The Indiscriminate Use of Pesticides Could Increase the Prevalence of Alzheimer's Disease? A SystematicReview

.

ABSTRACT

Aims: This review aims to perform an extensive literature search about the pesticides problems and to associate with AD in qualitative analysis, mainly.
Place and Duration of Study: Biomathematics Laboratory, Institute of Biomedical Sciences, Federal University of Alfenas, Alfenas, Brazil. Entre outubro de 2023 a abril de 2024.
Methodology: For the purpose of this systematic review, articles from 2014 onwards with the descriptors Alzheimer's disease and pesticides; neurodegenerative diseases and pesticides, were sought. Among these, articles considered most pertinent to the objective of the present review were utilized, i.e., those whose subject matter was associated with the effects of pesticides, especially glyphosate, on dementias, particularly Alzheimer disease (AD).
Results: After analyzed 35,590 articles, and applying exclusion criteria to journals with an impact factor equal to or lower than 4 and including topics most relevant to the objectives of this work, 35,531 articles were excluded, resulting in 59 remaining articles, of which 36 were qualitative in scope and 23 were quantitative. The articles considered most suitable for the objective of the present review were utilized, i.e., those whose topic was associated with the effects of pesticides, especially glyphosate, on dementia. The criteria for scrutinizing articles included a journal impact factor equal to or greater than 4 and the removal of duplicate articles using the freely accessible EndNote program from Web of Science. Articles and books on history and those outside the scope of the pesticide/AD relationship did not follow the criterion of having an impact factor equal to or greater than 4.
Conclusion: There appears to be a relationship between the increase in pesticide use, particularly Glyphosate, and the rise in Alzheimer's disease prevalence.

Keywords: Dementia. Alzheimer's disease. Pesticides. Agrochemicals.

1. INTRODUCTION

1.1 Pesticides

Agrochemicals, pesticides, chemical or agricultural pesticides are synonymous terms referring to substances used in agriculture for the management of agricultural pests. The nomenclature of agrochemicals highlights their toxicity to the environment, humans, and animals [1].

The advent of agriculture as a commercial enterprise trace back to the 16th century [2], propelled by the burgeoning global population and urban density, which precipitated a concurrent demand for increased food supply.

By 2025, there will be an estimated 8.4 billion people dependent on food sourced from rural areas [3], exerting pressure for increased agricultural productivity in technological and

organizational terms. This necessitates efforts to mitigate losses from the field to the final consumer, with pesticide usage remaining indispensable[4].

Historically, pesticides were developed and refined in the 20th century by the chemical industry to be used as weapons in World War II [1], particularly in Germany, where scientist Fritz Haber, Nobel Prize winner in 1918 for the synthesis of ammonia from its elements [5], served as a mentor for ammonia production. However, with the end of the war, the chemical weapons industry transformed into the industry of fertilizers and agricultural pesticides [1,4].

In post-war Europe, food poverty prevailed due to the scarcity of food resulting from the destruction of farmlands and pastures, as well as the lack of labor [2]. The "green revolution" was proposed in the 1950s to expand agricultural production in the old continent. However, in Brazil, the encouragement of agriculture arrived in the mid-1960s, as the country did not suffer the consequences of the war on its territory and supplied/exported goods to the European continent [1,4]. Nevertheless, greater agricultural production was deemed necessary to stimulate the economy and foster economic growth [2]. The agrochemical industry was favored by the Brazilian government, which instituted bank financing for the purchase of seeds associated with fertilizers and pesticides[1].

Notwithstanding the significance of pesticides for crop cultivation and food production to sustain the population, human and animal health may be at risk, as various types of pathologies related to the effects of pesticides have been observed [2]. These include an increase in the number of cases of neurological diseases, psychiatric disorders, memory-related disturbances, attention deficits [6,7], and cancer[8].

Indeed, pesticides are substances employed to control and mitigate pests [9], applied in activities targeting fungi, insects, vegetation along roads, gardens, parks, water systems [10], and in agriculture, where pesticide usage stands as the primary source of environmental contamination [11,12].

Among the pesticides used worldwide, glyphosate (N-phosphonomethylglycine) stands as the most consumed. It is an organophosphorus compound derived from glycine and utilized as a non-selective herbicide [13]. Its mechanism of action involves targeting the shikimic acid pathway, inhibiting the 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) enzyme responsible for synthesizing phenylalanine, tyrosine, and tryptophan, essential aromatic amino acids for plant survival [12,14], but not produced in animals [15,16].

The herbicidal action of glyphosate was utilized in the formulation of the globally renowned product Roundup®, introduced to the market by the Monsanto Company starting in 1974 [17,18]. It remains one of the most widely used herbicides worldwide [19,20],because that, at least hypothetically, if Glyphosate generate health problems it is plausible to conclude that other ones will generate the same since glyphosate is considered less toxic of the used pesticides.Glyphosate is recommended for crops such as soybeans, coffee, sugarcane, citrus fruits, and rice and exhibits persistence in the environment, as it has been detected in both groundwater [21] and surface water [22] long after its application.

Despite being considered a pesticide with low toxicity, both environmentally and for human and animal health, among those available on the market [23], studies have suggested that glyphosate may cause chronic malformations in certain animal species, such as chickens, frogs, and mammals[24,25].

In this regard, the use of glyphosate raises concerns for human and animal health, as it is an environmental contaminant of water, soil, and animals [26]. Furthermore, the extensive

application of this pesticide may render organisms capable of developing resistance against other non-selective herbicides[15].

Chronic exposure to Roundup® has been shown to cause human erythrocyte lysis [11] and high genotoxicity in bone marrow cells of Swiss mice [27] within concentrations recommended by the manufacturer. In 2015, the International Agency for Research on Cancer (IARC) [8] concluded that there is strong evidence indicating glyphosate may cause cancer, as pesticides in general [28].

Usually, organophosphates exhibit higher acute toxicity in humans and other mammals [29]compared to organochlorines,that affects neural development and behavior [30] and could increase the dementia risk [31,32,33,34]. Several organophosphates pose health risks to workers who apply them and individuals who may come into contact with these pesticides. Intoxication by these substances can occur through exposure to the products via inhalation, ingestion, or absorption through the skin[14].

The dispersion of these pesticides in agriculture occurs through spraying, and due to wind effects, can spread over areas of 1 km to 2 km. Aquatic environments are contaminated through three pathways: I) discharge of industrial waste or effluent discharge into water; II) infiltration of toxic residues into the soil, contaminating water sources; III) surface runoff during product application on the soil[14].

Other studies have indicated that chronic exposure to glyphosate may lead to neurodegenerative disorders, such as Alzheimer's (AD) [28] and Parkinson's diseases[7,35], as well as a decrease in serotonin, norepinephrine, and dopamine levels in the prefrontal cortex, hypothalamus, and hippocampus of rodents [36], which could impair learning and memory processes[37].

1.2 Alzheimer disease

Expenditures on dementia-related care surpass those on prevention efforts, and these diseases not only cause suffering to patients, their families, and caregivers but also necessitate substantial social care. Hence, prevention measures are crucial. It appears that governmental concern regarding Alzheimer's disease (the most prevalent form of dementia) [38], at least in the United States, is diminishing, thereby shifting more responsibility and financial burden onto families[39].

Alzheimer's disease (AD), initially discovered by the German psychiatrist Alois Alzheimer [40] in 1906, is the leading cause of senile dementia, characterized by heterogeneous neurodegenerative effects. It lacks a definitive lifelong diagnosis, and among its various causes, AD is linked to both environmental [41] and genetic factors[38].

Several studies have associated Alzheimer's disease with aging [38], primarily because the majority (approximately 90% of cases) [42] of AD occurs in individuals aged 65 and older. Its prevalence doubles every 5 years, leading to an exponential increase dependent on time[38,43].

Due to its neurodegenerative effects, Alzheimer's disease results in decreased cognition, such as speech impairment, praxis difficulties, memory loss, impaired judgment, and emotional instability, along with personality changes. It involves progressive neuronal loss, increased senile plaques, and neurofibrillary tangles [38], leading to the destruction of neural networks and evident hippocampal atrophy[40].

1.3 AD and pesticides

Recent research indicates that neurodegenerative diseaseshave increased in prevalence in recent years [44,45]dueto pesticides effects[46,47,48].Specifically, the etiology of Alzheimer's disease remains unclearandthe role of the environment as a probable risk factor is significant [38,49,50,51],nevertheless, some new treatments has been suggested for this affection, at least *in vitro*[52,53,54,55]. Of particular concern is the evidence suggesting that prenatal and postnatal exposures to harmful environmental factors predispose individuals to neurodegenerative diseases later in life[56].

In the context of associating pesticide effects with Alzheimer's disease prevalence, exposure of both animals and humans to these substances has been linked to Alzheimer's disease [57] due to their ability to increase beta-amyloid peptide (A-β) [50,51] and protein Tau phosphorylation (P-Tau) [7]. These compounds contribute to the formation of senile/amyloid plaques and neurofibrillary tangles (NFTs), which are common in Alzheimer's disease.

Moreover, epigenetic mechanisms involving maternal nutrient complementation and exposure to metals and pesticides have been proposed to elevate phenotypic diversity and susceptibility to neurodegenerative diseases[35].

One possible cause of the increased prevalence of Alzheimer's disease is that even "mild" environmental factors (such as behavioral or physical stress) and exposure below the recommended limit to pollutants and chemicals, such as pesticides, can elevate the risk of Alzheimer's disease[58].

Considering the current use of pesticides, particularly glyphosate, which has been approved in Brazil without efficient toxicological/environmental analysis by public agencies and environmental assessments via presidential decree [59], it is reasonable to hypothesize that there may be a relationship between the increased use or concentration of pesticides (glyphosate) and the rise in the prevalence of AD.

Therefore, the objective of this study was performing an extensive literature searchabout the pesticides problems and to associate with AD in qualitative analysis, mainly.

2. MATERIAL AND METHODS

For the purpose of this systematic review, articles from 2014 onwards with the descriptors Alzheimer's disease and pesticides; neurodegenerative diseases and pesticides, were initially searched on the CAPES journals platform, which includes the Web of Science, Scopus, MedLine, PubMed, PubMed Central, Elsevier ScienceDirect Journals, Directory of Open Access Journals, and Google Scholar. This search was conducted during the month of April 2024 to form the epistemological basis of the review, resulting in a total of 35,590 articles.

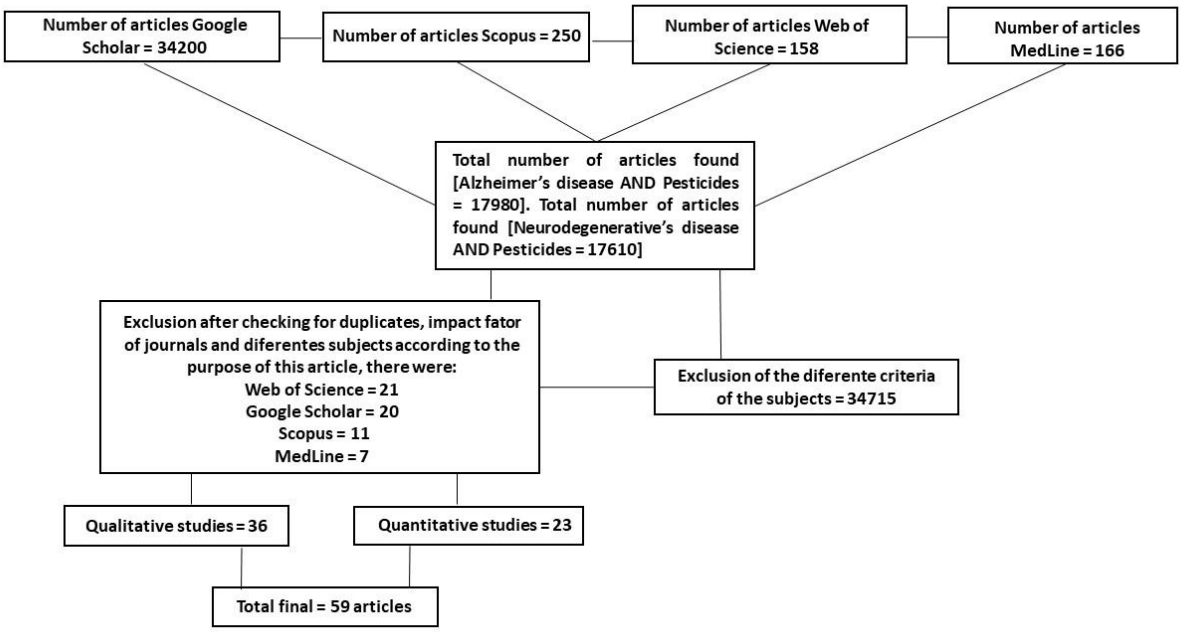
From these, articles considered most suitable for the objective of the present review were utilized, i.e., those whose topic was associated with the effects of pesticideson dementia, particularly Alzheimer's disease (AD). The criteria for scrutinizing articles included a journal impact factor equal to or greater than 4, firstly, however, other articles with impact factor minor than 4 were used due the importance for the theme, and the removal of duplicate articles using the freely accessible EndNote program from Web of Science. Articles and books on history and those outside the scope of the pesticide/AD relationship did not follow the criterion of having an impact factor equal to or greater than 4.The impact equal or greater than 4 was chosen because the high number of papers, however other considered important articles for this subject were used with impact minor than 4.

Based on this analysis and considering topics closer to the objective of this work, the exclusion criteria were a journal impact factor lower than 4 and duplicates within the keywords pesticides and dementia (30); pesticides and Alzheimer's disease (27); glyphosate and dementia (2), resulting in 20 articles derived from Google Scholar, 21 from Web of Science, 11 from Scopus, and 7 from MedLine (Graphic 1).

3. RESULTS AND DISCUSSION

3.1 Results

Of the initially analyzed 35,590 articles, after applying exclusion criteria to journals with an impact factor equal to or lower than 4 and including topics most relevant to the objectives of this work, 35,531 articles were excluded, resulting in 59 remaining articles, of which 36 were qualitative in scope and 23 were quantitative, as shown in Graphic 1. The exclusion criteria

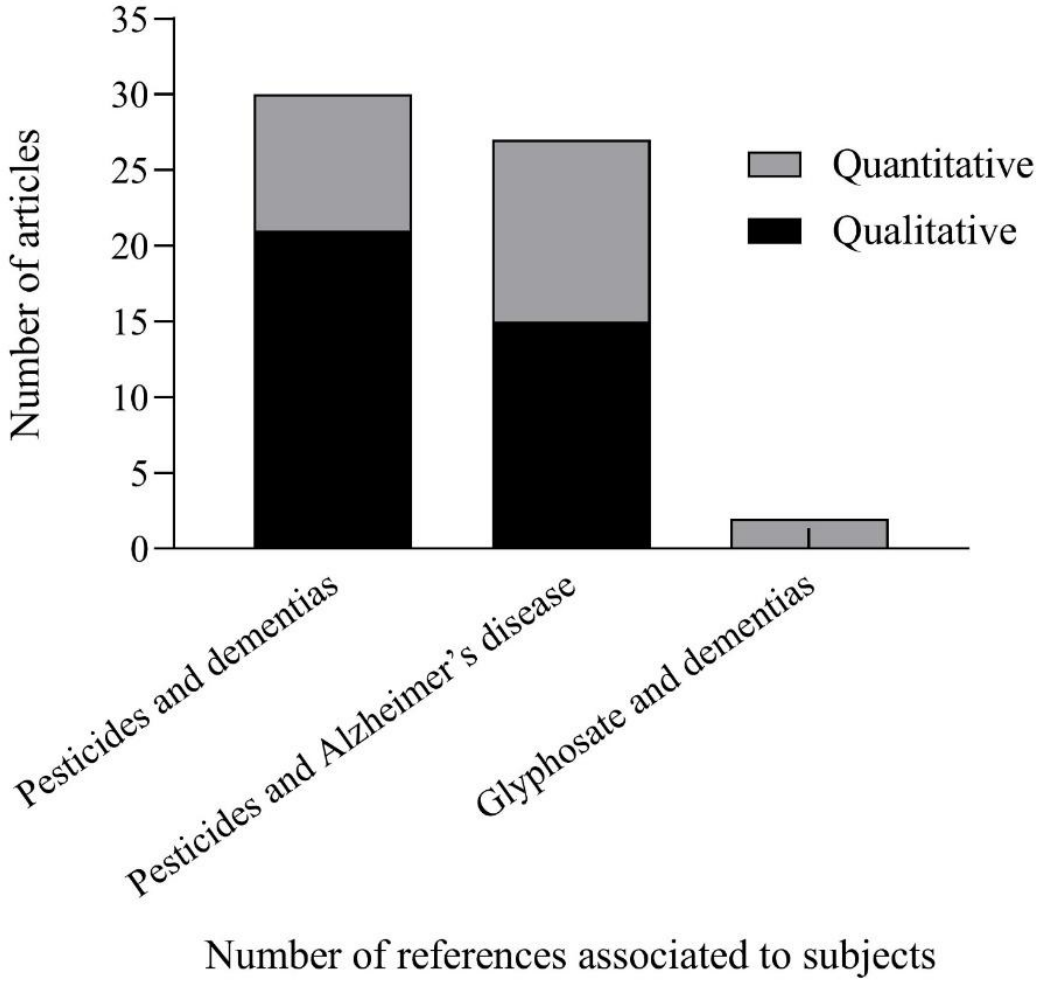


flowchart is presented in Figure 1.

Fig. 1. Diagram of inclusion and exclusion criteria for the articles used in this study.

Graphic 1 associates the identification data of the articles according to the reference system, the themes derived from the keywords and the qualitative and quantitative aspects of the 59 articles after scrutiny.

Graphic 1. Association between article identification and its subjects


35
30
25
20
15
10
5
0
Number of articles
Quantitative
Qualitative
Pesticides and dementias
Pesticides and Alzheimer's disease
Glyphosate and dementias
Number of references associated to subjects

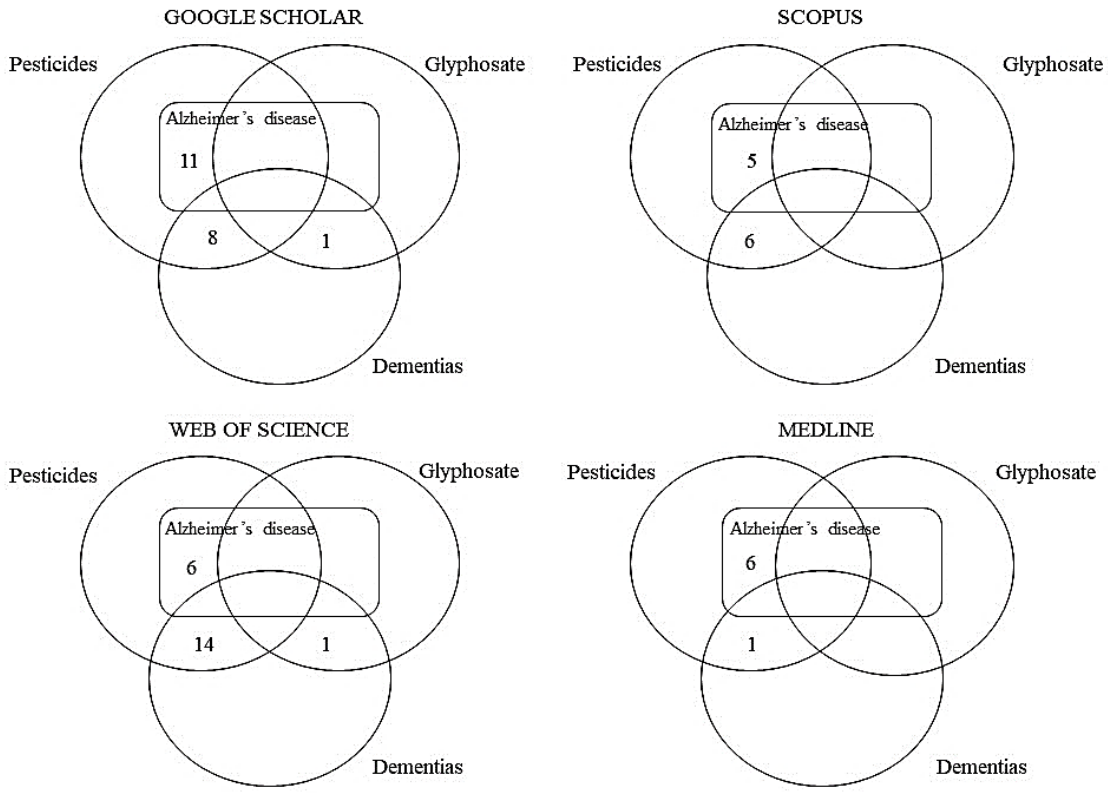


Fig. 2. Venn diagram of articles found in Google Scholar, Scopus, Web of Science, and MedLine after considering the exclusion and inclusion criteria.

According to the literature data observed in this article, the relationship between the prevalence of pesticide-related dementia was shown in 36 journal articles derived from qualitative data and 23 from quantitative data with an impact factor greater than 4. The topic of pesticides and dementia (30/59) was the most frequently encountered in the search within this scope.

The lowest number of topics found was for glyphosate and dementia (2/59), indicating that, despite the general concern regarding the association between pesticides and dementia, the effects of glyphosate appear to be underestimated (Fig. 2). This notion is reinforced by the fact that the topic of pesticides and AD (27/59) was the second most frequently encountered for the purpose of this study. In this regard, the data itself justifies the relationship between the most widely used pesticide in the world and one of the dementias affecting the elderly population with high prevalence [40].

The articles that served as the theoretical epistemological basis for this work were chosen to provide more specific and relevant data for the construction of the article. Some of these articles present quantitative data on the effects of glyphosate on erythrocyte osmotic fragility occurring within concentrations recommended by the manufacturer [12,18], as well as aspects that directly associate theories of aging with AD [38,39].

3.2 Pesticides,AD and environment

As the general population ages, the duration of contact with environmental agents [38], particularly pesticides, increases, contributing to the development of dementia. Therefore, in the impossibility of preventing aging progression, and for the entire population in general, preventive measures are necessary to avoid health risks, especially within the hypothesis that pesticides cause AD, which appears to be the case [35,38] (Graphic 1, Figure 2).

In general, neurodegenerative problems have both familial (genetic) and environmental origins [39,60,61], but they are primarily associated with environmental factors [44,62]. If we combine this information with the increasing global population age [38], it is obvious that the duration of human exposure to degenerative environmental factors will also increase.

Current scientific studies have raised the hypothesis that exposure to environmental factors may increase the prospective risk of neural system diseases [63,64].Indeed, variables asgenetic elements[65], neurodegenerative disorders can be sporadic in nature and are generally influenced by a range of environmental factors[66,67] and lifestyle[38,68].

Environmental factors can play a crucial role in slowing down or accelerating the progression of AD [38], with prolonged exposure to various heavy metals such as aluminum, lead, and mercury; pesticides; and metal-containing nanoparticles standing out as particularly significant [53,69,70].

The link between pesticide residues and AD is not clear and is difficult to establish [71]. However, studies conducted with mice have investigated the effects of pesticide residues on pathological markers of AD, revealing that serum concentrations of pesticides in the blood strengthened pre-existing pathological markers [11,72,73].

Dementia tends to increase in prevalence with advancing age [38] due to neuronal deterioration caused primarily by circulatory factors, which transport toxins and may decrease the supply of oxygen and nutrients to tissues [39]. In this regard, the increased erythrocyte fragility induced by glyphosate suggests decreased oxygen pressure in individuals, with repercussions on neural tissue [11,18] and those with higher metabolic rates.

Indeed, pesticides adversely affect human health [71], as environmental toxins have been implicated in neurodegenerative diseases, and pesticide exposure is a suspected environmental risk factor for AD [74], particularly because epidemiological analyses confirm the existence of a link between pesticides and the incidence of sporadic AD [75]. Elevated serum levels of pesticides are associated with an increased risk of AD [76]. Pesticides, especially glyphosate, elevate levels of the β-amyloid precursor protein, providing plausibility for the association of pesticide exposure with AD[77,78].

3.3 Pesticides actions on AD

The action of pesticides on the neural system increases the concentration of β-amyloid peptide (Aβ) along with the hyperphosphorylation of Tau protein, both persistent pathological markers in AD, forming senile plaques and neurofibrillary tangles that involve neural system cells, resulting in neuronal death [79,80,81]. In addition to the inhibition caused in the acetylcholinesterase enzyme, organophosphate pesticides can also cause disruptions in microtubules, another characteristic evidenced in AD [82,83,84]. This association is important for public health, given the increasing prevalence of dementia and the increasingly common use of pesticides [71].

The mechanism of acute toxicity of pesticides such as glyphosate in target and non-target organisms is mainly attributed to inhibitory actions on various forms of cholinesterase,

leading to excessive peripheral and central cholinergic activities [63,85]. Cholinesterase is classified into two types: acetylcholinesterase and pseudocholinesterase [64]. Acetylcholinesterase is synthesized in nervous tissue, skeletal muscles, and the liver, and plays an indispensable role in the destruction of acetylcholine at nerve synapses. Pseudocholinesterase, or nonspecific butyrylcholinesterase, is produced in various organs such as the liver, pancreas, small intestine, and in lower concentrations, the central and peripheral nervous systems [63,64].

Recent findings indicate that pre- and post-transcriptional mechanisms controlling AChE signaling coordinate the identity, functioning, dynamics, and communication between the brain and the body, allowing for the homeostatic maintenance of ACh signaling between the brain and body [86,87,88,89].

The main action of organophosphates, a class to which glyphosate belongs, involves the inhibition of the enzyme acetylcholinesterase (AChE) and various molecular targets such as hormones, neurotransmitters, neurotrophic factors, enzymes related to the metabolism of β-amyloid protein, and inflammatory changes [85,90],in general, could increases neuropsychiatric conditions [91].

Neuronal death is directly linked to dementia, which occurs in AD mainly in areas where the neurotransmitter is acetylcholine [39,92,88,89]; glyphosate alters the level of neurotransmitters in the cortex, hypothalamus, and hippocampus [37], reducing cognitive and mnemonic processes [38], and in the peripartum,affects maternal brain plasticity and behavior [93].

In this scope, if glyphosate is the most widely used pesticide worldwide [14], the population will be more susceptible to experiencing its effects in the environment[94], which persist with this substance in biogeochemical cycles such as in soils, springs [22,95], surfaces [23], air [83], and directly or indirectly in plant-origin foods or animal-origin foods [27,96].

Assuming the data from studies so far indicating that pesticides is toxic to the neural system, which is strongly suggested considering here the experimental research and less speculative studies, it is reasonable to indicate that exposure to it should be avoided as a way to prevent AD and dementia in general. AD, due to the strong environmental aspect associated with its prevalence, should be viewed with greater concern. Therefore, it can be said that there should be a relationship between the increase in the use or concentration of pesticides (glyphosate) and the increase in the prevalence of AD, as suggested in the hypothesis in this work.

3.4 Actions of prevention

In this regard, governmental actions in general should focus their attention on reducing the use of pesticides, notwithstanding the need for large-scale food production [2]; to stimulate research and production of biological inputs (bio pesticides); and to promote family farming, a type of agriculture developed on small properties that in Brazil sustains about 70% of the population [3]. Family farming is more closely linked to sustainability processes because it generates fewer environmental damages and less harm to the health of animals and humans, as managing small properties requires fewer industrial pesticides and allows for the use of natural defenses [1,2].

In addition, the dementia prevention process involves a multidisciplinary family medicine team to raise awareness about the dangers and risks, demonstrate care and detoxification processes for those who work in the field and/or live near pesticides [97]. Environmental

surveillance with prevention-focused management is a determining factor in avoiding the exacerbated use of chemical pesticides [3,59]. As proposed by Trevisan et al. (2019), individuals should start preventing AD and other dementias from youth, and in this regard, avoiding indiscriminate contact with pesticides can reduce health problems, especially considering that healthcare expenditures are greater than those allocated for prevention [40].

Indeed, a public health responsibilityis necessary added agovernmental policy on the environmental controls in the use of pesticides, *inter alia*, to reduce indiscriminate use of the pesticides to prevent environmental disorganization, however, providing food safety.
In this way, specific policies must ensure survival and quality of life for humans and animals; nevertheless, if it is not possible for now, at least, to reduce the damages, and the society could become aware about the abusive use of pesticides[98].
Future research could be directed for specific studies linking dementia, mainly AD, to pesticides indiscriminate use, in epidemiological terms for humans and laboratory tests, *in vitro* or using animal models.

4. CONCLUSION

Considering the data studied thus far, which strongly suggests that pesticides is toxic to the neural system based on experimental research observed from studied literature, it is compelling to indicate that there is, at least, a qualitative relationship between the increase in pesticide use and the increase in the prevalence of AD. Exposure to it should be avoided as a means of preventing AD and dementia in general by using the methods of prevention indicated against toxicity of pesticides with a rigid government policies and attention of health professionals in a preventive care.

REFERENCES

1. Santos JP, Polinarski CA. History of pesticides and possible impacts of their use on health. Cadernos PDE Unioeste.2012;1:1-21.

2. Frota MTBA, Siqueira CE. Pesticides: The hidden poisons on our table. Cad. Saúde Pública.2021;37(2):1-5. DOI: 10.1590/0102-311X00004321

3. ONU. United Nations, 2019. Department of Economic and Social Affairs. World populations prospect 2019. Disponível em: https://population.un.org/wpp/Download/Standard/Population/ Acessado em: junho/2022.

4. Jobim PFC, Nunes LN, Giugliani R, Cruz IBM. Existe uma associação entre mortalidade por câncer e uso de agrotóxicos? Uma contribuição ao debate. Ciênc. Saúde coletiva.2010;15(1):277-288. DOI: 10.1590/S1413-81232010000100033

5. Farias RF. Para gostar de ler a História da Química. 2ª ed. Editora Átomo: Campinas. 2005;1.

6. Wang GW, Fan X-N, Tan Y-Y, Cheng Q, Chen S-D. Parkinsonism after chronic occupational exposure to glyphosate. Parkinsonism Relat Disord. 2011;17(6):486–487. DOI: 10.1016/j.parkreldis.2011.02.003

7. Chen NN, Luo D-J, Yao X-Q, Yu C, Wang Y, Wang Q et al. Pesticides induce spatial memory deficits with synaptic impairment and an imbalanced Tau phosphorylation in rats. J Alzheimers Dis. 2012;30:585-594. DOI: 10.3233/JAD-2012-111946

8. International Agency for Reaserch on Cancer (IARC)Monographs Volume 112: evaluation of five organophosphate insecticides and herbicides. Lyon, 2015;112:1-2. Disponível em: <https://www.iarc.who.int/wp-content/uploads/2018/07/MonographVolume112-1.pdf>. Acessado em: de janeiro de 2022.

9. Kamel F, Hoppin J. Association of pesticide exposure with neurologic dysfunction and disease. Environ Health Perspect. 2004;112(9):950-958. DOI: 10.1289/ehp.7135

10. Solomon K, Thompson D. Ecological risk assessment for aquatic organisms from over-water uses of glyphosate. Toxicol Environ Health B Crit Rev. 2003;6(3):211-246. DOI: 10.1080/10937400306468

11. Rodrigues HG, Penha-Silva N, Araujo MFP, Nishijo H, Aversi-Ferreira TA. Effects of Roundup pesticide on the stability of human erythrocyte membranes and micronuclei frequency in bone marrow cells of Swiss Mice. Bentham Open.2011;4(1):54-59. DOI: 10.2174/1874196701104010054

12. Nascimento L, Melnyk A. The Chemistry of pesticides in the Environment and health. Revista Mangaio Acadêmico.2016;1(1):54-61.

13. Henderson AM, Gervais JA, Luukinen B, Buhl K, Stone D, Strid A et al. Glyphosate Technical Fact Sheet; National Pesticide Information Center, Oregon State University Extension Services, 2010. Acessado em: janeiro de 2022. Disponível em: http://npic.orst.edu/factsheets/archive/glyphotech.html#references

14. Steinrücken HC, Amrhein N. The herbicide glyphosate is a potent inhibitor of 5-enolpyruvyl-shikimic acid-3-phosphate synthase. Biochem Biophys Res Commun. 1980;94(4):1207–1212. DOI: 10.1016/0006-291x(80)90547-1

15. Busse MD, Ratcliff AW, Shestak CJ, Powers RF. Glyphosate toxicity and the effects of long-term vegetation control on soil microbial communities. Soil Biology & Biochemistry.2001;33(12):1777-1789. DOI: 10.1016/S0038-0717(01)00103-1

16. Kaneko N, Sawada M, Sawamoto K. Mechanisms of neuronal migration in the adult brain. J Neurochem. 2017;141(6):835–847. DOI: 10.1111/jnc.14002

17. Duke S, Powles S. Glyphosate: a once-in-a-century herbicide. Pest Manag Sci. 2008;64(4):319–25. DOI: 10.1002/ps.1518

18. Rodrigues HG, Batista MTA, Fonseca LC, Aversi-Ferreira, TA. Effects of pesticides on erythrocyte osmotic fragility – A briefreview. Biotemas.2009;1(22):7-16. DOI: 10.5007/2175-7925.2009v22n1p7

19. USDA. United States department of agriculture: pesticide use in U.S. agriculture-21 selected crops, 1960-2008. Economic Information Bulletin.2014;124(1):1–80.

20. Benbrook CM. Trends in glyphosate herbicide use in the United States and globally. Environ Sci Eur.2016;28(3). DOI: 10.1186/s12302-016-0070-0

21. Fava L, Crobe A, Orru MA, Caracciolo AB, Bottoni P, Funari E. Pesticide metabolites as contaminants of groundwater resources: assessment of the leaching potential of endosulfan sulfate, 2,6-dichlorobenzoic acid 3,4-dichloroaniline 2,4-dichlorophenol and 4-chloro-2-methylphenol. Microchem J. 2005;79(1-2):207-211. DOI: 10.1016/j.microc.2004.10.009

22. Skark C, Zullei-Seibert N, Willme U, Gatzemann U, Schlett C. Contribution of non-agricultural pesticides to pesticide load in surface water. Pest Manag Sci. 2004;60(6):525-530. DOI: 10.1002/ps.844

23. Environmental Protection Agency (EPA-US). Catchment Models and Management Tools for Diffuse Contaminants (Sediment, Phosphorus and Pesticides): Diffuse Tools Project, *US*. 2021;(396):1-64.

24. Antoniou M, Habib MAM, Howard CV, Jennings RC, Leifert C, Nodari RO et al. Teratogenic effects of glyphosate-based herbicides: divergence of regulatory decisions from scientific evidence. J Environ Anal Toxicol.2012;S4(06):1-13. DOI:10.4172/2161-0525.S4-006

25. Tabata H, Nagata KI. Decoding the molecular mechanisms of neuronal migration using in utero electroporation. Med Mol Morph. 2016;9(2):63–75. DOI: 10.1007/s00795-015-0127-y

26. Sawada Y, Nagai Y, Ueyama M, Yamamoto I. Probable toxicity of surface-active agent in commercial herbicide containing glyphosate. Lancet. 1988;331(8580):255-314. DOI: 10.1016/s0140-6736(88)90379-0

27. Choy WN. Genetic Toxicology and Cancer Risk Assessment. 1ª ed. New York, NY: Marcel Dekker, 2001; 406 p. DOI: 10.1201/9780203904237

28. Sabarwal A, Kumara K, Singh R. Hazardous effects of chemical pesticides on human health - Cancer and other associated disorders. Environ Toxicol Pharmacol. 2018;63:103-114. DOI: 10.1016/j.etap.2018.08.018

29. Faith AL, Von-Herrmann KM, Young AL, Havrda MC. Bbc3 Loss Enhances Survival and Protein Clearance in Neurons Exposed to the Organophosphate Pesticide Chlorpyrifos. Toxicol Sci. 2021;183(2):378-392. DOI: 10.1093/toxsci/kfab090

30. Saravi SSS, Dehpour AR. Potential role of organochlorine pesticides in the pathogenesis of neurodevelopmental, neurodegenerative, and neurobehavioral disorders: A review. Life Sci. 2016;15(145):255-264. DOI: 10.1016/j.lfs.2015.11.006

31. Medehouenou TCM, Ayotte P, Carmichael PH, Kroger E, Varreault R, Lindsay J et al. Exposure to polychlorinated biphenyls and organochlorine pesticides and risk of dementia, Alzheimer's disease and cognitive decline in an older population: a prospective analysis from the Canadian Study of Health and Aging. Environ Health. 2019;18(1):2-11. DOI: 10.1186/s12940-019-0494-2

32. Tang BL. Neuropathological Mechanisms Associated with Pesticides in Alzheimer's disease. Toxics. 2020;8(2):1-16. DOI: 10.3390/toxics8020021

33.Yan D, Zhang Y, Liu L, Yan H. Pesticide exposure and risk of Alzheimer's disease: a systematic review and meta-analysis. Nat - Sci Rep. 2016;6(32222):1-9. DOI: 10.1038/srep32222

34. Li Y, Fang R, Liu Z, Jiang L, Zhang J, Li H et al. The association between toxic pesticide environmental exposure and Alzheimer's disease: A scientometric and visualization analysis. Chemosphere. 2021;263:1-13. DOI: 10.1016/j.chemosphere.2020.128238

35. Rossetti MF, Stoker C, Ramos J. Agrochemicals and Neurogenesis. Mol Cell Endocrinol. 2020;15:1-8. DOI: 10.1016/j.mce.2020.110820

36. Chin-Chan M, Navarro-Yepes J, Quintanilla-Vega B. Environmental pollutants as risk factors for neurodegenerative disorders: Alzheimer and Parkinson diseases. Front Cell Neurosci. 2015;9(124):1-22. DOI: 10.3389/fncel.2015.00124

37. Wang GW, Cai JX. Disconnection of the hippocampal - prefrontal cortical circuits impairs spatial working memory performance in rats. BehavBrain Res. 2006;175(2):329–336. DOI: 10.1016/j.bbr.2006.09.002

38. Trevisan K, Pereira RC, Silva-Amaral D, Aversi-Ferreira TA. Theories of aging and prevalence of Alzheimer's disease. BioMed Res Int.2019;2019:1-10. DOI: 10.1155/2019/9171424

39. Verulava T, Dangadze B, Makharashvili A, Magaldadze M, Jorbenadze R, Chibukhaia G et al. Social Problems of Alzheimer Patients and Their Family Members. Home Health Care Manag Pract. 2018;30(4):175-178. DOI: 10.1177/1084822318775703

40. Korolev IO. Alzheimer's Disease: A clinical and basic science review. MSRJ.2014;4:24–33. DOI: 10.3402/msrj.v3i0.201333

41. Angelopoulou E, Paudel YN, Papageorgiou SG, Piperi C. APOE Genotype and Alzheimer's Disease: The Influence of Lifestyle and Environmental Factors. ACS Chem Neurosci. 2021;12(15):2749-2764. DOI: 10.1021/acschemneuro.1c00295

42. Herrup K. The case for rejecting the amyloid cascade hypothesis. Nat Neurosci. 2015;18(6):794–799. DOI: 10.1038/nn.4017

43. Charchat H, Nitrini R, Caramelli P, Samechima K. Investigation of clinical markers of the early stages of Alzheimer's disease with computerized neuropsychological tests. Psico. Reflexo. Crítico. 2001;14(2):305–316. DOI:10.1590/S0102-79722001000200006

44. Martínez MA, Ares I, Rodriguéz J-L, Martínez M, Martínez-Larrañaga M-R, Anadón A. Neurotransmitterchanges in ratbrainregionsfollowingglyphosateexposure. Environ Res. 2018;161(1):212–219. DOI: 10.1016/j.envres.2017.10.051

45. Mir RH, Sawhney G, Pottoo FH, Mohi-Ud-Din R, Madishetti S, Jachak SM et al. Role of environmental pollutants in Alzheimer's disease: a review. Environ Sci Pollut Res Int. 2020;27(36):44724-44742. DOI: 10.1007/s11356-020-09964-x

46. Pearson B, Simon JM, McCoy ES, Salazar G, Fragola G, Zylka MJ. Identification of chemicals that mimic transcriptional changes associated with autism, brain aging and neurodegeneration. Nat commun. 2016;7:1-12. DOI: 10.1038/ncomms11173

47. Steenland K, Wesseling C, Román N, Quirós I, Juncos JL. Occupational pesticide exposure and screening tests for neurodegenerative disease among an elderly population in Costa Rica. Environ Res. 2013;120:96-101. DOI: 10.1016/j.envres.2012.08.014

48. Sanchez-Santed F, Colomina MT, Hernández E. Organophosphate pesticide exposure and neurodegeneration. Cortex. 2016;74:417-426. DOI: 10.1016/j.cortex.2015.10.003

49. Rahman MA, Rahman MS, Uddin MJ, Mamun-Or-Rashid ANM, Pang M-G, Rhim H. Emerging risk of environmental factors: insight mechanisms of Alzheimer's diseases. Environ Sci Pollut Res Int. 2020;27(36):44659-44672. DOI: 10.1007/s11356-020-08243-z

50. Schmidt, S. Fungicide Exposure and Amyloid Plaques in Mice: Further Evidence of an Environmental Risk Factor for Alzheimer's Disease. Environ Health Perspect. 2020;128(9):094006-1–094006-2. DOI: 10.1289/EHP7021

51. Lafon PA, Wang Y, Arango-Lievano M, Torrent J, Salvador-Prince L, Mansuy M et al. Fungicide Residues Exposure and b-amyloid Aggregation in a Mouse Model of Alzheimer's Disease. Environ Health Perspect. 2020;128(1):017011-1–017011-20. DOI: 10.1289/EHP5550

52. Vincenza A, Naldi M, De Simone A, Bartolini M. A patent review of Butyrylcholinesterase inhibitor and reactivators 2010-2017. Expert Opin Ther Pat. 2018;28(6):455-465. DOI: 10.1080/13543776.2018.1476494

53. Colovic MB, Krstić DZ, Lazarević-Pašti TD, Bondžić AM, VasićVM. Acetylcholinesterase Inhibitors: Pharmacology and Toxicology. Curr. Neuropharmacol. 2013;11(3):315-335. DOI: 10.2174/1570159X11311030006

54. de Liyis BG, Halim W, Widyadharma IPE. Potential role of recombinant growth differentiation factor 11 in Alzheimer's disease treatment. Egypt J Neurol Psychiatry Neurosurg. 2022;58(49). DOI: doi.org/10.1186/s41983-022-00487-5

55. de Liyis BG, Sutedja JC, Kesuma PMI, Liyis S, Widyadharma IPE. A review of literature on Compound 21-loaded gelatin nanoparticle: a promising nose-to brain therapy for multi-infarct dementia. Egypt J Neurol Psychiatry Neurosurg. 2023;59(13). DOI: doi.org/10.1186/s41983-023-00621-x

56. Bible, E. Alzheimer's disease: High serum levels of the pesticide metabolites DDE – a potential environmental risk factor for Alzheimer disease. N R Neurol. 2014;10(3):125. DOI: 10.1038/nneurol.2014.25

57. Xiao J, Dong X, Zhang X, Ye F. Pesticides Exposure and Dopaminergic Neurodegeneration. Exp Health. 2020;13:295-306. DOI: 10.1007/s12403-021-00384-x

58. Nicolia V, Lucarelli M, Fuso A. Environment, epigenetics and neurodegeneration: Focus on nutrition in Alzheimer's disease. Exp Gerontol. 2015;68(2015):08-12. DOI: 10.1016/j.exger.2014.10.006

59. Brasil. Congresso, Senado. Decreto n°10.282 de março de 2020, que regulamenta a Lei nº 13.979, de 6 de fevereiro de 2020. Coleção de Leis da República Federativa do Brasil, Brasília, DF, 2020. Acessado em: 26 de fevereiro de 2022. Disponível em: http://www.planalto.gov.br/ccivil_03/_ato2019-2022/2020/decreto/D10282.htm

60. Lee DH, Lind PM, Jacobs-Jr. DR, Salihovic S, Van-Bavel B, Lind L. Association between background exposure to organochlorine pesticides and the risk of cognitive impairment: A

prospective study that accounts for weight change. Environ Int. 2016;89(90):179-184. DOI: 10.1016/j.envint.2016.02.001

61. Kim KS, Lee Y-M, Lee H-W, Jacobs-Jr. DR, Lee D-H. Associations between organochlorine pesticides and cognition in U.S. elders: National Health and Nutrition Examination Survey 1999–2002. Environ Int. 2015;75:87-92. DOI: 10.1016/j.envint.2014.11.003

62. Li C-Q, Zheng Q, Wang Q, Zeng Q-P. Biotic/Abiotic Stress Driven Alzheimer´s disease. Front Cell Neurosci. 2016;10(269):1-6. DOI: 10.3389/fncel.2016.00269

63. Dekosky ST, Gandy S. Environmental Exposures and the Risk for Alzheimer Disease: Can We Identify the Smoking Guns? JAMA Neurol. 2014;71(3):273-275. DOI: 10.1001/jamaneurol.2013.6031

64. Wainaina M, Chen Z, Zhong, C. Environmental factors in the development and progression of late-onset Alzheimer's disease. Neurosci Bull. 2014;30(2):253-270. DOI: 10.1007/s12264-013-1425-9

65. Collota M, Bertazzi PA, Bollati V. Epigenetics and Pesticides. Toxicology. 2013;10(307):35-41. DOI: 10.1016/j.tox.2013.01.017

66. Miranda HV, El-Agnaf AM, Outeiro TF. Glycation in Parkinson's Disease and Alzheimer's Disease. Mov Disord. 2016;31(6):782-790. DOI: 10.1002/mds.26566

67. Yadav RS, Tiwari NK. Lipid integration in neurodegeneration: An Overview of Alzheimer's Disease. Mol Neurobiol. 2014;50(1):168-174. DOI: 10.1007/s12035-014-8661-5

68. Patel S. Disruption of aromatase homeostasis as the cause of a multiplicity of ailments: A comprehensive review.J Steroid Biochem Mol Biol. 2017;168:19-25. DOI: 10.1016/j.jsbmb.2017.01.009

69. Richardson J, Roy A, Shalat SL, Von-Stein RT, Hossain MM, Buckley B et al. Elevated Serum Pesticide Levels and Risk for Alzheimer's Disease. JAMA Neurol. 2014;71(3)284-290. DOI: 10.1001/jamaneurol.2013.6030

70. Suresh S, Singh AS, Rushendran R, Vellapandian C, Prajapati B. Alzheimer's disease: the role of extrinsic factors in its development, an investigation of the environmental enigma. Front Neurol. 2023;14:1-18. DOI: 10.3389/fneur.2023.1303111

71. Voorhees J, Remy MT, Erickson CM, Dutca LM, Brat DJ, Pieper AA. Occupational-like organophosphate exposure disrupts microglia and accelerates deficits in a rat model of Alzheimer's diseases. NPJ Aging Mech Dis. 2019;5(3):1-14. DOI: 10.1038/s41514-018-0033-3

72. Kanthasamy A, Jin H, Anantharan V, Sondarva G, Rangasamy V, Rana A et al. Emerging Neurotoxic Mechanisms in Environmental Factors - Induced Neurodegeneration. Neurotoxicology. 2012;33(4):833–837. DOI: 10.1016/j.neuro.2012.01.011

73. Franco FC, Alves AA, Godoy FR, Avelar JB, Rodrigues DD, Pedroso TMA et al. Evaluating genotoxic risks in Brazilian public health agents occupationally exposed to pesticides: a multi-biomarker approach. Environ Sci Pollut Res Int. 2016;23(19):19723-19734. DOI: 10.1007/s11356-016-7179-y

74. Singh N, Gautam P. Neurodegenerative Diseases: Impact of Pesticides. J Experimental Bio Agricult Sci. 2021;9(5):572-579. DOI: 10.18006/2021.9(5).572.579

75. Farkhondeh T, Mehrpour O, Forouzanfar F, Roshanravan B et al.Oxidative stress and mitochondrial dysfunction in organophosphate pesticide-induced neurotoxicity and its amelioration: a review. Environ Sci Pollut Res Int. 2020;27(20). DOI: 10.1007/s11356-020-09045-z

76. Temeyer K, Tuckow AP, Brake DK, Li AY, León AAP. Acetylcholinesterases of blood-feeding flies and ticks. Chem Biol Interact. 2013;203(1):319-322. DOI: 10.1016/j.cbi.2012.09.010

77. Soreq H. Checks and balances on cholinergic signaling in brain and body function. Trends Neurosci. 2015;38(7). DOI: 10.1016/j.tins.2015.05.007

78. Wu D, Hu Y, Song M, Li G. Dichlorodiphenyltrichloroethane Impairs Amyloid Beta Clearance by Decreasing Liver X Receptor Alfa Expression. Front Aging Neurosci. 2021;13:1-9. DOI: 10.3389/fnagi.2021.634948

79. Cervellati C, Velacchi G, Tisato V, Zuliani G, Marsillach J. Evaluating the link between Paraoxonase-1 levels and Alzheimer's disease development. Minerva Med. 2019;110(3)238-250. DOI: 10.23736/S0026-4806.18.05875-5

80. Terry AV. Functional Consequences of Repeated Organophosphate Exposure: Potential Non-Cholinergic Mechanisms. Pharmacol Ther. 2012;134(3):355-365. DOI: 10.1016/j.pharmthera.2012.03.001

81. Eid A, Mhatre I, Richardson J. Gene-environment interactions in Alzheimer's Disease: A potential path to precision medicine. Pharmacol Ther. 2019;199:173-187. DOI: 10.1016/j.pharmthera.2019.03.005

82. Yadav SS, Singh MK, Yadav RS. Organophosphates induced Alzheimer's disease: An Epigenetic Aspect. J Clin Epigen. 2016;2(1):1-10. DOI: 10.21767/2472-1158.100010

83. Wingo T, Rosen A, Cutler DJ, Lah JJ, Levey AI. Paraoxonase 1 polymorphisms in Alzheimer's disease, Parkinson's disease, and AD-PD spectrum diseases. Neurobiol Aging. 2013;33(1):1-4. DOI: 10.1016/j.neurobiolaging.2010.08.010

84. Baltasar MT, Dinis-Oliveira RJ, Bastos ML, Tsatsakis AM, Duarte JA, Carvalho F. Pesticides exposure as etiological factors of Parkinson's disease and other neurodegenerative diseases - A mechanistic approach. Toxicol Lett. 2014;230(2):85-103. DOI: 10.1016/j.toxlet.2014.01.039

85. Venkatesan R, Park YU, Ji E, Yeo E-J, Kim SY.Malathion increases apoptotic cell death by inducing lysosomal membrane permeabilization in N2a neuroblastoma cells: a model for neurodegeneration in Alzheimer's disease. Cell Death Discov. 2017;3. DOI: 10.1038/cddiscovery.2017.7. eCollection 2017

86. Macdonald R, Barnes K, Hastings C, Mortiboys H. Mitochondrial abnormalities in Parkinson's disease and Alzheimer's disease: can mitochondria be targeted therapeutically? Biochem Soc Trans. 2018;46(4):891-909. DOI: 10.1042/BST2017050

87. Doty RL. Olfactory dysfunction in neurodegenerative diseases: is there a common pathological substrate? Lancet Neurol. 2017;16(6):478-488. DOI: 10.1016/S1474-4422(17)30123-0

88. Medehouenou TCM, Ayotte P, Carmichael PH, Kroger E, Varreault R, Lindsay J et al. Plasma polychlorinated biphenyl and organochlorine pesticide concentrations in dementia: The Canadian Study of Health and Aging. Environ Int. 2014;69:141-147. DOI: 10.1016/j.envint.2014.04.016

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

90. Pohanka M. Diagnoses of Pathological States Based on Acetylcholinesterase and Butyrylcholinesterase. Curr Med Chem. 2020;27(18):2994-3011. DOI: 10.2174/0929867326666190130161202

91. Barnett JA, Bandy ML, Gibson DL. Is the Use of Glyphosate in Modern Agriculture Resulting in Increased Neuropsychiatric Conditions Through Modulation of the Gut-brain-microbiome Axis? Front. Nutr. 2022;9:1-9

92. Heys KA, Shore RF, Pereira MG, Martin FL. Levels of Organochlorine Pesticides Are Associated with Amyloid Aggregation in Apex Avian Brains. Environ Sci Technol. 2017;51(15):8672-8681. DOI: 10.1021/acs.est.7b00840

93. Dechartres J, Jodi LP, Marie-Madeleine G, Jablaoui A, Maguin E, Rhimi M, et al. Glyphosate and glyphosate-based herbicide exposure during the peripartum period affects maternal brain plasticity, maternal behaviour and microbiome. J Neuroendocrinol. 2019;31(9):e12731

94. Bruggen AHCV, He MM, Shin K, Mai V, Jeong KC, et al. Environmental and Health effects of the herbicide glyphosate. Sci. Total Environ. 2018;616-617:255-268. DOI: 10.1016/j.scitotenv.2017.10.309

95. Van-Assema D, Lubberink M, Bauer M, Van Der Flier WM, Schuit RC, Windhorst AD et al. Blood–brain barrier P-glycoprotein function in Alzheimer's disease. Brain. 2012;135:181-189. DOI: 10.1093/brain/awr298

96. Hamidpour R, Hamidpour M, Hamidpour S, Shahlari M. Cinnamon from the selection of traditional applications to its novel effects on the inhibition of angiogenesis in cancer cells and prevention of Alzheimer's disease, and a series of functions such as antioxidant, anticholesterol, antidiabetes, antibacterial, antifungal, nematicidal, acaracidal, and repellent activities. J Tradit Complement Med. 2015;5(2):66-70. DOI: 10.1016/j.jtcme.2014.11.008

97. Zaganas I, Kapetanaki S, Mastorodemos V, Kanavouras K, Colosio C et al. Linking pesticide exposure and dementia: What is the evidence? Toxicology. 2013;307:3-11. DOI: 10.1016/j.tox.2013.02.002

98. Cristina-Pereira R, Trevisan K, Vasconcelos-da-Silva E, Figueredo-da-Silva S, Magri MPF, Brunelli LF, et al. Association between age gain, Parkinsonism and Pesticides: A Public Health Problem? Int. Neuropsy. Dis. J. 2023;19(3):44-73.