Cancer and exposure to pesticides: a bibliometric study from the last 10 years

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Abstract

Occupational exposure to pesticides has been identified as a promoting factor for the development of cancer. Pesticides can cause intoxication in the individuals who manipulate them, either by inhalation, ingestion, or dermal contact. Therefore, our study aimed to describe the association between cancer and occupational exposure to pesticides from 2011 to 2020 through a bibliometric analysis. We selected 62 papers in the Scopus database. The results indicated an exponential increase in studies in the last decade; on a geographic scale, the USA, France, India, and Brazil were the countries that most investigated the association of cancer and pesticides among the 21 nationalities found. The main classes of pesticides were insecticides, herbicides, and fungicides associated with intoxication and cancer. Among the most reported cancers were multiple myeloma, bladder cancer, non-Hodgkin's lymphoma, prostate, leukemia, and breast cancer. Although pesticides are associated with health problems, studies involving cancer and these products are still scarce when related to global use and the demand for agricultural production on the planet.

1. Introduction

Pesticides are used in most homes, businesses, and farms to control insects, weeds, fungi, rodents, and even microbial organisms (Langley and Mort 2012; Mostafalou and Abdollahi, 2017). These products are classified into the heterogeneity of chemical formulations, including conventional pesticides, such as herbicides, insecticides, rodenticides, plant growth regulators, miticides, nematicides, fungicides, fumigants, and antimicrobials (EPA 2020). Globally, almost 3 billion tons of pesticides are used every year, with a budget of approximately 40 billion dollars (Sharma et al., 2020). Although essential for agricultural productivity on the planet, pesticides are a problem for biodiversity and public health since the presence of a xenobiotic in the environment can cause a risk to biodiversity (Gil and Pla 2001; Parker, 2017; Shrestha et al., 2018; Vale et al., 2019; Sharma et al., 2020; Ramos et al., 2021).

Exposure to pesticides can occur mainly through inhalation or dermal contact (Cuenca et al., 2019; Godoy et al., 2019; Sharma et al., 2020; Ramos et al., 2021). In this case, exposure can lead to acute poisoning when individuals are exposed to large amounts of xenobiotics for a short period, or chronic when it has severe and late effects, that is, they appear months or years after exposure (Sharma et al., 2020; Ramos et al., 2021).

Thus, pesticide handlers, such as farmers dealing with transportation, delivery, cleaning of equipment, mixing, application, and spraying of pesticides, as well as people employed in the industry producing these compounds, are occupationally exposed to considerable amounts of pesticides, and therefore are characterized as a risk group (Damalas et al., 2016; Ye et al., 2017; Cuenca et al., 2019; Kalliora et al., 2019). This exposure may be related to cytotoxic, genotoxic mechanisms with immunotoxicity, hormonal changes, and carcinogenesis (VoPham et al., 2017; Kapeleka et al., 2019; Saad-Hussein et al., 2019). Once, because pesticides can increase the production of free radicals that induce oxidative stress, they promote changes in the enzymatic system of elimination and depletion of cellular antioxidant reservoirs, resulting in damage to all cellular components, including DNA, which can lead to mutation, double-strand breaks, chromosomal breaks and formation of DNA adducts (Eren et al., 2016; Barrón-Cuenca et al., 2019; Marcelino et al., 2019).

Thus, a series of diseases can arise, such as several types of cancers (Mostafalou & Abdollahi, 2017), congenital malformations (Castilho-Cadena et al., 2017; Rocha and Grisolia, 2018), problems in the reproductive system (García et al., 2017; Hu et al., 2020), depression, anxiety, Parkinson's disease, Alzheimer's disease and even death (Alavanja et al., 2004; Ch et al., 2019; Sharma et al., 2020).

In this context, monitoring diseases such as cancer-related to occupational exposure to pesticides is essential, especially in alerting about the potential risks of these products to human health, aiming to mitigate this problem. Although the impact of pesticides on human health is not new, in contrast, bibliometric studies that show the patterns and gaps in exposure to pesticides and cancer are still scarce. Therefore, this study was designed to describe the association between cancer and occupational exposure to pesticides in the past 10 years through a bibliometric analysis. We focus on investigations from January 2011 to December 2020, aiming to discuss variables such as (1) countries that have researched about pesticides associated with occupational exposure; (2) types of cancer; (3) the method used for the investigations; (4) that describe the main gaps related to studies linking cancer and pesticides and suggest future directions.

2. Material And Methods

2.1. Data and study selection

The present study was carried out in the database Scopus®, a registered trademark of Elsevier BV Scopus (www.elsevier.com), to review the association between cancer and occupational exposure to pesticides. We used the following terms for the search: "pesticides" and "farmers," and "cancer." After evaluating the papers, those classified as bibliographic review, conference papers, letters or not related to the approach of the proposed theme, and those that could not be accessed to collect necessary information were excluded. The theme was revised, covering a period between January 2011 and December 2020. We selected studies that related the risk and development of cancer and specific types of the disease associated with occupational exposure to pesticides.

2.2. Database analysis

In each analyzed paper, we extracted the following variables: i) Year of production; ii) Place of origin (for this variable, the source of the first author and its clusters); iii) Number of papers per year of publication; iv) Clusters of authors most frequently found; v) Relevant keywords and their clusters; vi) Analysis of co-authorship and its clusters; vii) Type of cancer; vii) Type of pesticide (categorized by groups according to the purpose of the compound); ix) Type of methodology (methodologies that had practical applicability and that were directly related to the proposed theme were considered). We used the VOSviewer program from the University of Leiden (http://www.vosviewer.com/).

2.3. Data analysis

A correlation was performed if there was an increase in the number of publications over the past decade, in which a p-value < 0.05 was considered significant to verify the growth of scientific production using the software R (version 3.6.1). A map was generated in the QGIS software (version 3.14.1) to demonstrate the studies' geographic distribution.

3. Results And Discussion

3.1. Geographical aspects of studies involving cancer and pesticides

A total of 104 articles were found; however, we selected 62 for the present study (Fig. 1). We excluded types of research other than articles and those not available in the Scopus.

The selected papers indicated a considerable increase in the number of studies over the past decade (Fig. 2). The growth points in the literature were mainly between the years 2017 to 2019. The low number of studies in 2020 was possibly related to the SARS-Cov-2 pandemic.

As for the geographic distribution of the research, the selected studies were published by 21 countries, in which the United States (USA) held 19.35% of the scientific production (n = 12), followed by France (n = 9; 14.52%), India (n = 8; 12.9%; Fig. 3) and Brazil (n = 7; 11.29%). This highlight of the USA in the number of publications is nothing new since this country has been leading in scientific productivity in different areas of knowledge (Haeffner et al., 2019). When analyzing the relationship between scientific production, countries, and co-authorships (Fig. 4), in the publication clusters per year (a), scientific output in the United States is predominant; however, countries like India, Brazil, and Spain have more recent publications. Besides, a consistent co-authorship relationship is evidenced between the United States and countries in Asia, Europe, and Brazil (b).

According to the Science and Engineering Indicators report of the National Science Foundation (NSF, 2018), the United States is a world scientific power, with the research of high quality and impact, but which has been losing ground due to the competitiveness of the scientific scenario (Tollefson, 2018). A reflection of this is that countries such as China, India, and Brazil have been investing in science and technology production and have stood out regarding the number of published scientific papers (Klebis, 2018). It is noteworthy that the research related to pesticide use in the USA is that the country demonstrates the consequences of these products on agricultural production since they are one of the largest agricultural producers and users of pesticides in the world (Human Rights Watch, 2018).

In addition to the United States, Europe, Brazil, and China also stand out regarding the use of large amounts of pesticides in crops, which ends up bringing problems to non-target organisms, including humans (Hossar et al., 2017; Paumgartten, 2020; Zheng et al., 2020). In France, a study showed at least 408 cases of occupational exposure to insecticides (54.4%), herbicides (33.3%), and fungicides (12.2%) in a Poison Control center from 2012 to 2016 in that country (Boucaud-Maitre et al. 2019). In another study, Tual et al. 2019 also demonstrated the use of pesticides in some frequent crops in France and insecticides in animals, which may increase the risk of cancers such as multiple myeloma. In India, since the Green Revolution, the intensification of pesticides has brought the significant long-term impact of such practices on public health and the environment (Keswani et al., 2019). It is worth mentioning that the Indian economy is predominantly agricultural, with about 70% of the country's population linked to agriculture (Keswani et al., 2019). Based on this solid agricultural dependence, cancer associated with occupational exposure to pesticides can be an eminent problem if there is no conscious use of these xenobiotics.

Finally, Brazil's agrarian model is based on monoculture for export in which mechanized and pesticide technologies are used (Porto and Soares 2012; Rocha et al., 2019). Brazil has become a significant consumer of pesticides, and in 2019, for example, the unbridled release of such products was unprecedented, having been the largest documented by the Ministry of Agriculture since 2005. (Nascimento et al., 2020; Ramos et al., 2021). Because it is highly dependent on the application of pesticides, it certainly attracted not only companies that lawfully marketed pesticides but also smugglers (Sant'Ana et al., 2019), making it a big problem for management.

Because of this rampant use of pesticides, a positive correlation between poisoning and cultivated areas has recently been demonstrated (Nascimento et al., 2020), which indicates an emerging problem in the country, mainly because the agricultural expansion requires new sites for land use. In this study, among the main types of pesticides, the most reported implications of cancer risk and development in occupationally exposed individuals were insecticides, herbicides, and fungicides. These findings agreed with Mostafalou and Abdollahi (2017) when they indicated these pesticides' classes followed by fumigants for their carcinogenic potential. On the other hand, the least studied pesticides were: acaricides, rodenticides, and larvicides, which indicates a knowledge gap concerning the diversity of the types of pesticides.

Concomitantly, it was possible to observe that the studies investigated mainly if there was direct occupational exposure (in which the worker is occupationally exposed, directly manipulating pesticides: making storage, preparation, mixing, and application) and indirectly to pesticides (those individuals who live in close to areas where pesticides are applied, or who have contact with occupationally exposed workers, as well as during the process of washing clothes and objects used in the application of these products). Also, it was possible to observe that 16 (26.7%) of the evaluated studies addressed both types of exposure.

In general, pesticides target the physiological system's essential metabolic pathways, these chemicals being non-biodegradable and toxic (Sharma et al., 2020). They can interact with each other in various ways according to the compound itself and the chemical family, the dose, and the target organs, leading to multiple effects (Hernandez et al., 2017). Human exposure to pesticides can occur through different routes, including occupations dealing with the production, transportation, delivery, and application of these products, living in places with a high content of pesticide residues, circulation, and accumulation in the food chain (Mostafalou and Abdollahi, 2017). Due to the wide availability of liquids, solids, and gases, these products can quickly attack various tissues, mainly by contact with the skin, inhalation, or ingestion (Ch et al., 2019; Sharma et al., 2020).

3.2. Types of cancer and associations with pesticides

In this section, 48 types of cancers associated with pesticides were found (Fig. 5). The cancers most commonly reported in the surveys were multiple myeloma with 4.04% (n = 8), followed by bladder cancer with 4.04% (n = 8), non-Hodgkin's with 3.54% (n = 7) and prostate with 3.54% (n = 7). However, it is important to note the number of studies that have an indirect association between cancer and pesticide predominant, making 33 of the studies analyzed (16.75%).

We tabulated the studies that seek to point out evidence of a direct and positive association between the risk and development of cancer with occupational exposure to pesticides and the association with different classes of pesticides (Table 1). For this, we considered the variables: i) type of pesticide, ii) type of cancer, iii) methodology, iv) results, and v) the authors.

Table 1
Synthesis of case-control studies associated with occupational exposure to pesticides.

Pesticides	Cancer types	Exposure evaluation	Results	References
Fungicide and Herbicide	Non-Hodgkin's lymphoma and multiple myeloma	Questionnaire	↑	Ferri et al., 2017
-	Bladder cancer	Questionnaire	↑	Jackson et al., 2017
-	Acute lymphoid leukemia	Questionnaire	↑	Gunier et al., 2017
Herbicide	Oral, colorectal, non-melanoma skin, esophagus, pharynx, liver, biliary, glandular, small intestine, larynx, leukemia, lymphomas, breast, melanoma, mesothelial, myeloma, bone, ovary, pancreas, penis, peritoneal, lung, prostate, kidney, stomach nervous system, testis, thymus, thyroid, uterus, bladder, vulvar	Questionnaire	↑	Salerno et al., 2016
Insecticides	Bladder cancer	Questionnaire, PCR* and chromatography	↓	Boada et al., 2016
Fungicide, Insecticide and Herbicide		Questionnaire	↓	Jeephet et al., 2016
-	Colorectal and Leukemia	Medical record and histopathology	↑	Salerno et al., 2014
Insecticides	Hepatocellular carcinoma		↑	Persson et al., 2012
Fungicide, Insecticide and Herbicide	Glioma		↓	Yiin et al., 2012
Fungicide, Inseticide and Herbicide	Lymphoma, Hodgkin's lymphoma and multiple myeloma		↑	Zakerinia et al., 2012
Fungicide, Inseticide and Herbicide	Prostate cancer		↑	Band et al., 2011
Fungicide, Inseticide and Herbicide	Lymphomas and myelodysplastic syndrome		↑	Kokouva et al., 2011
* Polymerase chain reaction				
↑ There is an association between cancer and exposure to pesticides				
↓ There is no association between cancer and exposure to pesticides				

Mostafalou and Abdollahi (2017) observed in a review the possible role of exposure to pesticides in the incidence of diseases such as cancer, Alzheimer's, Parkinson's, amyotrophic lateral sclerosis, asthma, bronchitis, infertility, congenital malformations, a deficit of attention, hyperactivity, autism, diabetes, and obesity. Most of the studies analyzed for the development of this review reinforce the evidence that occupational exposure to pesticides may have contributed to an increased risk for the development of cancers in farmers (Jeephet et al., 2016; Ferriet al., 2017; Gunier et al., 2017; Tualet al., 2019). When compared to the general population, rural workers are in a condition of greater vulnerability and susceptible to other factors that corroborate the worsening of the oncological situation of these individuals (Salerno et al., 2014; Salerno et al., 2016; Gunier et al., 2017; Jackson et al., 2017).

In this context, multiple myeloma, a hematopoietic malignancy of plasma cells, is one of the most common hematological cancers in men and women (Tual et al., 2019). This type of cancer has an etiology that promotes a frequent manifestation of this disease in farmers occupationally exposed to pesticides; the reason is still under investigation and is not very well elucidated (Ferri et al., 2017; Packard et al., 2019). Boulanger et al. (2017) reinforced the relationship between bladder cancer and exposure to pesticides. They also draw attention to the fact that there is an exposure-response relationship with the number of years in the profession's exercise and that the risk could be more significant in women.

Similar results are described by other studies, which also report an increased risk for the development of non-Hodgkin's lymphoma, prostate, leukemia, and breast cancer (Band et al., 2011; Wagooner et al., 2011; Zakerinia et al ., 2012; Salerno et al., 2012; Salerno et al., 2016; Jackson et al., 2017). However, it is possible to observe the findings' inconsistency since there are reports that the relationship between cancer and pesticides is not significant. Boada et al. (2016) demonstrated no meaningful relationship between the risk of bladder cancer and occupational exposure to pesticides. Besides, Jeephet et al. (2016) also showed that cholangiocarcinoma is not associated with pesticides.

It is possible to establish a relationship between the toxic levels of pesticides within the body and the response to such compounds. It is a complex situation since it depends on several factors, such as toxicokinetics and genetics, and pesticides can induce disturbances in the individual's immune system, and even carcinogenesis through the increased production of reactive oxygen species, which contribute to DNA damage, immunotoxicity lymphocytes and chromosomal aberrations (Gil and Pla 2001; Pressuti et al., 2016; Jacobsen-Pereira et al., 2020).

It should also be noted that farmers tend to be highly resistant to the use of personal protective equipment (whether due to climatic adversities or misinformation) and could be exposed to pesticides at various stages of the production process (storage, preparation, application, and consumption); so, there is a lack of inspection in the majority of agricultural properties and a lack of guidance on the handling and use of these products (Salerno et al., 2016; Godoy et al., 2019; Ramos et al., 2020).

Finally, it is essential to note that the number of studies whose association between the development of cancer and pesticides is indirect and predominant, making a total of 33 studies analyzed (16.75%). This finding demonstrated the scarcity of studies addressing cancer and pesticides since cancer is regularly indicated as one of the main risks to human health as a result of occupational exposure to agrochemicals and is also associated with other comorbidities (Brust et al., 2019; Jacobsen-Pereira et al., 2020; Mongedet al., 2020). Even if this evidence is reported, the mechanisms and techniques that elucidate and determine how this relationship occurs and why it exists are not explicit (Elebead et al., 2012; Tual et al., 2013; Jin et al., 2017; Tarar et al., 2019; Hutter et al., 2020).

3.3. Method of investigating the association between cancer risk and development with pesticides

The questionnaire application was frequently used in studies related to pesticides and the risk of developing cancer (Fig. 6). Therefore it is possible to retrieve a series of evidence that enables greater clarification about the individual's lifestyle, socio-economic profile, and social context. Based on a diagnosis obtained with the interviewee, it is possible to decide on the best method for the population of interest. On the other hand, traditional techniques based on biological material collection were also observed as the main investigation mechanisms. Among these techniques, the most frequent are micronucleus test (n = 5; 5.88%), chromatography (n = 4; 4.71%), hematological (n = 4; 4.71%) and biochemical tests (n = 4; 4.71%).

Other techniques such as acetylcholinesterase quantification, comet assay and methylation profile, although less frequent, have also been documented in studies involving this theme. Finally, among the methodologies used by the researchers were mainly cohort studies (n = 24; 38.71%), case-control (n = 23; 37.1%), cross-sectional (n = 9; 14.52%), longitudinal (n = 3; 4.84%), descriptive (n = 1; 1.61%) and monitoring (n = 1; 1.61%) (Rusiecki et al., 2017; Kumar et al., 2018; Joshi et al., 2019; Shearer et al., 2019; Ratna et al., 2020).

In the studies used to develop this review, it was clear that there are many reports on the scarcity of data regarding the topic of cancer and pesticides, despite the method. As an example, Cepeda et al. (2020) warn that even though the factors that lead to cancer development are discussed, absolute numbers of these cancers' types and frequency are still lacking. Besides, other difficulties were also noted, for example, the fact that when the farmer arrives home after work, he may have pesticides impregnated in his clothes, hands, shoes, tools, and other objects, which would take other people to contaminate themselves indirectly (Zakerina et al., 2012).

Studies show that women married to farmers or who have contact with rural workers are at a greater risk of developing bladder cancer. The same was observed for the increased frequency in the number of leukemia cases in children under five years of age, which was not observed a relationship between cause and maternal or intrauterine exposure to pesticides, but due to the paternal perinatal exposure (Salerno et al., 2016; Gunier et al., 2017; Jackson et al., 2017). These factors make it challenging to decide which test should be chosen for analysis and arrange so that the data is reliable to the studied population's characteristics.

Another limiting factor is when carrying out a test aimed at toxicological and genotoxic analysis; for example, often, the data found cannot be attributed to specific components of a pesticide, which can potentiate different effects since farmers are usually exposed to a complex mixture of pesticides (Ramos et al., 2021; Hutter et al., 2020). This still corroborates as one of the problems encountered during the application of questionnaires; due to this varied exposure, almost half of the rural workers do not know which pesticides they were exposed to (Vindas et al., 2004).

In short, it was possible to observe that the need to examine in detail the issue of overuse of pesticides and the increase in the number of cancer cases is commonly demonstrated. More complete and comprehensive studies will contribute so that it is possible to actively intervene in raising awareness about the correct use of these compounds, encouraging the use of personal protective equipment and that the information reaches these workers, in addition to the need for prevention with the realization routine periodic examinations by farmers occupationally exposed to pesticides.

4. Final Considerations And Future Directions

In this study, we analyzed the scientific production related to cancer and pesticides in the last decade. Worldwide, few methods of surveillance have been considered, which could bring awareness to individuals. In general, workers are aware of the risks that pesticides expose them to difficult situations, but this does not encourage to change their workplace behavior. In contrast, although they are aware of the risks associated with pesticides, the big problem seems to be losing crops if there is variation in the methods used and the quantity to be applied.

The fear of losing crops hinders the investigation process, assistance measures, and standardization of health guidance protocols, which prevent these farmers from becoming ill due to occupational exposure. Bearing in mind that, although the application of questionnaires is efficient for data interpolation, there is still a great diversity of applied methodologies. As a consequence of this, some studies indicate the relationship between cancer risk and development with occupational exposure to pesticides, and that do not describe ways and mechanisms for this to happen, demonstrating the knowledge gap that the scientific community still has on this topic, even with the gradual expansion of investments in science and technology. Unfortunately, it becomes more challenging in Brazil to view the massive cut in funds allocated to science and the little investment made in education in recent years.

Besides, the conventional pesticide market has strong power to convince and persuade global agriculture. While countries such as the United States and Europeans check pesticide records available on the market every 10 and 15 years, respectively, Brazil releases these products for life. It is worrying the relative laxity in the inspection of such a process, exemplified by the release of more and more compounds for consumption that add nothing since thousands of similar formulations are available and used. This fact is aggravated by environmental and human health problems, well described in the literature.

Therefore, the way to solve this problem can be started with health care providers. It would also be necessary for cooperative extension agents and pesticide manufacturers to contribute to the education of workers, encouraging the use of less toxic agents and the practice of integrated pest management, as well as carrying out new scientific investigations on the use of pesticides, their relation to the development of diseases in general.

5. Declarations

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5.2. Contributions

T.M.A.P., F.G.R. and D. M.S. conceived the presented idea.

T.M.A.P., F.A.N., M.B-S and J.W. verified the analytical methods.

T.M.A.P. wrote the manuscript with support from J.W., M.B-S, F.G.R and D.M.S.

All authors provided critical feedback and helped shape the research, analysis, and manuscript.

5.3.Data availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

5.4. Ethical approval

Not applicable.

5.5. Consent for publication

Not applicable.

5.6. Consent to participate

No consent to participate is required because no human participants were involved.

5.7. Competing interests

The authors declare no competing interests.

References

Band PR, Abanto Z, Bert J, Lang B, Fang R, Gallagher RP, Le ND (2011) Prostate Cancer Risk and Exposure to Pesticides in British Columbia Farmers. Prostate, 71: 168-183. doi: 10.1002/pros.21232

Barrón Cuenca J, Tirado N, Barral J, Ali I, Levi M, Stenius U, Berglund M, Dreij K (2019) Increased levels of genotoxic damage in a Bolivian agricultural population exposed to mixtures of pesticides. Sci. Total Environ. 695, 133942. https://doi.org/ 10.1016/j.scitotenv.2019.133942.

Boada LD, Henriquez-Hernandez LA, Zumbado M, Almeida-Gonzalez M, Alvarez-Leon EE, Navarro P, Luzardo OP (2016) Organochlorine Pesticides Exposure and Bladder Cancer: Evaluation from a Gene- Environment Perspective in a Hospital-Based Case-Control Study in the Canary Islands (Spain). Journal of Agromedicine, 21: 34-42. doi: 10.1080/1059924X.2015.1106374

Boucaud-Maitre D, Ranabourg MO, Sinno-Tellier S, Puskarczyk E, Pineau X, Kammerer M, Bloch J, Langrand J (2019) Human exposure to banned pesticides reported to the French Poison Control Centers: 2012-2016. Environmental Toxicology and Pharmacology, 69: 51-56. doi: 10.1016/j.etap.2019.03.017

Castillo-Cadena, J., Mejia-Sanchez, F. & López-Arriaga, J.A (2017) Congenital malformations according to etiology in newborns from floricultural zone of Mexico state. Environ Sci Pollut Res 2, 7662-7667 Doi: 10.1007/s11356-017-8429-3

Ch R, Singh AK, Pathak MK, Singh A, Kesavachandran CN, Bihari V, Mudiam MKR (2019) Saliva and urine metabolic profiling reveals altered amino acid and energy metabolism in male farmers exposed to pesticides in Madhya Pradesh State, India. Chemosphere, 226:636-644. doi: 10.1016/j.chemosphere.2019.03.157

Cohen L, Jefferies A (2019) Environmental Exposures and Cancer: Using the Precautionary Principle ecancer 13 ed91

Corcino CO, Teles RBD, Almeida JRGD, Lirani LD, Araujo CRM, Gonsalves AD, Maia GLD (2019) Evaluation of the effect of pesticide use on the health of rural workers in irrigated fruit farming. Ciência & Saúde Coletiva, 24:3117-3128

Cristina H, Sonia RZ, Helena B. Nader and Jorge AG (2019). Contrasting High Scientific Production with Low International Collaboration and Scientific Impact: The Brazilian Case, Scientometrics Recent Advances, Suad Kunosic and Enver Zerem, IntechOpen, DOI: 10.5772/intechopen.85825.

Cuenca JB, Tirado N, Vikström M, Lindh CH, Steinus U, Leander K, Berglund M, Dreij K (2019) Pesticide exposure among Bolivian farmers: associations between worker protection and exposure biomarkers. J. Expo. Sci. Environ. Epidemiol. 30, 730–742. https://doi.org/10.1038/s41370-019-0128-3.

Damalas CA, Koutroubas SD (2016) Farmers' Exposure to Pesticides: Toxicity Types and Ways of Prevention. Toxics. 8;4(1):1. doi: 10.3390/toxics4010001. PMID: 29051407; PMCID: PMC5606636

Dias LA, Gebler L, Niemeyer JC, Itako AT (2020) Destination of pesticide residues on biobeds: State of the art and future perspectives in Latin America. Chemosphere. Elsevier Ltd. https://doi.org/10.1016/j.chemosphere.2020.126038

Donley N (2019) The USA lags behind other agricultural nations in banning harmful pesticides. Environmental Health, 18: 44. doi: 10.1186/s12940-019-0488-0

Engel LS, Werder E, Satagopan J, Blair A, Hoppin JA, Koutros S, Lerro CC, Sandler DP, Alavanja MC, Freeman LEB (2017) Insecticide Use and Breast Cancer Riskamong Farmers' Wives in the Agricultural Health Study. Environmental Health Perspectives, 125: 097002. doi: 10.1289/EHP1295

EPA (2020) U.S. Environmental Protection Agency. What is a pesticide? Disponível em: <http://www.epa.gov/pesticides/about/index.htm> Acesso em: 21 de Outrubro de 2020

Eren Y, Erdogmus SF, Akyıl D, Ozkara A (2016) Mutagenic and cytotoxic activities of benfuracarb insecticide. Cytotechnology 68, 637–643

Ferri GM, Specchia G, Mazza P, Ingravallo G, Intranuovo G, Guastadisegno CM, Congedo ML, Lagioia G, Loparco MC, Giordano A, Perrone T, Guadio F, Spinosa C, Minoia C, D'Onghia L, Strusi M, Corrado V, Cavone D, Vimercati L, Schiavulli N, Cocco P (2017)

Risk of lymphoma subtypes by occupational exposure in Southern Italy. Journal of Occupational Medicine and Toxicology, 12:31. doi: 10.1186/s12995-017-0177-2

García J, Ventura MI, Requena M, et *al*. (2017) Association of reproductive disorders and male congenital anomalies with environmental exposure to endocrine active pesticides. Reprod. Toxicol., 71 (2017), pp. 95-100

Gil F, Pla A (2001) Biomarkers as biological indicators of xenobiotic exposure. Journal of Applied Toxicology, 21: 245-255. doi: 10.1002/jat.769

Gilson IK, et al. (2020) Agrotóxicos liberados nos anos de 2019 - 2020: Uma discussão sobre a uso e a classificação toxicológica. Braz. J. of Develop., Curitiba, v. 6, n. 7, p. 49468 49479

Godoy FR, Nunes HF, Alves AA, Carvalho WF, Franco FC, Pereira RR, da Cruz AS, da Silva CC, Bastos RP, Silva DM (2019) Increased DNA damage is not associated topolymorphisms inOGGIDNA repair gene, CYP2E1detoxification gene, and biochem-ical and hematologicalfindings in soybeans farmers from Central Brazil. Environ. Sci.Pollut. Res. 26, 26553–26562.

Gunier RB, Kang A, Hammond SK, Reinier K, Lea CS, Chang JS, Does M, Scelo G, Kirsch J, Crouse V, Cooper R, Quinlan P, Metayer C (2017) A task-based assessment of parental occupational exposure to pesticides and childhood acute lymphoblastic leukemia. Environmental Research, 156: 57-62. doi: 10.1016/j.envres.2017.03.001

Hernandez AF, Gil F, Lacasana M (2017) Toxicological interactions of pesticide mixtures: an update. Archives of Toxicology, 91: 3211-3223. doi: 10.1007/s00204-017-2043-5

Hossard L, Guichard L, Pelosi C, Makowski, D (2017) Lack of evidence for a decrease in synthetic pesticide use on the main arable crops in France. Science of the Total Environment, *575*, 152–161. https://doi.org/10.1016/j.scitotenv.2016.10.008

Hu, Y., et al. (2020) “Organophosphate and Pyrethroid Pesticide Exposures Measured before Conception and Associations with Time to Pregnancy in Chinese Couples Enrolled in the Shanghai Birth Cohort.” Environmental Health Perspectives, vol. 126, no. 7, 2018, pp. 077001(-76999).

Jackson SS, St George DM, Loffredo CA, Amr S (2017) Non occupational exposure to agricultural work and risk of urinary bladder cancer among Egyptian women. Archives of Environmental & Occupational Health, 72:166-172. doi: 10.1080/19338244.2016.1169155

Jacobsen-Pereira CH, Cardoso CC, Gehlen TC, dos Santos CR, Santos-Silva MC (2020) Immune response of Brazilian farmers exposed to multiple pesticides. Ecotoxicology and Environmental Safety, 202:110912. doi: 10.1016/j.ecoenv.2020.110912

Jeephet K, Kamsa-ard S, Bhudhisawasdi V, Kamsa-ard S, Luvira V, Luvira V (2016) Association between Pesticide Use and Cholangiocarcinoma. Asian Pacific Journal of Cancer Prevention, 17: 3979-3982. doi: 10.14456/apjcp.2016.201

Kalliora C., Mamoulakis C, Vasilopoulos E, Stamatiades GA, Kalafati L, Barouni R, Tsatsakis A (2018) Association of pesticide exposure with human congenital abnormalities. Toxicology and Applied Pharmacology. Academic Press Inc. https://doi.org/10.1016/j.taap.2018.03.025

Kapeleka JA, Sauli E, Ndakidemi PA (2019) Pesticide exposure and genotoxic effects as measured by DNA damage and human monitoring biomarkers. Int. J. Environ. Health Res. 00, 1–18. https://doi.org/10.1080/09603123.2019.1690132.

Keswani C, Dilnashin H, Birla, H, Singh SP (2019) Regulatory barriers to Agricultural Research commercialization: A case study of biopesticides in India. Rhizosphere, 11:100155. doi: 10.1016/j.rhisph.2019.100155

Klebis, D (2018) China é o país que produz mais artigos científicos no mundo. Brasil é o 12º. Jornal da Ciência. Acesso em 24 de março de 2021. Disponíel em <http://www.jornaldaciencia.org.br/china-e-o-pais-que-produz-mais-artigos-cientificos-no-mundo-brasil-e-o-12o/>

Kokouva M, Bitsolas N, Hadjigeorgiou GM, Rachiotis G, Papadoulis N, Hadjichristodoulou C (2011) Pesticide exposure and lymphohaematopoietic cancers: a case- control study in an agricultural region (Larissa, Thessaly, Greece). BMC Public Health, 11(5). doi: 10.1186/1471-2458-11-5

Langley RL, Mort SA (2012) Human Exposures to Pesticides in the United States. 17: 300-315. doi: 10.1080/1059924X.2012.688467

Li Z, Jennings A (2018) Global variations in pesticide regulations and health risk assessment of maximum concentration levels in drinking water. Journal of Environmental Management, 212, pp. 384-394. https://doi.org/10.1016/j.jenvman.2017.12.083

Marcelino AF, Wachtel CC, Ghisi N de C (2019) Are our farm workers in danger? Genetic damage in farmers exposed to pesticides. Int. J. Environ. Res. Public Health 16. https://doi.org/10.3390/ijerph16030358

Montes-Grajales D, Olivero-Verbel J (2020) Structure-based Identification of Endocrine Disrupting Pesticides Targeting Breast Cancer Proteins. Toxicology, *439*. https://doi.org/10.1016/j.tox.2020.152459

Mostafalou S, Abdollahi M (2017) Pesticides: an update of human exposure and toxicity. Archives of Toxicology, 91:549-599

Nascimento AF, Alves, AA, Nunes HF, Miziara F, Parise MR, de Melo e Silva D (2020) Cultivated areas and rural workers' behavior are responsible for the increase in agricultural intoxications in Brazil? Are these factors associated? Environmental Science and Pollution Research, 27:38064–38071. Doi:10.1007/s11356-020-09988-3

National Science Board (2018) Science and Engineering Indicators *2018*. NSB-2018-1. Alexandria, VA: National Science Foundation. Acesso em 24 de março de 2021, disponível em <https://www.nsf.gov/statistics/indicators/>

Packard E, Shahid Z, Groff A, et al. (2019) Multiple Myeloma in an Agricultural Worker Exposed to Pesticides. Cureus 11(5): e4762. DOI 10.7759/cureus.4762

Parker AM, et al. (2017) UV/H202 advanced oxidation for abatement of organophosphorus pesticides and the effects on various toxicity screening assays. Chemosphere. 182, 477-482

Paumgartten FJR (2020) Pesticides and public health in Brazil. Current Opinion in Toxicology. Elsevier B.V. https://doi.org/10.1016/j.cotox.2020.01.003

Presutti R, Harris SA, Kachuri L, Spinelli JJ, Pahwa M, Blair A, Zahm SH, Cantor KP, Weisenburger DD, Pahwa P, McLaughlin JR, Dosman JA, Freeman LB (2016) Pesticide exposures and the risk of multiple myeloma in men: An analysis of the North American Pooled Project. Int J Cancer. Oct 15;139(8):1703-14. doi: 10.1002/ijc.30218. Epub 2016 Jun 28. PMID: 27261772.

Porto FP, Soares WL (2012) Development model, pesticides, and health: a panorama of the Brazilian agricultural reality and proposals for an innovative research agenda. Revista Brasileira de Saúde Ocupacional, 37:17-50

Ramos JSA, Pedroso TMA, Godoy FR, Batista RE, de Almeida FB, Francelin C, Ribeiro, Francis LEE, Parise MR, de Melo e Silva, D (2021) Multi-biomarker responses to pesticides in an agricultural population from Central Brazil. Science of The Total Environment 754:141893-141900.

Rocha A, Gonçalves E, Almeida E (2019) Agricultural technology adoption and land use: evidence for Brazilian municipalities, Journal of Land Use Science, 14:4-6, 320-346, DOI: 10.1080/1747423X.2019.1707312

Saad-Hussein A, Beshir S, Taha MM, Shahy EM, Shaheen W, Abdel-Shafy EA, Thabet E (2019) Early prediction of liver carcinogenicity due to occupational exposure to pesticides. Mutation Research - Genetic Toxicology and Environmental Mutagenesis, *838*, 46–53. https://doi.org/10.1016/j.mrgentox.2018.12.004

Sant'Ana GDF, Araujo SHC, Pereira JL, Oliveira EE (2019) Apprehension of illegal pesticides, agricultural productivity and food poisoning on the Brazilian state of Mato Grosso do Sul. Revista de Ciencias Agricolas, 36: 52-62. doi: 10.22267/rcia.1936E.106

Salerno C, Carcagnì A, Sacco S, Palin LA, Vanhaecht K, Panella M, Guido D (2016) An Italian population-based case-control study on the association between farming and cancer: Are pesticides a plausible risk factor? Arch Environ Occup Health, 3;71(3):147-56. doi: 10.1080/19338244.2015.1027808.

Salerno C, Sacco S, Panella M, Berchialla P, Vanhaecht K, Palin LA (2014) Cancer risk among farmers in the Province of Vercelli (Italy) from 2002 to 2005: an ecological study. Ann Ig. 26(3):255-63. doi: 10.7416/ai.2014.1983.

Sharma A, Shukla A, Attri K, Kumar M, Kumar P, Suttee A, Singh G, Barnwal RP, Singla N (2020). Global trends in pesticides: A looming threat and viable alternatives. Ecotoxicology and Environmental Safety, 201:110812. doi: 10.1016/j.ecoenv.2020.110812

Shrestha S, Parks CG, Keil AP, Umbach DM, Lerro CC, Lynch CF, Chen HL, Blair A, Koutros S, Hofmann JN, Freeman LEB, Sandler DP (2019) Overall and cause- specific mortality in a cohort of farmers and their spouses. Occupational and Environmental Medicine, 76:632-643. doi: 10.1136/oemed-2019-105724

Tollefson, J (2018). China declared largest source of research articles. Spring Nature. v.553. https://doi-org.ez49.periodicos.capes.gov.br/10.1038/d41586-018-00927-4

Tual S, Busson A, Boulanger M, Renier M, Piel C, Pouchieu C, Pons R, Perrier S, Leveque-Morlais N, Karuranga P, Lemarchand C, Marcotullio E, Guizard AV, Monnereau A, Baldi I, Lebailly P (2019) Occupational exposure to pesticides and multiple myeloma in the AGRICAN cohort. Cancer Causes & Control, 30: 1243-1250. doi: 10.1007/s10552-019-01230-x

Vale RL, Netto AM, Toríbio LXB, Lâvor MPB, Siqueira JPS (2019) Assessment of the gray water footprint of the pesticide mixture in a soil cultivated with sugarcane in the northern area of the State of Pernambuco, Brazil. Journal of Cleaner Production. Elsevier Ltd. https://doi.org/10.1016/j.jclepro.2019.06.282

VAN ECK, Nees Jan; WALTMAN, Ludo (2010) Software survey: VOSviewer, a computer program for bibliometric mapping. scientometrics, v. 84, n. 2, p. 523-538

Vindas, R.; Ortiz, F.; Ramírez, V.; Cuenca, P. (2004) Genotoxicidad de tres plaguicidas utilizados en la actividad bananera de Costa Rica. Rev. Biol. Trop. 52, 601–609

VoPham et al (2017) Pesticides exposures and liver cancer: a review. Cancer, Causes & Control, [s.l.], v. 28, n. 3, p. 177-190, DOI 10.1007/s10552-017-0854-6

Ye M, Beach J, Martin JW, Senthilselvan A (2017) Pesticide exposures and respiratory health in general populations. Journal of Environmental Sciences (China). Chinese Academy of Sciences. https://doi.org/10.1016/j.jes.2016.11.012

Yiin JH, Ruder AM, Stewart PA, Waters MA, Carreon T, Butler MA, Calvert GM, Davis-King KE. Schulte PA, Mandel JS, Morton RF, Reding DJ, Rosenman KD (2012) Environmental Health, 11(19). doi: 10.1186/1476-069x-11-39

Zakerinia M, Namdari M, Amirghofran S (2012) The Relationship between Exposure to Pesticides and the Occurrence of Lymphoid Neoplasm. Iranian Red Crescent Medical Journal, 14: 337-344

Zheng W, Luo B, Hu X (2020) The determinants of farmers' fertilizers and pesticide use behavior in China: An explanation based on label effect. Journal of Cleaner Production, 272. https://doi.org/10.1016/j.jclepro.2020.123054

Figures

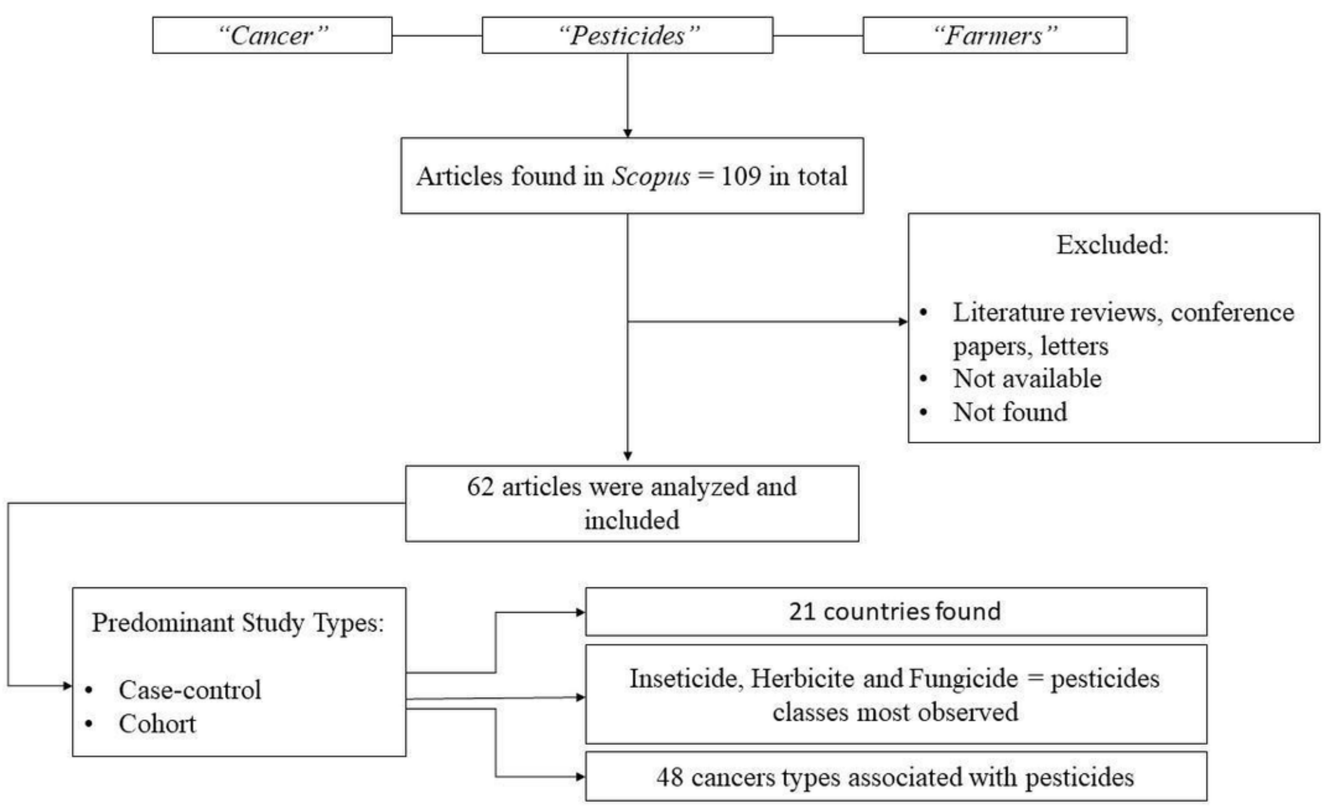

Figure 1

Flowchart of selection, inclusion and exclusion of the papers for bibliometrics involving occupational exposure to pesticides and cancer.

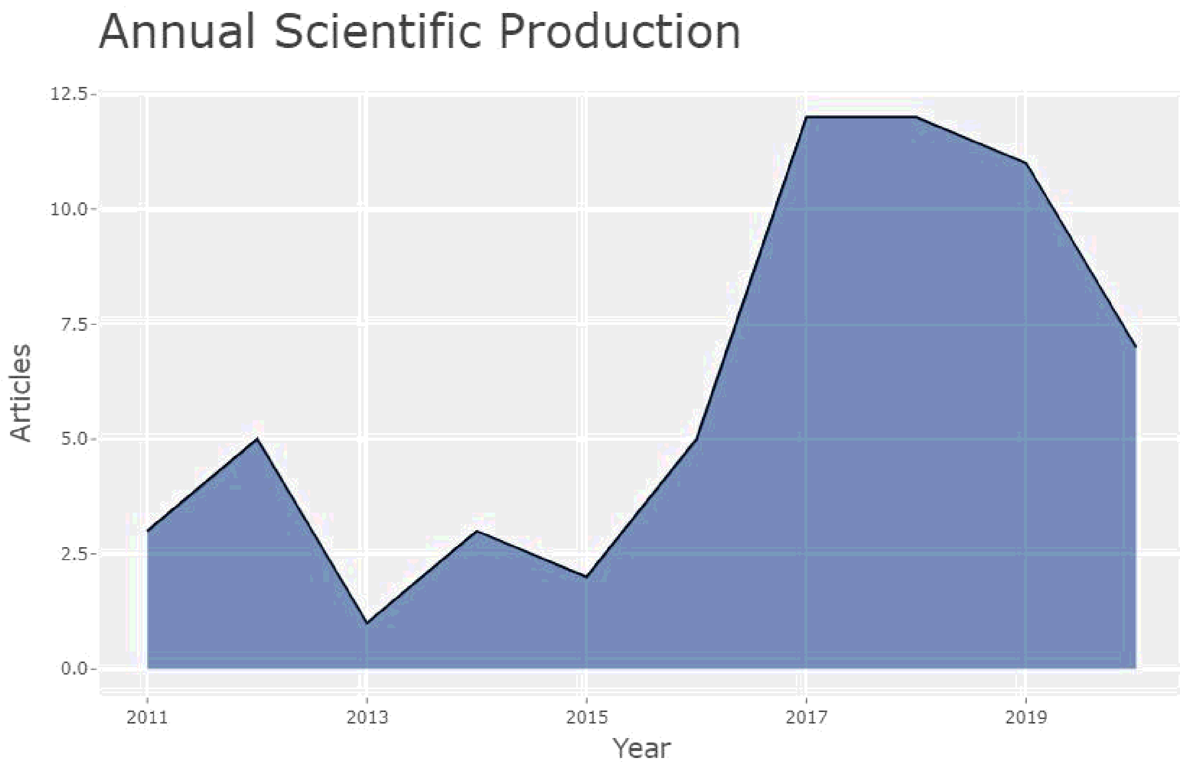

Figure 2

Scientific production associating cancer with occupational exposure to pesticides in rural workers from 2011 to 2020.

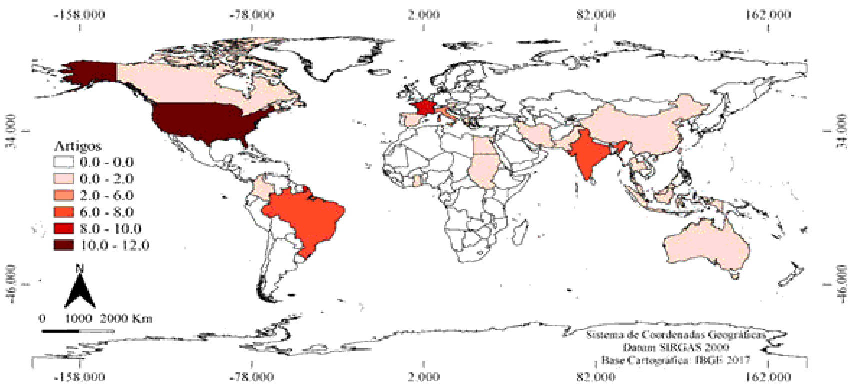

Figure 3

Geographical aspects of scientific production on cancer associated with occupational exposure to pesticides. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

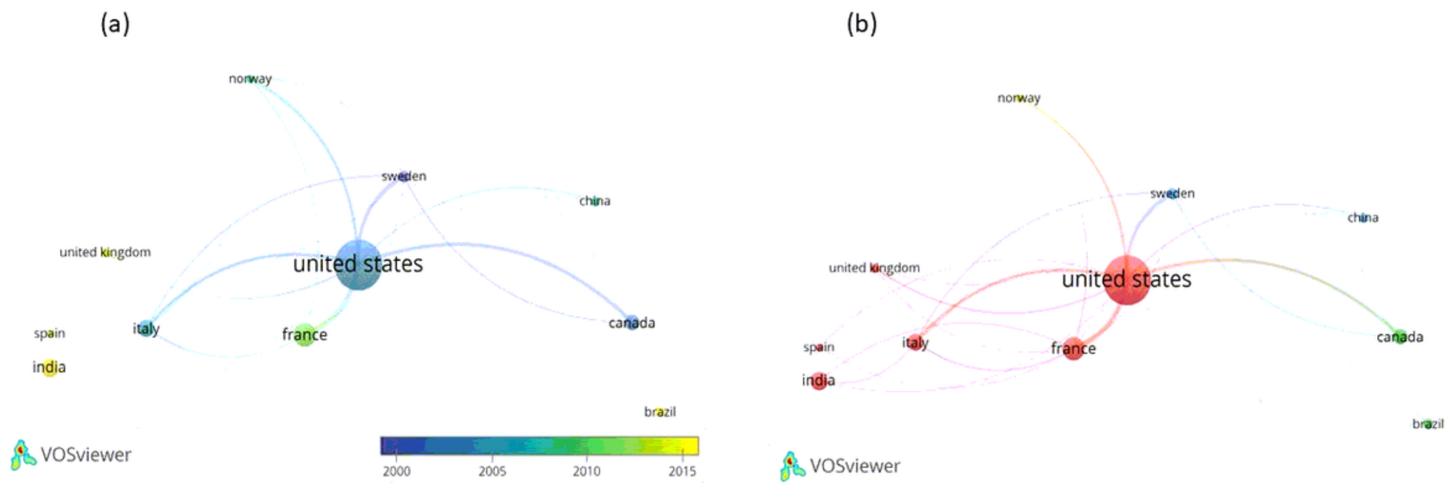

Figure 4

(a) Clusters of scientific production per year, the cluster referring to American scientific production is centralized concerning the other groups, and (b) co-authorship clusters demonstrating a close relationship between the United States, European countries, Asian countries, and Brazil.

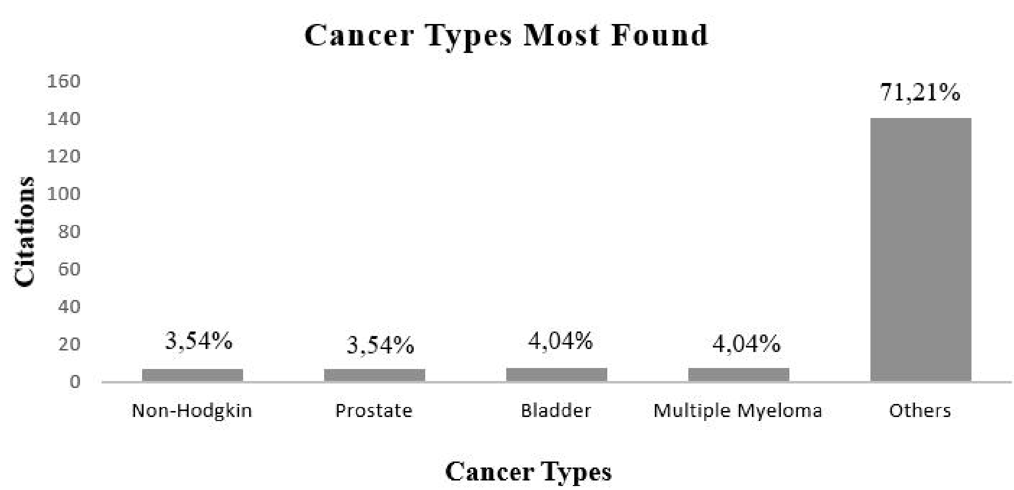

Figure 5

Types of cancer frequently associated with the occupational use of pesticides.

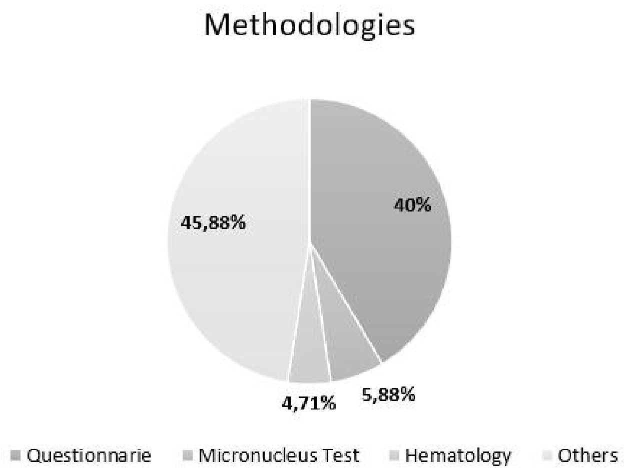

Figure 6

Methods employed in investigations that associate cancer risk and development with pesticides.

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