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REVIEW ARTICLE

Integrative Review: Verification of the Influence of Atrazine Exposure on Behavioral, Neurochemical and Parkinson's Disease Disorders

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ABSTRACT

Herbicides represent the largest portion of pesticides used both worldwide and in Brazil. Many of these compounds are applied on a large scale in native forests and in urban and industrial water environments, including atrazine. Due to its low cost, ability to remain active in the soil for long periods and potential effect on weed removal, atrazine ranks 5th in the ranking of most used pesticide in Brazil. Although the use of pesticides increases agricultural production, their intensive use can often cause negative effects on fauna and flora. Studies have shown that exposure to atrazine can cause various harmful effects in mammals, of both sexes, such as structural, neuroendocrine and/or behavioral changes. Considering the seriousness of the situation and the possible toxicological and pathological implications that atrazine can generate in the animal organism, the objective of this work was to carry out an integrative literature review in order to verify the scientific panorama on issues related to atrazine exposure and its impacts, mainly with regard to its toxicity on the central nervous system. To carry out this article, a bibliographic survey of scientific material obtained in the following databases was carried out: US National Library of Medicine - National Institutes of Health (PubMed), Virtual Health Library (Latin American and Caribbean Literature in Health Sciences - LILACS), Science Direct and Google® Academic, in the last 25 years. The MeSH Terms used in the search were: "Parkinson's disease", "atrazine", "herbicide" and "endocrine disruptor". The following were found in the Science Direct indexers: 115 records, PubMed 52 records, in LILACS no articles were found, and 1330 records were found in Google® Academic.

INTRODUCTION

Pesticides

Pesticides, according to Brazilian legislation, are synthetic chemical products with functions, mainly, herbicides, fungicides, and insecticides, used in the population control of insects, larvae, fungi, ticks, and weeds, in the management of vectors of various diseases and growth regulation vegetation, both in rural and urban environments [1,2]. The terms pesticides and agricultural defensives, among others, are also used as a synonym for pesticides, which shows how controversial the debate on the use of these products is currently.

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These products are used in agricultural and non-agricultural activities. Agricultural activities are related and intended for use in the production, land cleaning and soil preparation sectors, in the crop monitoring stage, in the storage, storage and processing of agricultural products, in pastures and planted forests. Non-agricultural use, on the other hand, occurs to protect native forests or other ecosystems, such as lakes and weirs, and urban, water and industrial environments, whose purpose is to change the composition of flora or fauna, to preserve them from action of living beings considered harmful [1,3].

The use of these products is related to the concept of "One Health" which is the inseparable union between human, animal, and environmental health, which was proposed at the beginning of this century by the World Organization for Animal Health (OIE), by the Organization World Health Organization (WHO) and United Nations Food and Agriculture Organizations (FAO). Another relevant point in this context is related to the use of pesticides and their benefits for food production and for human and animal health, in such a way that it is not possible to prohibit the use of these agents without compromising the production of food of animal origin and plant, as these are valuable tools in the control of pests and vectors responsible for diseases in humans and animals [4]. The widespread use of pesticides can lead to pest resistance to these products, as well as bioaccumulation and biomagnification in the food chain, causing damage to the health of living beings and the environment. To prevent the presence of pesticide residues in products of plant and animal origin, the Ministry of Agriculture, Livestock and Supply (MAPA) and the Health Surveillance Agency (ANVISA - linked to the Ministry of Health) carry out the monitoring of waste from pesticides, establishing the Maximum Residue Limits (MRL), as well as the risk assessment [4]. Pesticides have also been associated with the occurrence of poisoning, which can be accidental or intentional [5]; therefore, the toxicological knowledge about them is essential to understand the intoxication pictures, both acute and chronic. Data from the International Labor Organization (ILO) indicate that, annually in underdeveloped countries, pesticides are responsible for 70 thousand cases of acute and chronic poisoning that progress to death, in addition to more than seven million cases of non-acute and chronic diseases [1]. Nationally, highlights that since 2008 Brazil has been the country that consumes the most pesticides due to the economic development of agribusiness, in addition to the expansion of permission to use pesticides already banned in other countries and the illegal sale of banned pesticides [3]. The population at risk regarding exposure to pesticides are farmers, ranchers, agents to control endemic diseases and workers in the pesticide industries, who directly suffer the effects of these products during handling and application [6]. However, the entire population is susceptible to multiple exposures to pesticides through consumption of contaminated food and water. Pregnant women, children and adolescents are considered the highest risk group due to the important metabolic, immunological, and hormonal changes that occur in these periods of life [7].

Atrazine

Atrazine (2-chloro-4-ethylamino-6-isopropylamino-s-triazine) (Figure 1) is a herbicide of the chlorotriazine family, whose agricultural use is widely applied in the pre- and post-emergence control of weeds in weed crops, corn, sorghum, and sugarcane, among others (Table 1), for over 50 years. The molecule was obtained in 1958 by Geigy Laboratories and its wide use is due to its low cost, ability to remain active in the soil for long periods and effectiveness in removing weeds, since plant death results from starvation and oxidative damage, caused by binding to protein D1 located in the thylakoid membrane of chloroplasts, thus blocking the transport of electrons necessary for photosynthesis, a mechanism that does not exist in animal cells [8-10]. Atrazine also has non-agricultural uses, such as post-emergence of weeds in chemical weeding to eradicate weeding vegetation along fences, firebreaks, roadsides, pipelines, railway beds and strips under high tension

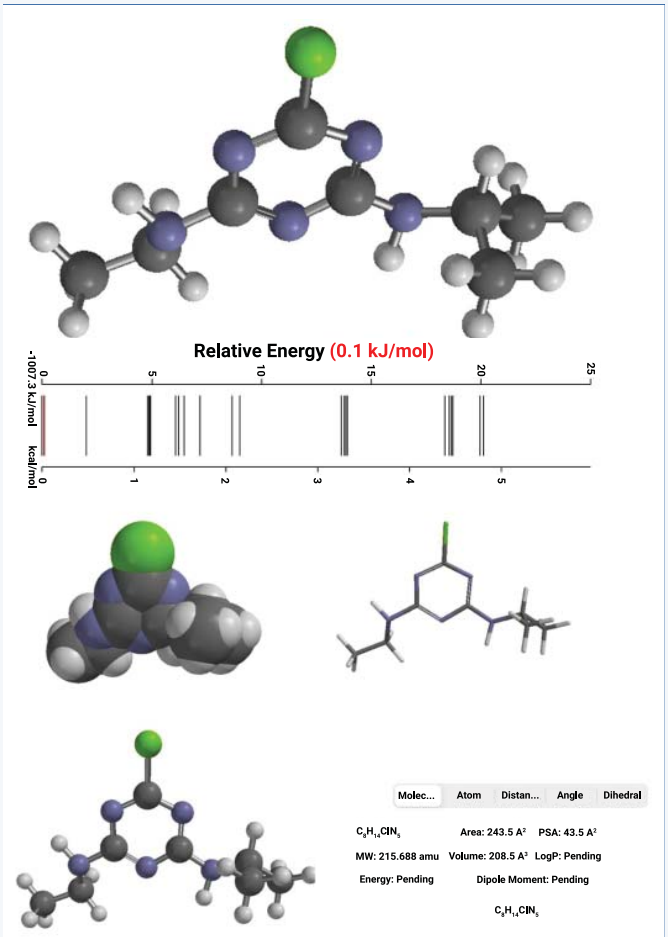

Figure 1 Chemical structure of atrazine.
Source: Spartan Wave function, Inc.

Table 1: Authorized agricultural use of atrazine in Brazil. Cultures Application LMR (mg/kg).

Cultures	Application	MRL (mg/kg)
Pineapple	Pre/Post-emergence	0.02
Sugar cane	Pre/Post-emergence	0.25
Corn	Pre/Post-emergence	0.25
millet	Pre-emergence	0.25
pine	Pre/Post-emergence	Non-food use
Rubber tree	Pre/Post-emergence	Non-food use
Sisal	Pre/Post-emergence	Non-food use
Soy	Pre/Post-emergence	0.01
Sorghum	Pre/Post-emergence	0.25

Source: [11].

networks [11]. Herbicides correspond to 59.56% - equivalent to 369,578 tons of active ingredient - of pesticides consumed in Brazil. Atrazine is one of the 10 active ingredients most used nationally as a pesticide; in 2019 it occupied 5th place in the sales ranking, with 23,429 tons of active ingredient being sold [2] (Table 2). Its use is prohibited in the European Union, but it is authorized for use in the United States, Japan, China, and other Mercosur countries [12,13]. However, the United States Environmental Protection Agency has designated atrazine as a Restricted Use Pesticide (RUP), so only licensed herbicide users can purchase or use it because of this. Its persistence in water and adverse effects on human health [14].

Davis reported that the annual use of atrazine was 70,000 to 90,000 tons worldwide, and that this herbicide and its metabolites were detected in surface and groundwater in the midwestern United States, where its use is more abundant [15]. Due to atrazine's long half-life, which ranges from 30 to 100 days, high solubility, soil mobility and widespread water contamination, this compound was found in higher concentrations in the urine of farmers and their families compared to households [16]. Atrazine may also be present in umbilical cord plasma, breast milk and urine of the general population that is exposed to this substance, mainly through drinking water [17,18]. There are several ways in which atrazine reaches the environment, mainly through precipitation, runoff and leaching processes, causing pollution of the soil, surface, and underground water, culminating in damage to the environment [16]. Its high capacity to contaminate water is a consequence of its low chemical affinity for the organic fraction of the soil and its intermediate hydrophilicity, which can be easily leached or driven by surface runoff, reaching water bodies [19]. The routes of exposure in animals can be oral, inhalation and dermal. In rats, the half-life of this compound is 1.3 days and 95% of the dose is eliminated within seven days. This herbicide is biotransformed mainly by the liver and its excretion occurs 75% in urine and 20% in feces [20]. According to the World Health Organization (WHO), the toxicity and mode of action of atrazine metabolites in the human body are like those of atrazine itself. Atrazine by-products most found in the environment are: desethylatrazine - DEA, Desisopropylatrazine - DIA, Didealkylatrazine - DDA, Desethylhydroxyatrazine - DEHA and Hydroxyatrazine - HA (Figure 2).

Table 2: The 10 most sold active ingredients in Brazil in 2019.

Active Ingredient (AI)	Sales (tons of AI)	Ranking
Glyphosate and its salts	217,592.24	1º
2,4-D	52,426.92	2º
Mancozeb	49,162.59	3º
Acephate	28,432.5	4º
atrazine	23,429.38	5º
Chlorothalonil	16,653.05	6º
paraquat dichloride	16,398.14	7º
Malathion	13,576.47	8º
Sulfur	11882.33	9º
Chlorpyrifos	10,827.78	10º

Source: [2].

The US Environmental Protection Agency (US EPA) has set the maximum allowable level for atrazine in drinking water supplies at 3 µg/L; however, during the spring and summer period this level is often exceeded [13]. ANVISA classified atrazine in category 3 of toxicity in which the moderately toxic compounds fall (Figure 3); thus, its maximum allowed value (VMP) in human water supply was established [11]. Thus, in Brazil the VMP for atrazine in drinking water is 2 µg/L and the Acceptable Daily Intake (ADI) is 0.02 mg/kg, but in many regions of the country this value is exceeded. The WHO defined the VMP in 100 µg/L, corresponding to the sum of atrazine and its metabolites [11,19].

Effects of exposure to atrazine: Human exposure to atrazine occurs mainly through the ingestion of drinking water, in which, generally, the concentration of this substance is between 0.01 and 5 µg/L [21]. There is detection of atrazine in human body fluids, including follicular fluid, spermatic fluid, and cervical mucus, as well as association with miscarriages, premature births, and small-for-gestational-age fetuses support its potential to negatively affect human reproductive health [22-24]. Harper emphasized that the

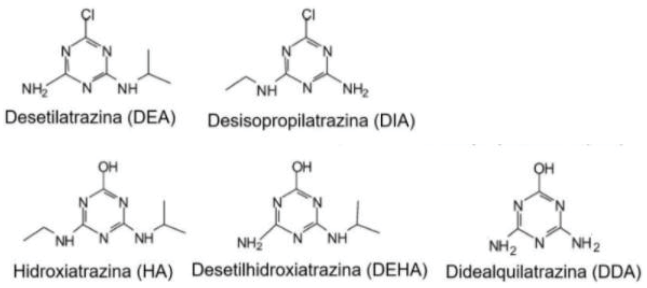

Figure 2 Chemical structure of atrazine metabolites found in the environment. Source: [19].

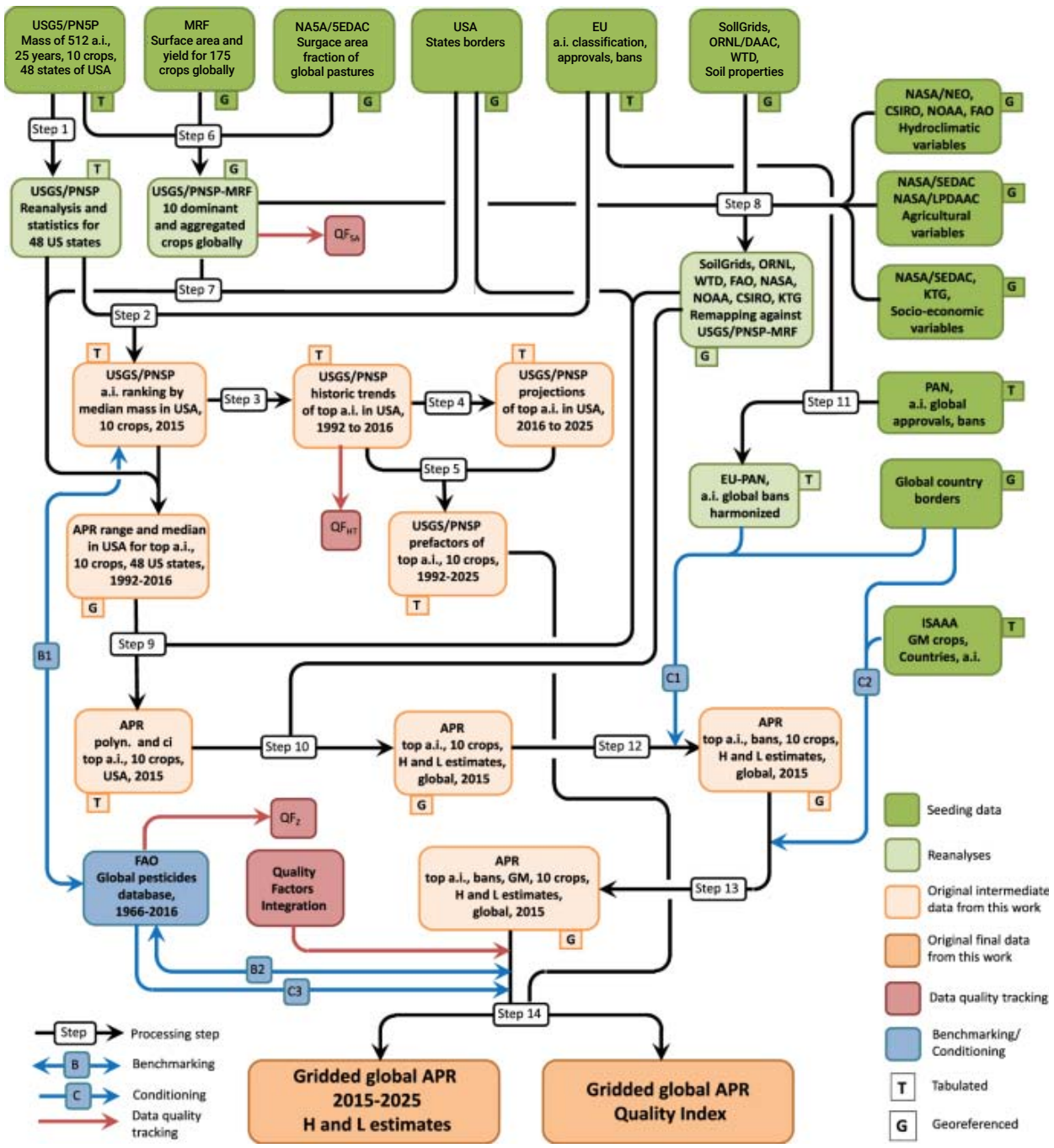

Figure 3 Processing steps implemented to elaborate source data sets and produce globally gridded yearly application rates of the top 20 crop-specific pesticides and their quality index maps.
Source: [119].

effects of atrazine on the reproductive system are supported by evidence from studies in the animal model, which show its effects as an endocrine disruptor in various classes of animals, including amphibians, fish, reptiles, and rodents [25]. Knowing the negative influence of atrazine on the reproductive system, this agent was included in the list of endocrine disrupting chemicals by some organizations and countries, such as the European Community, Japan, and the United States, as it has environmental estrogenic activity with carcinogenic potential and that it can persist in the environment for long periods [16]. The mechanism underlying neuroendocrine interference caused by atrazine remains to be elucidated, but it is known to be involved in the disruption of many pathways, including the Hypothalamic-Pituitary-Gonadal (HHG) axis, monoaminergic systems in the central nervous system, changes in cyclic Adenosine Monophosphate (cAMP)-dependent signaling pathway, as well as in epigenetic mechanisms, including microRNAs

and expression of DNA methyltransferases [26]. Results of a systematic literature review conducted by Wirbisky and a study was demonstrated that atrazine affects the HHG axis, with effects on the reproductive and endocrine systems in rats and with differences depending on the stage of life, dose, duration of exposure and strain of rats used. Almberg reported that atrazine is an endocrine disruptor that affects the HHG axis by inhibiting the production of Luteinizing Hormone (LH), which leads to increased aromatase production and interruption of ovarian function [27].

Furthermore, a study by Lamb evaluated the effects on male offspring of zebrafish exposed to doses of 0.3, 3 or 3 Parts Per Billion (ppb) of atrazine; their findings showed that endocrine and neuroendocrine disrupting chemicals can alter or interrupt some animal behaviors, especially typical reproductive behaviors, but can also lead to anxiety, aggression, and risky behavior, especially when exposure to these agents occurs early in life [26]. Thus, the scientific literature shows that early exposure to endocrine disruptors can permanently modify phenotypes behavior of the animal until adulthood, interfering with molecular mechanisms such as gene expression, hormone levels and neurotransmitter levels.

Neuroendocrine, neurochemical, and behavioral effects: The main toxic action of atrazine is manifested by the disturbance of the neuroendocrine system, of the HHG axis, manifested through the attenuation of the pulsatile secretion of GnRH and the LH surge. The interruption of the LH peak induced by this compound in rats is considered the main event in the cascade of changes that lead to adverse reproductive outcomes after exposure to atrazine. A study by Kucka showed that atrazine is an inhibitor of cAMP-specific cyclic nucleotide Phosphodiesterase (PDEs), which leads to intra- and extracellular cAMP accumulation and Protein Kinase (PKA) Activation [28]. PEDs are a large family of enzymes responsible for the hydrolysis of cAMP and Cyclic Guanosine Monophosphate (cGMP), and for cyclic nucleotide efflux pumps that transport them from the cytosol to the extracellular fluid. The increase in intracellular cAMP levels was sufficient to increase the basal release of prolactin in pituitary cells and the production of androgens in Leydig cells [28]. Thus, atrazine acts as an endocrine disruptor both in cells that secrete pre-stored hormones by exocytosis and in cells that secrete by hormone synthesis. These effects are fast and do not require a change in protein expression, because cAMP/PKA is involved in the control of transcriptional activity [28]. Atrazine also induces aromatase expression in human adrenocortical carcinoma cells after exposure, causing increased conversion of testosterone to estrogen and decreased androgen synthesis and activity. This effect has been reported across all vertebrate classes, including human cell lines. The endocrine disrupting effects of atrazine include antiestrogenic activity, altered prolactin release, and increased glucocorticoid release from the adrenal glands [29].

A study by Lin showed that atrazine targets monoaminergic systems, especially the nigrostriatal dopaminergic system, resulting in a series of cellular, molecular, and behavioral abnormalities, considering that oral exposure to doses of 125 to 250 mg/ kg of atrazine for 10 days induced hypoactivity, memory and anxiety deficits, accompanied by changes in the levels and/or turnover of dopamine, serotonin, and noradrenaline, mainly in the striatum and prefrontal cortex of mice [30,31]. Atrazine also reduced the levels of dopamine and its metabolite, as well as the number of dopaminergic neurons in the pars compact of the substantia nigra and the ventral tegmental area of mice [32,33]. Prolonged exposure (one year) to atrazine by diet altered motor activity and decreased striatal dopamine levels in rats [34]. Oral exposure to environmentally relevant doses of DG 14 atrazine on the Postnatal Day (DPN) 21 altered motor activity in juvenile offspring and caused neurodegenerative changes in the cortex, striatum, hippocampus, and hypothalamic areas of adult mouse offspring [35], suggesting that the developing nervous system is particularly sensitive to atrazine and that some effects are only observed or present in adulthood. In humans, environmental exposure to atrazine during pregnancy has been associated with several adverse effects at birth, including preterm birth [36]. Study by Lin suggest that atrazine affects dopaminergic neuronal differentiation in vitro and that the developing dopaminergic system may be particularly vulnerable to atrazine when dopaminergic neurons are undifferentiated, providing evidence that exposure to atrazine induces various behavioral abnormalities involving motor, emotional, and/or cognitive functions in mothers and offspring, which are, in some cases, age- and sex-specific [37,38]. Pharmacokinetic studies suggest that, after gestational and/or lactational exposure of rodents to atrazine, orally, the fetus is exposed to atrazine and its metabolites at levels like maternal plasmatic levels and the neonate is mainly exposed to the main metabolite of atrazine, the DDA [39]. Both atrazine and ADD can bind to brain tissue proteins and culminate in protein dysfunction [40,41]. Furthermore, these substances can disrupt the morphological differentiation of dopaminergic neurons in vitro, therefore, behavioral abnormalities observed in adult offspring long after the end of perinatal exposure may occur because of atrazine and/or ADD directly affect the main neurodevelopmental processes, such as neuronal differentiation. Lin investigated, in mice, the neurobehavioral and neurochemical effects of exposure to a low dose of atrazine (estimated at 1.4 mg/kg per day in drinking water) from day 6 of gestation to DPN23. These authors noted that perinatal exposure to atrazine targets the nigrostriatal dopaminergic pathway of mothers and especially juvenile offspring, concluding that exposure to atrazine during pregnancy and lactation can cause adverse effects on the nervous system in both offspring and mothers.

Considering the studies discussed here, atrazine causes deleterious effects in the animal organism, including changes in behavior and in the development of sexual

structure in males, females, and exposed offspring, as well as in cerebral monoaminergic systems, however, there are few studies that assess the effects of exposure to atrazine during puberty and its consequences in adulthood.

Atrazine and parkinson's disease

Parkinson's disease is a common progressive neurodegenerative disorder that causes significant morbidity and declines in quality of life [42]. Parkinson's disease is the second most frequent neurodegenerative disease, second only to Alzheimer's disease [43]. The clinical manifestations of Parkinsonism arise mainly due to the loss of dopaminergic neurons in the pars compact zone of the substantia nigra of the midbrain and clinical signs include tremor, rigidity, bradykinesia, shuffling gait and imbalance [44]. Other symptoms, such as apathy, anxiety, and depression, present as the disease progresses and covers additional areas of the brain, mainly affecting monoaminergic neurons [45]. The onset of the most prevalent sporadic idiopathic form of Parkinson's disease usually begins after age 60 years, although familial forms have an earlier onset [45]. The contribution of environmental contaminants to the etiology of neurodegenerative diseases, such as Parkinson's disease, is widely recognized [46]. Although several environmental factors have been implicated in the etiology of Parkinsonism, evidence for a positive relationship between the incidence of this disease and exposure to pesticides is increasing [47,48]. Mice exposed to Maneb fungicide, Paraquat herbicide or their combination exhibited the symptoms of Parkinson's disease [49,50]. Other pesticides, such as Dieldrin and Heptachlor, also cause dopaminergic disturbances in vivo and in vitro [51,52]. The potential role of pesticides in the etiology of Parkinsonism was first raised and then identified rural areas of residence and drinking water from wells as two predisposing factors for Parkinson's disease. Since then, several epidemiological studies have tried to verify whether there is a causal relationship between pesticides and Parkinson's disease. A meta-analysis concluded that prolonged exposure to pesticides was associated with an elevated risk of Parkinson's disease by up to 11%; another meta-analysis of case-control studies developed by Ahmed who concluded that pesticides are associated with an increased risk of Parkinson's disease and changes in related genes [53,54].

In a systematic literature review conducted by Freire and Koifman [55], most studies showed a correlation between Parkinson's disease and pesticides. Atrazine also demonstrates to be a herbicide directly toxic to dopaminergic neurons, suggesting that an exacerbated exposure to this substance can culminate in Parkinsonism [56]. The pathogenesis of Parkinson's disease is multifaceted and involves several mechanisms, such as mitochondrial dysfunction, oxidative stress and inflammation, which can lead to the death of dopaminergic neurons in the substantia nigra pars compact, the main evidence of this disease [57]. Several cellular dysfunctions simultaneously trigger disease onset, including mitochondrial dysfunction, autophagy and apoptotic dysregulation, and oxidative and endoplasmic reticulum stress [58]. Previous research has investigated potential biological mechanisms associated with cell depletion and neuron toxicity. The proposed mechanisms are the inhibition of aldehyde dehydrogenase involved in the metabolism of xenobiotics, alternation of dopamine catabolic pathways and glutathione levels, and dopaminergic neurotoxicity initiated by the decrease in striatal dopamine after exposure to atrazine, which can affect vesicular and synaptosomes uptake [59]. In addition, polymorphisms in several genes, including the ATP-binding cassette, subfamily B, member 1 (ABCB1), glutathione S-transferase pi 1 (GSTP1-Alw26I) and serum paraoxonase/arylesterase 1 (PON1) may increase susceptibility to Parkinson's disease after exposure to pesticides [60,61]. The nigrostriatal system, strongly related to motor function, originates in the pars compact zone of the substantia nigra and sends projections to the dorsal striatum. The mesolimbic dopaminergic system, on the other hand, originates from dopaminergic cells in the ventral tegmental area and projects to the ventral striatum, the nucleus acumens [62], which is important for motivational functions including reward processing and learning reinforcement. Studies have shown that these dopaminergic pathways are damaged by exposure to atrazine, because these changes were detected at molecular, cellular, and behavioral levels [63].In this sense, this article glimpsed develops an integrative review to verify the relationship between exposure to atrazine and neurobehavioral changes, as well as with cases of Parkinson's disease.

METHODOLOGY

To carry out this article, a bibliographic survey of scientific material obtained in the following databases was carried out: US National Library of Medicine - National Institutes of Health (PubMed), Virtual Health Library (Latin American and Caribbean Literature in Health Sciences - LILACS), ScienceDirect and Google® Academic, in the last 25 years.

The MeSH Terms used in the search were: “Parkinson’s disease”, “atrazine”, “herbicide” and “endocrine disruptor”. The following were found in the ScienceDirect indexers: 115 records, PubMed 52 records, in LILACS no articles were found, and 1330 records were found in Google® Academic.

The inclusion criteria were articles published in the last 25 years in Portuguese and English that met the proposed theme, being initially identified by title and abstract, so that those that were selected could be read in full. In addition, articles with in vivo, quantitative, and qualitative studies and population studies with open access were included.

Exclusion criteria were studies that addressed the effectiveness of compounds in cell cultures, which were

published in other languages, not available for free, abstracts or in incomplete text and outside the proposed period, and duplicate articles in the indexers. Considering the inclusion and exclusion criteria, 40 records were selected for reading and 21 were read and added to the final document, with 16 articles being eligible for the composition of tables 3,4 (eight scientific articles in each). It should be noted that for the total of 43 references obtained, in addition to scientific articles, other publications such as leaflets, regulations and documents were considered. The selection of articles occurred independently, two authors, who checked the titles initially, abstracts when the titles met the established objectives, and the full text of selected articles to verify eligibility for inclusion in this review. Discrepancies were resolved by group discussion. For articles accessed in full, we searched the references for potential studies for inclusion in the analysis.

RESULTS AND DISCUSSION

Effects on female rodents

Several studies have been carried out to evaluate, in female rodents, the effects of exposure to atrazine. These studies focus on the analysis of the estrogenic endocrine disrupting potential of atrazine and focused mainly on the analysis of the development of the mammary gland, the time of vaginal opening, reproductive senescence, decreased relative organ weight and changes in the estrous cycle [64,65], as summarized in table 3 and detailed below.

Rayner analyzed female offspring of female rats exposed to 100 mg/kg of atrazine, orally, on gestation days (DG) 13 to 19, with a significant delay in vaginal opening and breast development, indicating that exposure to atrazine during pregnancy delayed puberty in female rats [66].

Studies in which peripubertal exposures of 50, 100 or 200 mg/kg of atrazine were performed orally showed a delay of more than two days in vaginal opening and a significant decrease in body weight, as well as in the weight of reproductive organs and of the adrenal glands of rats [67,68]. Eldridge showed in chronic studies, with doses of 25 and 200 mg/kg of atrazine administered orally, they caused an increase in the duration of the estrous cycle and an increase in the number of days in estrus, which was related with the increase in the number of breast tumors in adult female rats [69,70]. Cooper [71] observed that adult rats that received 75 or 300 mg/kg of atrazine, by gavage, for 14 to 23 days, spent more time in the diestrus suggestive of pseudo-pregnancy. The impact of atrazine on cyclicity has been related to a decrease in the concentration of gonadotropin releasing hormone (GnRH) that signals to the pituitary, resulting in the interruption of LH secretion and subsequent ovulation suppression [71].

Davis in a study on the effects of prenatal exposure to atrazine on pubertal and postnatal reproductive indices in female rats, observed that interruption of the estrous cycle induced by atrazine resulted in estrus and persistent exposure to estrogen and prolactin, indicative of endocrine change similar to that seen in reproductive senescence, common in female rats around one year of age. Davis administered 1, 5, 20 or 100 mg/kg of atrazine in Sprague-Dawley rats from DGs 14 to 21 once or twice a day and no differences were observed in estrus cyclicity across the DPN272. It is noteworthy that in this study, in DPN216, 100% of the animals in the 100 mg/kg dose group of both studies continued to cycle normally, while animals in all other dose groups entered persistent estrus. In this study, the irregularities in cyclicality were often transient and followed by normal cycle periods of 4 and 5 days. This indicates that irregular episodes are not biologically significant.

A study conducted by Shibayama [72] treated female rats with 3, 30 or 300 mg/kg/day for 2 to 4 weeks and demonstrated that exposure to atrazine caused histological changes in ovarian tissue. The results revealed loss of corpora lutea, increase in atresic follicles, edema of luteal cells and prolonged estrous cycle. These findings suggested

Table 3: Effects of oral exposure to atrazine in female rodents.

Authors	Atrazine dose	Exposure period	Animal Species	Results observed
[8]	100 mg/kg	DG 13 to 19	female offspring of rats	Delay in vaginal opening and breast development; decrease in uterine weight
[67,68]	50, 100 or 200 mg/kg	peripubertal period	Rats in the peripubertal period	Delay in vaginal opening and decrease in body weight, reproductive organs, and adrenal gland
[69,70]	25 and 200 mg/kg	chronic exposure	adult rats	Increased duration of the estrous cycle, the number of days in estrus and the number of breast tumors
[71]	75 or 300 mg/kg	14 to 23 days	adult rats	Longer duration of diestrus and pseudo-pregnancy
[72]	3, 30 or 300 mg/kg	2 to 4 weeks	adult rats	Histological alterations of ovarian tissue and prolonged estrous cycle
[39]	5 or 25 mg/kg	DG 14 to 20	Female offspring of rats exposed during pregnancy and/or lactation	Higher levels of ADD in plasma, adrenal gland, brain, and breast tissues
[74]	200 mg/kg	14 days	adult rats	Accumulation of atrazine in ovarian tissue
[73]	400 mg/kg	14 days	adult rats	Alteration in the estrous cycle, ovotoxicity and infertility

Source: GD: Gestational Day; DDA: Desethylhydroxyatrazine.

that atrazine can cause infertility, impair folliculogenesis, and alter ovarian function. In addition, an additional toxic mechanism to the increase in progesterone after exposure to atrazine was the reduction in the expression of LH receptors in granulosa cells, which may cause a decrease in LH and estradiol functions in the ovary, including the development of the corpus luteum, the size of ovaries and estrus cyclicity.

Fraites [39] investigated the distribution of atrazine and its metabolites in offspring after gestational and/or lactational exposure; for this, pregnant rats were exposed to 5 or 25 mg/kg in DGs 14 to 20, and the results showed that their offspring had higher levels of the DDA metabolite in plasma, adrenal gland, brain and breast tissues. Juliani exposed Wistar rats to 0.75 or 400 mg/kg for 14 days, ovotoxicity caused by the highest dose was reported [73]. These data demonstrate changes in estrus cyclicity resulting from exposure to high doses of atrazine, which may also be accompanied by infertility and deleterious effects on folliculogenesis.

A study conducted by Quignot showed that exposing female rats to 200 mg/kg of atrazine for 14 days caused the accumulation of atrazine in ovarian tissue [74]. The results of these studies provide support for the reproductive dysfunction caused by exposure to atrazine and that this substance, as well as its metabolite DDA, is present in brain tissue and breast tissue, supporting the findings that demonstrate that gestational and lactational exposure is harmful to development [8]. Furthermore, the identification of atrazine in the adrenal glands reinforces that atrazine also targets additional neuroendocrine pathways, including the Hypothalamic-Pituitary-Adrenal (HHA) axis. Quignot reported that the effects of atrazine on the HHG and HHA axes may culminate in adverse impacts on in vitro, gestational, peripubertal and adult exposures. These changes ranged from puberty delays, altered estrous cycle, atresic ovarian follicles, reduced gonadotropins, and cellular and genetic alterations [74]. These data provide support for considering atrazine as an endocrine disruptor and its ability to cause reproductive dysfunction at various stages of life.

Furthermore, these studies together provide strong evidence that atrazine acts by altering the activity of the hypothalamic-pituitary-ovarian axis. Cooper showed that atrazine specifically inhibits estrogen-induced increases in Luteinizing Hormone (LH) and Prolactin (PRL) in rats, demonstrating further support for this current mode of action in estrus cyclicity [75]. In this sense, the scientific literature is consensual to highlight the endocrine disrupting estrogenic effects of atrazine. These effects can generate numerous situations regarding reproductive toxicity and can lead to severe dysfunctions, when this agent comes into contact with human beings and numerous economic losses with regard to the area dedicated to agriculture.

Effects on male rodents

Studies focusing on peripubertal exposure of atrazine in male rats observed delay in preputial separation, decrease in serum and intratesticular testosterone, increase in estradiol concentration, reduction in body weight, prostate, seminal vesicle and pituitary and variations in the relative weight of testes, also reduced sperm count, viability, and motility and led to decreased fertility, as summarized in table 4 and detailed below [76-78].

The exposure of 100 mg/kg of atrazine orally from DG14 until parturition altered reproductive development, decreased serum and testicular concentrations of testosterone and estrone, reduced anogenital distance and delayed preputial separation and puberty in male rats [79]. Regarding puberty delay, one hypothesis is that the observed

Table 4: Effects of oral exposure to atrazine in male rodents.

Authors	Atrazine dose	Exposure period	Animal species	Results observed
[79]	100 mg/kg	DG 14 until delivery	Male offspring of female rats exposed during pregnancy	Decrease in testosterone and estrone concentrations; reduction of anogenital distance and delay in preputial separation
[81]	5, 25, 125 or 250 mg/kg	Single dose	male mice	Detection of atrazine and ADD in urine, plasma, brain, liver, kidney, spleen, and thymus
[25]	5 mg/kg	DG 9.5 up to 12 weeks of age	male mice	Decrease in liver weight, epididymal sperm concentration and number of embryonic cells generated
[82]	100 mg/kg	DG 12.5 to 16.5	Male offspring of female mice exposed during pregnancy	Change in the position of the urethral meatus and testicle descent; reduction of anogenital distance and penis size in DPN 21
[122]	100 mg/kg	DG 15 to 19	Male offspring of Long-Evans rats exposed during pregnancy	Did not cause differences in testicular weights, seminal vesicle weights or changes in prostate morphology
[83]	200 or 300 mg/kg	7, 15 or 40 days	adult male rats	7 or 15 days: decrease in body weight and increase in testes and adrenal; 40 days: testicle weight reduction
[85]	12.5, 25, 50,100, 150 or 200 mg/kg	DPN23 to 53	adult male rats	Reduction in body weight, ventral prostate, and seminal vesicle; no change in testicular weight
[84]	38.5, 77 or 154 mg/kg	30 days	adult male rats	Decrease in testicle weight, no changes in seminal vesicle, prostate, or epididymis weight

Source: GD: Gestational Day; DDA: Desethylhydroxyatrazine; DPN: Postnatal Day

effects may be due to hormonal changes or early postnatal brain development, especially around median eminence, which is critical for the moment of preputial separation. Ojeda, in their findings, suggest that atrazine may affect factors in the median eminence that regulates GnRH release, ghrelin levels or changes in leptin leading to changes in male rat weight and body composition [80].

A study conducted by Ross exposed male mice to a single dose of 5, 25, 125 or 250 mg/kg of atrazine, by gavage, and measured the levels of atrazine and its metabolites in urine, plasma and in various fabrics; at these sites, an increase dependent on the concentration of atrazine and DDA was observed, which was higher [81]. Atrazine and ADD have also been identified in plasma, brain, liver, kidney, spleen, and thymus. A study by Harper investigated how chronic exposure to atrazine at a dose of 5 mg/kg/day in DG 9.5 drinking water up to 12 weeks of age affected metabolic and reproductive characteristics in male mice. It was shown that this exposure culminated in a decrease in liver weight and changes in gene expression in the liver and testis, specifically in genes involved in lipid uptake and fatty acid metabolism in the liver, as well as in the conversion of androgens in the testis, exposure to atrazine decreased the concentration of epididymal sperm and the number of embryonic cells generated. In a study by Tan [82], pregnant female mice received orally different doses of atrazine from DGs 12.5 to 16.5. Although no signs of systemic toxicity were seen in their male offspring, prenatal exposure to 100 mg/kg/day of atrazine affected penile morphology, urethral meatus position and testis descent reduced anogenital distance and penis size on Postnatal Day (DPN) 21.

The evaluation for male offspring exposed to atrazine during pregnancy. To this end, pregnant Long-Evans rats were treated by gavage with 100 mg/kg of atrazine from DGs 15 to 19 and the observations of offspring were carried out in the DPNs 120 and 180. The results demonstrated that gestational exposure to atrazine did not cause significant differences in testicular weights, seminal vesicle weights, or changes in prostate morphology. The results of work by Victor-Costa [83] demonstrated that exposure to atrazine of 200 mg/kg for 15 days and 300 mg/kg for 7 days caused a decrease in body weight and an initial increase in relative and absolute testes and adrenal weight, while the dose of 200 mg/kg for 40 days caused a reduction in the relative and absolute weight of the testes. A study exposing Wistar rodents to doses of 12.5, 25, 50, 100, 150 or 200 mg/kg per gavage from DPN23 to 53 found a significant reduction in body weight, ventral prostate weight, and seminal vesicle weight in the exposed animals at the highest dosage, but no change in testicular weight.

An additional study addressing the hormonal and histological changes caused by atrazine exposed adult male Sprague-Dawley rats to 38.5, 77 or 154 mg/kg of atrazine for 30 days. Once dosing was completed, the testicles were removed and analyzed. A decrease in testicular weight was observed in the treatment of 154 mg/kg with no changes in the weight of the seminal vesicle, prostate, or epididymis [84].

As reported, changes in testicular weight have been controversial. The results showed an initial increase in testicular weight with shorter exposures to atrazine but observed a decrease with longer exposure periods. Also in this sense, conclude, based on their results, that no change was identified in the relative weight of the reproductive organs or in the histology of the testis, and this is probably due to the lower dose of atrazine used, since previous studies report changes with much higher doses, above 100 mg/kg [76,83,85].

Scientific literature shows that, when evaluating the effects on reprotoxic or even on the sexual behavior of male animal models, there is evidence that atrazine has a potential endocrine disrupting estrogen that has a direct impact on the male biological system.

Behavioral effects of atrazine exposure in animal models

According to Lamb [20], more and more studies are revealing that endocrine disruptors, including atrazine, can alter animal behavior. Early exposure to these agents can permanently change phenotypes into adulthood.Exposure to endocrine and neuroendocrine disrupting chemicals are reported to induce a variety of abnormal behaviors [86,87], particularly when individuals are exposed early in life [64,65]. It was seen that endocrine disruptors interfere with the molecular mechanisms that support behavior, such as gene expression, hormone levels and neurotransmitter levels [29,88]. The effects of exposures to these compounds are predominantly implicated in the interruption of typical reproductive behaviors, such as cohort and parental sexual behavior [89], but also with non-reproductive behaviors, such as anxiety, aggression, and risk behavior [90,91]. Some studies focusing on the deleterious effects on the behavior of rodents due to exposure to atrazine are briefly described in table 5 and detailed below.

In a study by Lin [17], exposure to atrazine caused a tendency to hyperactivity and increased locomotor activity in male and female juvenile offspring, but this effect was transient and did not persist into adulthood. This finding is in line with previous studies that found that 1-year chronic exposure to a diet enriched with a dose of 10 mg/kg of atrazine increased locomotor activity in male rats and oral exposure to atrazine at doses ≥0.001 mg/kg DG14 to DPN16 increased open field motor activity in male and female juvenile mice offspring, suggesting that the developing nervous system is particularly sensitive to atrazine [35]. On the other hand, short-term exposures of less than 14 days at doses of 100 to 250 mg/kg of atrazine resulted in hypoactivity lasting up to 5 days in adult male rodents. These findings suggest that exposure to atrazine consistently disrupts motor function

Table 5: Behavioral changes in oral exposure to atrazine in rodents.

Authors	Atrazine dose	Exposure period	Animal species	Results observed
[34]	10 mg/kg	1 year	male rats	Increased locomotor activity
[35]	≥0.001 mg/kg	DG14 to DPN16	Male and female juvenile mice pups	Increased locomotor activity
[30,56]	100 to 200 mg/kg	Short term (less than 14 days)	adult male rodents	Hypoactivity lasting up to 5 days
[24]	25 mg/kg	28 days	Young and old mice	Increased anxiety and depression; deficits in spatial learning and memory function, changes in motor activity, grip strength and sociability

Source: GD: Gestational Day; PND: Postnatal Day.

in both sexes and across multiple exposure paradigms, and the intensity of this effect may depend on dose and time. Lin further states that exposure to a relatively low dose of atrazine in drinking water, during pregnancy and lactation, causes harmful effects on the nervous system and multiple abnormalities behavior in the exposed female and her offspring [18]. These behavioral changes, which include deficits in memory, motor, and cognitive impairment, are associated with disturbance of monoaminergic brain homeostasis and, in some cases, in a gender- and time-specific manner. The finding that atrazine causes sex-specific behavioral changes in offspring suggests that overexposure to this herbicide may be an environmental factor contributing to the development of sex-influenced neurodevelopmental disorders [18]. Study by Genovose also contributes with these ideas [24]. Exposure for 28 days to an aerosol containing 25 mg/kg of atrazine by young and elderly mice increased anxiety and depression, as well as deficits in spatial learning and memory, alterations in motor activity, grip strength and sociability. Notably, Lim [92] who identified obesogenic effects of atrazine in rodents, that is, for these authors, atrazine was able to change the metabolic activity, interfering with mitochondrial function. These authors used rodent models and chronic exposure to an environmentally relevant dose of atrazine of 30 µg/kg induced body weight gain, insulin resistance and hepatic steatosis with a high-fat diet. This hypothesis was confirmed by more recent studies by Foulds [93], who state that early exposure to endocrine disruptors, including atrazine, is considered a causal factor that may explain the increased incidence of hepatic steatosis (fatty liver disease) in humans.

In this sense, Roa and Katib elucidated that these negative effects on metabolism may have an impact on reproductive function, as both systems are controlled by overlapping regulatory pathways [94,95].

Notably, in a study by Harper [25], chronic exposure in mice to atrazine at a dose of 5 mg/kg given in DG9.5 water until 12 or 26 weeks of age caused a decrease in liver weight at 12 weeks and thus, the authors conclude that exposure to atrazine, beginning in the prenatal period, negatively affects metabolic and reproductive characteristics, as well as organ development and liver gene expression, including an increase in the expression of several genes involved in liver lipid uptake, specifically, Slc27a5, which encodes the fatty acid transporter protein 5; this would result in disturbances in metabolic homeostasis. In contrast, no difference in liver weight was observed at 26 weeks of life, suggesting that although there may be differences in liver development, eventually the chronic dose was not high enough to permanently delay development, and the liver grows to a size like the control.

Based on findings from other studies, a mechanism that justifies this finding may be through the ability of atrazine to alter mitochondrial function by interfering with complexes I and III in the electron transport chain [92], which it can interrupt energy metabolism and induce oxidative stress, thus creating an unfavorable environment for organ development [93]. This is supported by studies in human liver cells that revealed that exposure to atrazine at a dose of 0.625 µg/ml decreased cell proliferation rates and induced mitochondrial dysfunction [96-98]. The findings reported here are in addition to the growing amount of work in the literature that proposes that stressors in early life during and/or critical periods of development can change the structure and physiology of the liver [92,99]. Notably, these effects on metabolism are likely to impact reproductive function, as these regulatory pathways often overlap [95].

Neuroendocrine and neurochemical effects of atrazine exposure in animal models

Animal studies have shown that exposure to relatively high doses of atrazine (≥10 mg/kg) based on the acute guidelines of the EPA Dietary Development Study targets cerebral monoaminergic systems, especially nigrostriatal Dopamine (DA), culminating in a series of cellular, molecular, and behavioral abnormalities [32,100]. Hypoactivity, memory deficits and anxious-like behavior are accompanied by alterations in DA and serotonin (5-HT) homeostasis in the striatal and prefrontal cortex in adult mice. Atrazine also reduced the substantia nigra and DA neurons in the ventral tegmental area in juvenile mice [32]. A developing nervous system is more sensitive than a mature system to various toxics, including heavy metals and pesticides; this increased sensitivity is attributed not only to the presence of an immature blood-brain barrier, but also to the complex temporal and regional appearance of critical developmental processes, for example, proliferation and differentiation [101]. Study suggests that atrazine affects

dopaminergic neuronal differentiation in vitro and that the developing dopaminergic system may be particularly vulnerable to atrazine when dopaminergic neurons are undifferentiated. Behavioral tests are commonly used to assess motor, emotional and cognitive functions in rodents and thus elucidate the normal or non-normal function of brain regions that receive rich monoaminergic innervations, including the prefrontal cortex, nucleus acumens, striatum, cortex perirenal and hippocampus [102,103]. Neurochemical assays show that striatal DA homeostasis was altered in male and female juvenile offspring; other neural pathways were affected by atrazine in exposed offspring, suggesting that the most consistent neurochemical outcome, affected by gestational and lactational exposure to atrazine from drinking water, is striatal AD. These data agree with previous studies in adult rodents and suggest greater sensitivity and regardless of sex in young animals [100]. Therefore, the results of the studies indicate that exposure to atrazine causes detrimental effects on the nervous system and multiple behavioral abnormalities. These behavioral changes are associated with disturbance of cerebral monoamine homeostasis in a region of the brain and, in some cases, in a gender- and time-specific manner. So, the exposure to atrazine can lead to changes in monoamine levels in the perirenal cortex that are related to memory deficits, while changes in striatal AD homeostasis may be responsible for the altered motor activity. Findings that perinatal atrazine exposure delayed effects on cognitive function and long-term effects on certain monoamine systems in offspring suggest that developmental exposure to atrazine may increase vulnerability to neurodegenerative diseases involving later monoaminergic dysfunction in life. The finding that atrazine causes sex-specific behavioral changes in offspring suggests that atrazine overexposure may be an environmental factor contributing to the development of sex-influenced neurodevelopmental disorders.

Neurodegenerative effects of atrazine exposure

Considering the relationship of the nigrostriatal system to motor function, and its target of action atrazine, which lead to molecular, cellular and behavioral changes, it was shown that exposure to atrazine alters the brain homeostasis of AD and serotonin (5-HT), suggesting that this herbicide modifies tyrosine and tryptophan metabolism. In addition, several studies have shown that exposure to atrazine decreased striatal DA levels, an effect that is associated with loss of tyrosine hydroxylase (TH+) positive dopaminergic neurons in the substantia nigra compact area and the ventral tegmental area in rodents [32,100]. Another possible link between Parkinson's disease and pesticide exposure has been suggested, and recently the herbicide atrazine has been shown to modulate catecholamine metabolism in PC12 cells and affect basal ganglia function in vivo [104] .

Stretch marks exposed to atrazine at concentrations of ≥100 µM had a dose-dependent decrease in tissue DA levels. At doses of ≥50 µM and above, the DOPAC + HVA/DA ratio increased in a dose-dependent manner. Protein tyrosine hydroxylase (TH, the rate-limiting enzyme in DA synthesis) levels and activity were not affected by treatment with atrazine. However, the high potassium-induced DA release into the medium was diminished, whereas the increase in medium DA observed in the presence of the DA uptake inhibitor nomifensin was further increased by atrazine in a dose-dependent manner. All these effects of atrazine were observed at levels that were not tissue toxic, as the release of LDH into the medium (lactate dehydrogenase, an index of non-specific cytotoxicity) was not affected by atrazine. Thus, the results of this study suggest that atrazine decreases tissue DA levels, not affecting TH activity, but possibly interfering with vesicular storage and/or cellular DA uptake [104]. In terms of the potential of atrazine to be toxic to basal ganglia, in vitro exposure to atrazine for up to 24 hours, in a dose-dependent manner, decreased cellular levels of DA in PC12 cells [104]. Atrazine treatment also decreased intra and extracellular Norepinephrine (NE) levels, however, NE levels were less sensitive to atrazine than DA and a longer duration of exposure was required to observe the effects [105]. This suggests a possible increased sensitivity of DA to atrazine. More recently, two in vivo studies observed that exposure to atrazine altered striatal neurochemistry and caused the loss of dopaminergic neurons in the substantia nigra of rats and mice. The most significant finding of this study was that exposure to atrazine decreased DA levels in striated tissue. The decrease was associated with increased DA levels in the mean and ratio (DOPAC + HVA)/increased DA, whereas TH and activity levels were not affected in this exposure paradigm. Thus, data from the described experiments suggest that atrazine is dopaminergic toxic and agree with previous in vitro studies that showed that exposure to atrazine dose-dependently decreased cellular DA levels in PC12 cells [105]. In more detail, they performed an experiment on samples of rats with atrazine induced Pankinson's disease. The researchers focused on miRNA-7, as it is known to repress α-synuclein production [106] and found that it is down-regulated in peripheral blood samples but regulated, positively in substantia nigra tissues. They suggested that this change reflects a continuing change in the early stages of Parkinson's disease and this molecule could be used as an early diagnostic biomarker. Maquéz [107] repeatedly exposed adult male Sprague-Dawley rats to 6 injections of 100 mg/kg of atrazine for two weeks and one injection of saline solution two days after atrazine administration. Locomotor activity was assessed for 15 minutes and/or 2 hours after the injection of atrazine or saline solution and 2 months after the final administration of atrazine. This model of administration resulted in immediate, short- and long-term hypoactivity and reduced specific binding of [3H]-SCH23390 in the dorsal striatum of rats evaluated 2 months after the last injection.

Atrazine can alter other characteristics of D1-DA receptors. Particularly, specific binding to striatal D1-DA receptors decreased and this drop was accompanied

by hypoactivity in rats after treatment with atrazine. This finding is supported by reports on other herbicides mentioned above, such as 2-4 D, parathion and glyphosate, as they can modify the affinity, density and/or translocation of D1 or D2 receptors in the brain [108,109].

These findings together may be the result of the effect that atrazine has on dopaminergic metabolism, such as decreases in the content of DA and its metabolites.

In this regard, a meta-analysis of existing data carried out by Priyadarshi not only confirmed exposure to pesticides as a risk factor for Parkinson's disease, but also found a significant association between well water consumption and the incidence of Parkinson's disease [110,111].

Results of an epidemiological study carried out by James and Hall [112] show that there is a significant association between the level of pesticide in the groundwater and the occurrence of Parkinson's disease and separately, the concentrations of atrazine in groundwater and Parkinson's disease during the adjustment for age in years and sex. These results suggest that for every 0.01 mg/L increase in pesticide levels in the water table, there is an increase of 3% in the risk of Parkinson's disease, and for every 0.01 mg/L increase in atrazine levels, there is a 4% increase in the risk of Parkinson's disease. At the same time, for every year of increase in age, the risk of Parkinson's disease increases by 7%. Therefore, populations residing in the highest pesticide areas have a 200% increased risk of developing Parkinsonism.

The spatial distribution of measured pesticide levels in groundwater is in predominantly agricultural lands, and this coincided with areas with higher age-standardized Parkinson's disease prevalence rations. This finding is like other study populations, both in residence and occupation. Two studies examined populations residing in predominantly agricultural regions and found that patients with Parkinson's disease were more likely to have been agricultural workers [113-118]. These studies support the theory that rural life and agricultural work are risk factors for Parkinson's disease.

As the link between Parkinson's disease and pesticide exposure is now well established, collectively, these studies indicate that, in addition to rotenone, paraquat, maneb, dieldrin and heptachlor, exposure to the herbicide atrazine may also be a contributing factor to Parkinson's disease and other neurological disorders where AD levels are affected [119-124]. Modulation of DA metabolism by possible inhibition of vesicular and/or cellular uptake seems to be involved in the atrazine toxicity mechanism.

CONCLUSION

The review gathered the studies published in the literature both in vivo, in vitro, and epidemiological studies, which demonstrated that atrazine has deleterious effects on behavioral and neurochemical parameters, as well as its relationship with degenerative diseases, in particular, Parkinson's disease through alteration of dopaminergic neurotransmission.

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