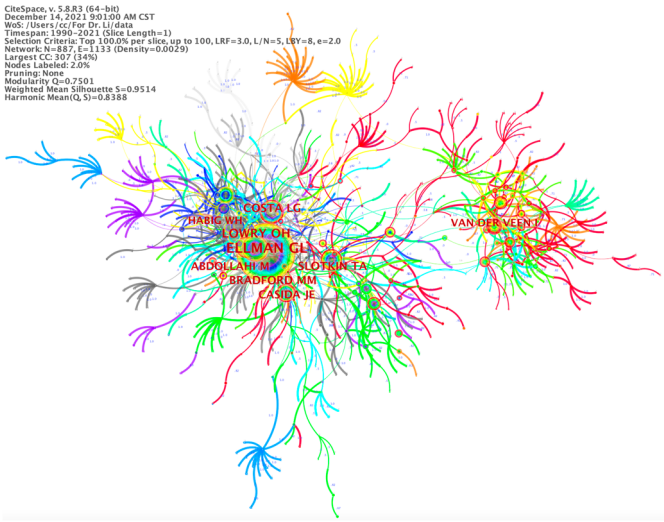

Figure 5: Author co-citation map (1990-2021).

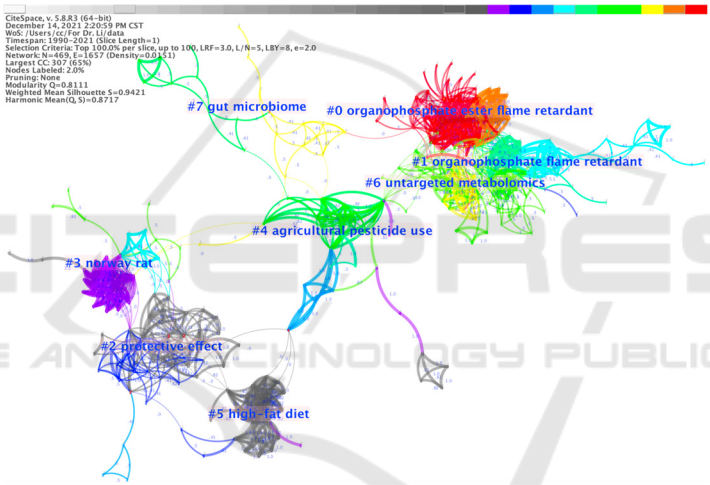

Figure 6: Document co-citation cluster map.

We imported all the document data into CiteSpace, and selected the "Cited Author" module to analyze the author's co-citation. The author's co-citation graph was generated and composed of 887 nodes and 1133 links, as shown in Figure 5.

3.4 Literature Co-Citation Clustering

We imported the data of 491 documents and their 19605 references into CiteSpace to perform document co-citation cluster analysis by using the Log-Likelihood Ratio (LLR) algorithm. The time span is set to 1990-2021, and the time slice option is set to 1 year. The document co-citation graph was generated and composed of 469 nodes, 1657 lines and 8 clusters, as shown in Figure 6.

The average publication year of clustering reflects the dynamic state and current development trend of research in this field. The earliest three clusters of average publication year were #5 protective effect (2005), #5 high-fat diet (2006) and #3 Norway mice (2008). Clusters over the past decade were #1 organophosphate flame retardants (2011), #4 agricultural pesticide use (2011), #6 non-target metabonomics (2014) and #7 intestinal microbiomics (2014). The average publication year of cluster #0 organophosphate ester flame retardants is closest to the current time. The cluster results of literature co-citation are shown in Table 1.

Table 1: The cluster results of literature co-citation.

Cluster	Size	Silhouette	Means (Year)	Top Terms (LLR)
0	54	0.906	2016	Organophosphate ester flame retardant
1	49	0.898	2011	Organophosphate flame retardant
2	46	0.949	2005	Protective effect
3	35	1	2008	Norway rat
4	29	0.908	2011	Agricultural pesticide use
5	26	0.976	2006	High-fat diet
6	26	0.933	2014	Untargeted metabolomics
7	20	0.995	2014	Gut microbiome

Note: *The closer the contour coefficient value is to 1, the higher the credibility of clustering.*

Table 2: Documents with co-citation burst characteristics in the past 5 years.

Rank	Begin	End	Strength	References
1	2016	2021	6.31	Van der Veen I, 2012, CHEMOSPHERE, V88, P1119
2	2018	2021	4.12	Liu X, 2012, AQUAT TOXICOL, V114, P173
3	2016	2019	5.37	Colovic MB, 2013, CURR NEUROPHARMACOL, V11, P315
4	2017	2019	4.38	Grube A, 2011, PESTICIDES IND SALES, V0, P0
5	2018	2019	3.6	Su GY, 2014, ENVIRON SCI TECHNOL, V48, P13511
6	2018	2019	3.6	Du ZK, 2016, SCI REP-UK, V6, P0
7	2015	2018	4.2	Dishaw LV, 2011, TOXICOL APPL PHARM, V256, P281

3.5 Burst Literature

Based on the cluster results of literature co-citation, 29 burst documents were obtained by using the burst document detection tool “burstness”. There were a total of 7 documents with burst characteristics in the past 5 years. Two articles still had strong co-citation burst until 2021. Among them, the article published by Van der Veen I in “Chemosphere” in 2012 had the strongest co-citation burst. Documents with co-citation burst characteristics in the past 5 years are shown in Table 2.

4 DISCUSSION

The research in the field of non-cholinergic toxicity of organophosphorus compounds can be divided into two stages (1990-2009, 2010-2021). The first phase was the primary stage, the annual publication amount is less than 20. There was no significant increase and the growth rate of the document citation amount was also low. The second stage was the rapid development stage. The number of articles published has increased sharply, and the annual number of articles published is more than 30 in the recent 5 years. The growth rate of document citation amount has accelerated significantly. The annual publications amount was increasing steadily, and the annual citation amount was increasing exponentially. It showed that this field has received extensive attention from researchers. The United States is ranked No. 1 in the number of publications, and had more than 50% of the top 10 institutes with the largest published articles.

A total of 7 journals were ranked in the top 10 of published article amount and co-citation amount at the same time, including “Pesticide Biochemistry and Physiology”, “Chemosphere”, “Toxicology and Applied Pharmacology”, “Toxicology”, “Toxicology Letters”, “Ecotoxicology and Environmental Safety” and “Toxicological Sciences”. These journals have great influence in this field.

Two authors were ranked in the top 10 of publication amount and co-citation amount at the same time, including Slotkin TA and Abdollahi M, indicating that they have contributed a lot. In the initial stage and rapid development stage in this field, the influential authors were Ellman GL and Van der

Veen I respectively. Ellman GL mainly studied the toxicity of organophosphorus pesticides, while Van der Veen I mainly studied the toxicity of organophosphorus flame retardants.

Eight literature clusters were obtained by the LLR algorithm. According to different research objects, all clusters can be divided into two main research directions. One is the study on the non-cholinergic toxicity of organophosphorus pesticides, which includes six clusters (ID: #2, #3, #4, #5, #6, #7). The second is the study on the non-cholinergic toxicity of organophosphorus flame retardants, including two clusters (ID: #0, #1).

4.1 The Non-Cholinergic Toxicity of Organophosphorus Pesticides Includes Neurodevelopmental Toxicity, Lipid Metabolic Toxicity and Antioxidant Toxicity.

4.1.1 Neurodevelopmental Toxicity

Continuous exposure to low concentrations of organophosphorus pesticides can lead to autism in pregnant women (FURLONG M A, 2017); fetal neurodevelopmental disorders (GUNIER R B, 2017), birth defects and death in fetuses (ROBERTS J R, 2010); and abnormal peripheral axon diffraction during fetal development (JACOBSON S M, 2010). Organophosphorus pesticides affect axonal transport by regulating intestinal bacterial population composition and functional gene expression (GAO, BIAN, MAHBUB R, 2017; Gao, NAUGHTON S X, BECK W D, 2017), and hinder neuronal development and mature neuronal function (GAO, BIAN, CHI, 2017).

4.1.2 Lipid Metabolic Toxicity

Organophosphorus pesticides aggravate oxidative stress by inhibiting the activity of antioxidant enzymes in the body, leading to lipid peroxidation (ULLAH S, 2018). Thereby sperm function was affected (LEONG C T, 2013), and cancer and neurodegenerative diseases were caused (LÓPEZ O, 2007). Also, OP can destroy cell signal transduction mediated by cyclic adenosine monophosphate, resulting in impaired metabolic function, increased glucose metabolism and imbalance in lipid metabolism, thereby causing metabolic symptoms similar to early diabetes (ADIGUN A A, WRENCH N, LEVIN E D, 2010; ADIGUN A A, WRENCH N, SEIDLER F J, 2010).

4.1.3 Antioxidant Toxicity

Organophosphorus pesticides reduce the concentration of paraoxonase (PON1), glutathione peroxidase (GSH-Px) and catalase (CAT) by affecting the expression of key genes in the hepatocyte antioxidant system (HASSANI S, 2021). It can also significantly reduce the plasma antioxidant capacity while reaching the peak plasma level, which has potential acute toxic effects (BIRDANE Y O, 2021).

4.2 The Non-Cholinergic Toxicity of Organophosphorus Flame Retardants Includes Mouse Fetal Development Toxicity, Liver Toxicity and Dopaminergic Nervous System Toxicity.

4.2.1 Mouse Fetal Developmental Toxicity

Organophosphorus flame retardants disrupt the placental nerve signal transduction by affecting the expression of endocrine and inflammation-related genes in the placenta, which causes placental dysfunction and fetal forebrain dysplasia (ROCK K D, 2021). These compounds can also cause an excessive stress response in the endoplasmic reticulum, endochondral ossification and chondrodysplasia in limb buds (YAN H, 2021).

4.2.2 Liver Toxicity

Organophosphorus flame retardants cause mitochondrial dysfunction and lipid accumulation by affecting gene expression in human hepatocytes, which is the reason for non-alcoholic fatty liver and other diseases (NEGI C K, 2021). This kind of compound also can induce metabolic reprogramming of mesenchymal stem cells, reduce bone mineral density and cause obesity (MACARI S, 2020).

4.2.3 Dopaminergic Nervous System Toxicity

Organophosphorus flame retardants can change the transcriptional profiles of adenylate cyclase signal transduction components by affecting the signal cascade of adenylate cyclase and its connection with G-protein coupled receptor, which destroy the dopaminergic system (OLIVERI A N, 2018). Those compounds can also accumulate in the body and cause the level of dopamine and serotonin in the brain to decrease, and affect the function of the dopamine nervous system (WANG, 2015).

Burst literature that has a sharp increase in citations in a certain period, is widely concerned by researchers (CHEN, 2021). There are seven documents with burst characteristics in the past five years. According to the research content, they can be divided into two main research directions, which may become research hotspots in the future. One is the study on the gene expression effect of organophosphorus flame retardants. Organophosphorus flame retardants affect the function of related pathways such as glycosphingolipid biosynthesis and fatty acid elongation by affecting DNA replication, base excision repair and other ways of destroying gene expression (GRUBE A, 2021), which interfere with carbohydrate and lipid metabolism (DU, 2016) and cause neurodevelopmental toxicity (DISHAW L V, 2011). Those compounds can also lead to endocrine disorders by changing the transcription of genes related to the synthesis of sex hormones and steroids (Liu, 2012). Metabolites of organophosphorus flame retardants accumulate in the liver, which causes cancer (VAN DER VEEN I, 2012) and more genetic changes in the embryo. The toxicity of metabolites is greater (SU, 2014).

The second is to study the non-cholinergic prevention and treatment of organophosphorus pesticide poisoning. By injecting phosphatase or carboxylesterase, the pesticide can be hydrolyzed or oxidized before it reaches the target, so as to achieve the purpose of detoxification. (COLOVIC M B, 2013)

5 CONCLUSIONS

The toxicity of most organophosphorus compounds is unexplained only by the cholinergic toxicity mechanism. And the research on the non-cholinergic toxicity mechanisms has attracted great attention. In this paper, bibliometric analysis was carried out to clearly understand the research progress of non-cholinergic toxicity of organophosphorus compounds, which has been proved that bibliometrics can provide valuable information for researchers. The United States is the most influential country in this field, and the U.S. military attaches great importance to the research on the non-cholinergic treatment of organophosphate poisoning. The research mainly covers the effects of organophosphorus pesticides and organophosphorus flame retardants on organisms. The future research focus may be the effect of organophosphorus flame retardants on gene expression and the non-cholinergic prevention and treatment of organophosphorus pesticide poisoning.

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