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Neonicotinoids, agriculture and food security of brazilian honey: a review

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Abstract:
Pesticides used in agriculture have the function of controlling pests, diseases and preventing the development and growth of weeds, increasing the quality and productivity of crops. However, when they reach unwanted targets, such as bees, humans and other living beings, they cause harmful damage to ecosystems. Neonicotinoids, insecticides widely used in monocultures, such as soybeans and corn in Brazil, are especially harmful to bees, whether native or exotic, interfering with the foraging and pollination performance of plants. The global decline in the bee population is related to the use of insecticides, a fact that directly threatens the production of various foods. Honey, the main beekeeping product, is not only a source of food for bees, humans and other animals, but also an indicator of environmental quality, as its composition reflects the conditions of the environment in which it was produced, and determinations made therein can reveal the presence of contaminants such as pesticides and toxic metals providing information about ecosystem health and the presence of environmental contaminants. Furthermore, consuming pesticide-free foods is crucial for human health and environmental sustainability, as the intake of neonicotinoids is associated with several health problems such as hormonal disorders and nervous system diseases and is especially dangerous for children. This article reviews the neonicotinoid insecticides imidacloprid and thiamethoxam and the contamination they cause in the honey of bees Apis mellifera Linnaeus (1758) and Tetragonisca angustula Latreille (1811) in Brazil, evaluating the impacts of these insecticides on bees, the implications for ecosystems and safety to feed.
Keyword*: Food contamination; Imidacloprid; Thiamethoxam; Apis mellifera; Tetragonisca angustula.*

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I. Introduction

Neonicotinoids are a class of insecticides widely used in agriculture to combat pests and insects [1]. A few years after the start of their mass application, many studies have shown growing concern about the effects of these pesticides on the environment and humans [2]. Reasons for the increasing use of this insecticide are population growth and intense agricultural production that seeks productivity and quality [3].

According to the latest Demographic Census released by the Instituto Brasileiro de Geografia e Estatística (IBGE), in August 2022, the brazilian population reached 203,062,512 inhabitants [4]. Since 2010, when the previous Demographic Census was conducted, the country's population has increased by 6.5%, that is, 12,306,713 more people, corresponding to an annual growth rate of 0.52% [4]. Population growth is correlated with the country's food demand, implying the need to increase food productivity, especially in the agricultural sector, a situation that puts even more pressure on the intensive use of pesticides [5].

Bees, the main pollinators of native and agricultural plants, have been a focus of study in this regard. During the collection of nectar and pollen, bees can encounter a variety of contaminants present in the agricultural environment, including pesticides, toxic heavy metals and other pollutants, and these can cause the death of these insects, and the honey produced is exposed to contamination. Thus, interfering with its quality, which may cause harmful effects to consumers of this product [6]. Furthermore, the possibility of contamination of honey would interfere with its added value, as it is popularly consumed as a natural and healthy product, and can be sold for different prices, depending on its origin and characteristics [7].

Honey quality is an important indicator of the environmental quality around the hives, serving as a measure of environmental integrity [8], and also the presence of pesticide residues in it represents a concern for food safety and public health, requiring regulations and constant monitoring of this product [9].

According to the Instituto Nacional do Câncer (INCA), ingestion and short-term exposure to pesticides, such as neonicotinoids, can result in health problems such as nausea, vomiting, headache and dizziness, and if prolonged or chronic it can lead to more serious problems. , such as neurological dysfunctions, hormonal problems, immune system disorders and even cancer [10]. Furthermore, children and pregnant women are particularly vulnerable to the effects of pesticides and may suffer impacts on their cognitive and physical development [10]. Therefore, it is essential to carefully investigate the possible contamination of honey, so that we have knowledge about the quality of these products and thus establish limits that guarantee the safety of this food.

II. Pesticides

Pesticides are synthetic chemical products used to exterminate and control pests such as insects, larvae, fungi and ticks under the justification of controlling diseases caused by these vectors, in addition, regulating the growth of weeds, which may interfere with development and consequently production. Of diverse cultures, whether in rural or urban environments [11]. In the agricultural environment, pesticides are crucial to ensure food supply, minimizing losses, increasing productivity and quality.

According to the Food and Agriculture Organization (FAO) [12], the United States of America was the largest user of pesticides in 2020, with 408 kt of pesticide applications for agricultural use. Next are Brazil (377 kt) and China (273 kt). Brazil stands out along with the other two countries because agriculture is among the most important economic activities, with the agricultural sector responsible for a significant portion of the Brazilian Gross Domestic Product (GDP), reaching 24.8% in 2022 [13], generating employment for millions of people and being responsible for a large part of brazilian exports. Furthermore, the country has a wide variety of agricultural crops, which are adapted to different climates and soil, allowing for diverse and robust production [14].

Although pesticides have the function of protecting agricultural crops against pests, diseases and invasive plants, their excessive use can pose risks to human health and the environment [15] leading to contamination of soil, surface water and underground, and food, resulting in a chain spread (Fig. **1**), which can cause toxic effects on aquatic and terrestrial organisms, including humans [15].

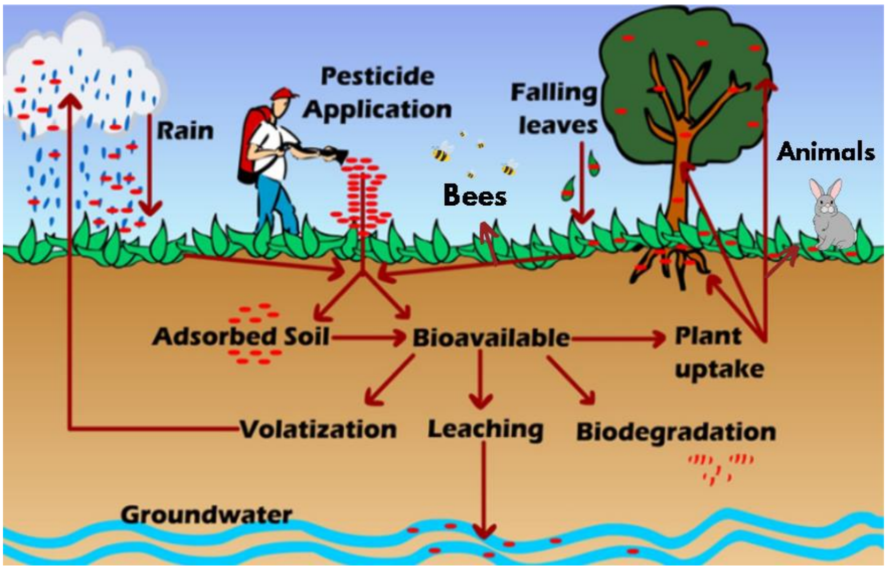

Fig. 1 Dynamics of pesticides in the environment (Adapted from Langenbach [16]).

Exposure to pesticides can cause a few diseases, depending on the product (active ingredient) used, the exposure time and the amount of product absorbed by the body [5]. Factors such as distinct behavioral and social issues, difficulty in making decisions regarding exposures, and longer life expectancy, which results in longer contact with toxic substances throughout life, contribute to a substantial risk of diseases in this population group [18].

Due to the development of agribusiness in the economic sector and the broad market, there are serious problems regarding the use of pesticides in the country: permission of pesticides already banned in other countries and illegal sales of pesticides that have already been banned [18].

Neonicotinoids: A brief history

Until the 1990s, the global insecticide market was dominated by organophosphate compounds, carbamates and pyrethroids [3]. Neonicotinoids were developed as an alternative to these insecticides due to increasing pest resistance, concerns about cumulative worker exposure, and evidence that these compounds could be linked to problems in neural development in children [19]. The development of neonicotinoids began in the early 1990s, based on the insecticidal effects of nicotine [20].

Since the 19th century, botanists and farmers have used infusions of tobacco leaves as insecticides [21]. The commercialization of synthetic molecules with a structure like nicotine began in the mid-1990s, with imidacloprid being the first neonicotinoid registered for use in 1991 [21].

Neonicotinoids are fourth-generation pesticides, which emerged after organophosphates, pyrethroids and carbamates and are widely used in vegetables, fruits, cotton, rice and other industrial crops to control insect pests [2]. Over the years, neonicotinoids have been applied more widely than any other type of insecticide and represent more than a quarter of the pesticides used worldwide [22].

Currently, neonicotinoids are widely used in the treatment of agricultural crop seeds in Brazil, according to a study by Whalen et al. [23], these pesticides are applied to approximately 50% of the area planted with soybeans (approximately 18.2 million hectares), almost 100% of the area planted with corn, more than 36.4 million hectares, and 95% of area planted with cotton, around 15 million hectares.

Mode of action of neonicotinoids

Neonicotinoids function as agonists (Fig. **2**) of acetylcholine (Ach), which is the main and fastest neurotransmitter of excitation in insects. Therefore, these compounds mimic the action of acetylcholine, repeatedly stimulating nerve cells. By binding to nicotinic receptors, the enzyme acetylcholinesterase (AChE), which is responsible for degrading acetylcholine molecules and interrupting nerve signals, does not act on them, thus the insect is killed by nervous overexcitation [24].

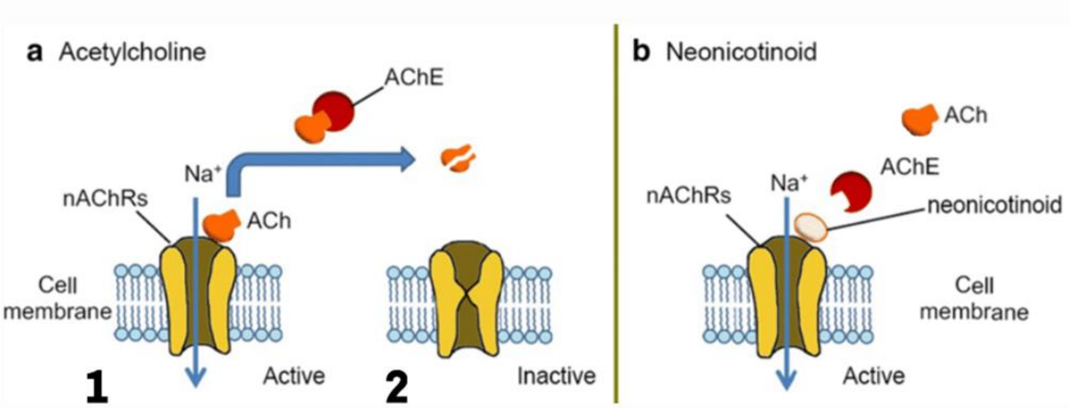

Fig. 2 Mode of action of neonicotinoids (Adapted from Chang et al. [25]).

The similarity between these molecules (Fig. **3**) is due to the alignment of their structures with key areas on the insect nAChR receptors that interact with certain parts of the ellipses. The cationic site contains a tryptophan residue that attracts the charged nitrogen atom in both ACh and nicotine. In neonicotinoids for example, the corresponding partially positively charged nitrogen atom in imidacloprid also binds to this residue [26]. A second bond occurs between the carbonyl group of ACh and the pyridine group of the other molecules. Furthermore, insect receptors also contain groups that bind to the nitro group of imidacloprid, further contributing to the selectivity of these molecules. Therefore, neonicotinoids are nothing more than synthetic molecules analogous to nicotine, with the same mode of action [26].

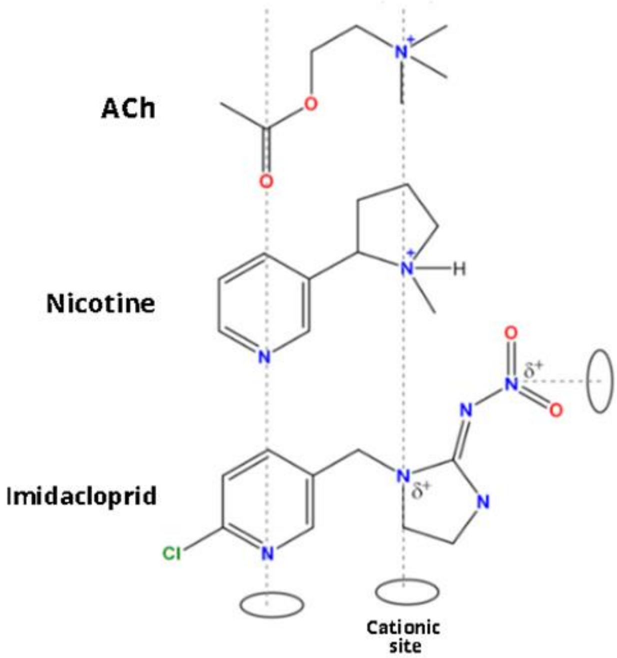

Fig. 3 Symmetry of the active sites of neonicotinoids (Adapted from BASF [26]).

In insects, nAChRs have high affinity for neonicotinoids. However, they are widely expressed in vertebrates and invertebrates. In humans and other mammals, nAChRs are found in the peripheral and central nervous systems [27].

The actions of neonicotinoids on nAChRs are not limited to agonist or antagonist actions. Imidacloprid and clothianidin potentiate vertebrate (avian) nAChRs when applied with ACh at concentrations lower than those that result in agonist actions. Such potentiating actions were attenuated by increasing ACh concentrations, suggesting that such actions occur at orthostatic sites, and with these complex and diverse actions, neonicotinoids are now referred to as the molecular basis of their target selectivity [28].

Imidacloprid (Fig. **4**, molecule 1) is a neonicotinoid insecticide, generally applied as a systemic insecticide, which causes the death of insects via ingestion or contact, damaging their central nervous system by blocking postsynaptic acetylcholine receptors, and in addition It has specific toxicity for insects and low toxicity for mammals [2].

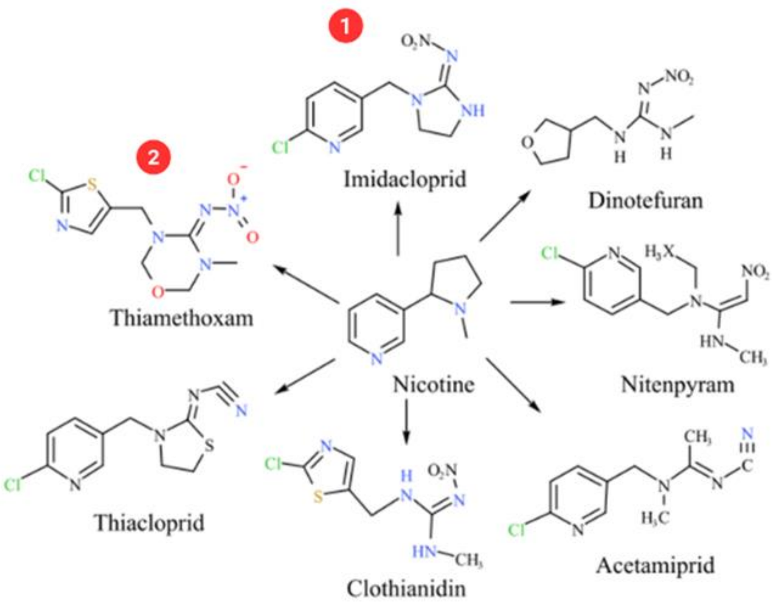

Fig. 4 Nicotine molecule and the seven most used neonicotinoids, including Imidacloprid (1) and Thiamethoxam (2) (Adapted from Zhang et al. [2]).

Imidacloprid was the first representative of the neonicotinoid class to be placed on the market and has been used extensively since then [29]. It is used in cotton, rice, sugar cane, citrus, beans, tobacco, corn, soybeans, tomatoes and wheat crops [29]. Intensive use of imidacloprid may contribute to contamination of soil and water resources through spray drift and soil leaching.

Thiamethoxam (Fig. **4**, molecule 2) is one of the main neonicotinoid insecticides present on the current market. Widely used in the treatment of soybean, corn, rice and wheat seeds, it acts systemically to prevent damage from stink bugs, leafhoppers, aphids, whiteflies and coró, protecting seedlings very well at the beginning of crop development [1] .

The constant and intensified use of these pesticides has caused collateral impacts in several agricultural systems, where one of the main effects is related to the death of bees, the main plant pollinators, which leads to a decline in agricultural production. Among the pesticides responsible for the death of bees, neonicotinoids are one of the most harmful groups of insecticides.

Exposure to neonicotinoids

High exposure to this class of insecticides in humans can result in toxic effects including reproductive, neurological, hepatic, hepatocarcinogenicity, immunological and genetic toxicity [30]. In addition to these adverse neurological development, immunological and carcinogenic problems in humans, the phenomenon of toxicity has been observed in bees, impairing the sense of communication, reproductive capacity and feeding [31].

Another worrying factor is its persistence in plants, fruits, vegetables and seeds, which consequently leads animals and humans to constant exposure to the substance. Therefore, imidacloprid can represent a risk to the health of these organisms and cause a wide range of adverse effects and depending on the amount absorbed and time of exposure can even lead to death [32].

Neonicotinoids have been frequently detected in foods [6]. Despite the frequency of detection, estimates of daily intake indicate that consumption does not typically exceed established tolerance levels [33]. The low molecular weight and high-water solubility of neonicotinoids provide the systemic property to allow insecticides to enter plant tissues [34]. It has been shown that several neonicotinoids can be transported into pollen, vegetables and fruits and therefore represent a potential route of human exposure. as washing does not completely remove neonicotinoid insecticides present in consumed fruits and vegetables [35].

The Instituto Brasileiro do Meio Ambiente e dos Recursos Naturais Renováveis (IBAMA) in 2021, published a document detailing the environmental reassessment of the neonicotinoid imidacloprid. The reassessment aims to update and verify the environmental impacts associated with the use of this pesticide, especially in relation to the contamination of water bodies and the effects on biodiversity, including non-target organisms such as bees [36].

Furthermore, in 2024 IBAMA highlighted the need for a more rigorous analysis of the scientific data available on thiamethoxam and recommended the implementation of mitigating measures to reduce environmental risks. Among the recommendations are the restriction of use in certain crops and times of the year, in addition to the adoption of agricultural techniques that minimize the dispersion of the product in the environment [37].

The problem of neonicotinoids goes beyond Brazil. A study by Ospina et al. [38] representatively assessed the national level of exposure to various neonicotinoids in the USA. They found that 49.1% of the general US population aged 3 years and older had recently been exposed to neonicotinoids. The study also noted the need for investigation to identify additional biomarkers of neonicotinoid exposure to assess changes in neonicotinoid exposure over time.

Chen et al. conducted a comprehensive survey on neonicotinoid residues determined in food samples commonly consumed by Chinese adults [9]. It was the first work to study the health risks of chronic exposure to neonicotinoids in China. Most samples analyzed contained more than one neonicotinoid. Imidacloprid and acetamiprid were the most frequently detected, and thiamethoxam and clothianidin were agricultural products increasingly used in China. The high detection rates of neonicotinoids in Chinese dietary composite samples provided a snapshot of the ubiquity of this class of insecticides in China. Vegetables were the main source of dietary exposure [9].

Exposure through cereals, beverages and water was also addressed due to the high consumption of these products in China. The results of this study by Chen et al. showed that dietary exposure to total neonicotinoids poses an acceptable health risk to the average Chinese adult population [9]. The researchers concluded that there is a need for additional studies on toxicological limits in mammals, the importance of routine measurements in food and environmental samples, as well as the risks of dietary exposure to neonicotinoids, should not be neglected.

III. Bees

Bees are considered the most important pollinating agents, due to their enormous number, as they represent around 25,000 of the 40,000 species of pollinators, and they also pollinate a wide variety of flowers

[39]. In addition to pollination, there are honey-producing species, such as those of the *Apis* genus , which are the best known and most widespread.

Bees belong to the order *Hymenoptera* and the apid family. There are more than twenty thousand cataloged species of bees, and due to its continental proportions and rich ecosystems, Brazil is privileged in this aspect, housing around 10% of these species [40]. Despite efforts to understand the *Apoidea* fauna, brazilian bees are still little known and studied [41]. The *Apis* genus contains the most commercially used social bees [42]. They are important for pollination, agriculture and the production of honey, royal jelly, wax, propolis and pollen.

There are also meliponids species, without stingers. The breeding of stingless bees, in addition to its economic and social relevance, is a traditional activity in all regions of Brazil [43], being conducted by small and medium-sized producers. The genus *Melipona,* which has the largest number of species, including *Tetragonisca angustula* , is notable for its great richness in biodiversity [44].

Apis mellifera

The *Apis mellifera* bee (Fig. **5**) that inhabits Brazil, popularly known as Africanized, is the result of the crossing of European and African races, bee species present throughout the world (Fig. **6**). Despite being very defensive, Africanized bees are active all year round, highly productive and resistant to disease. It is generalist and stands out for being easy to manage, allocate, efficiency and produce products with high added value [7]. They have an adult size of 12 mm to 13 mm, and fly, on average, 3 km away from their colonies [7].

Fig. 5 (A) Bees *Apis mellifera*) and (B) *Tetragonisca angustula*.

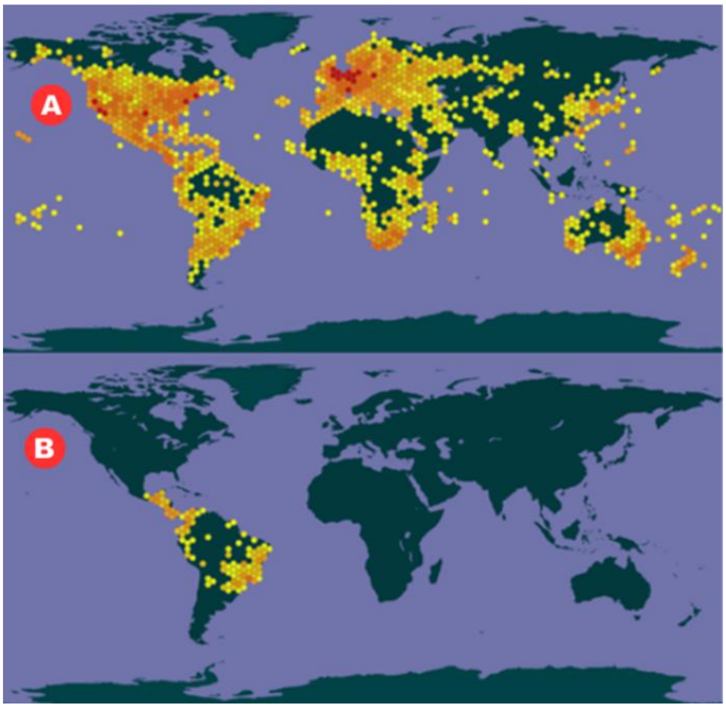

Fig. 6 (A) Georeferenced records of *Apis mellifera* and (B) bees *Tetragonisca angustula* (Adapted from Global Biodiversity Information Facility (GBIF) [45]).

Studies indicate that *Apis mellifera* is frequently exposed to neonicotinoids, due to its proximity to agricultural areas intensively treated with these pesticides [8]. Neonicotinoid concentrations vary, but the most common include imidacloprid, clothianidin, and thiamethoxam. These compounds are often detected at levels that can cause sublethal effects in bees, including disorientation, memory loss and reduced navigation ability, which can contribute to colony collapse [6].

Furthermore, its toxic effect on bees has been widely described in literature and associated with the causes of decline in the pollinator population. For example, non-lethal exposure to thiamethoxam has been found to decrease the foraging success of the western honey bee (*Apis mellifera*) [46] and induce a variety of behavioral changes [47].

Tetragonisca Angustula

The best-known stingless bee in the ecosystems of the Neotropical region (Fig. **6**) is the bee *Tetragonisca angustula* (Fig. **5**), native to the state of Paraná, known by the Indigenous name "Jataí" [48]. Its foraging distance is approximately five hundred meters, a significantly shorter distance than *Apis mellifera* , this is due, among other factors, to its size, approximately 4-5 mm [49].

Although they produce honey in smaller quantities, Jataí bees provide a product that is different from *Apis mellifera honey*, due to its characteristic sweetness and aroma, with its own nutritional properties and, consequently, having consumers willing to pay high prices for the product on the market [7].

The breeding of stingless bees has several purposes, including the preservation of biodiversity, the commercialization of their honey and the maintenance of cultural practices. They play an essential role as pollinators for several plant species in tropical and subtropical ecosystems, in addition to contributing pollination services to agricultural crops that have great economic value [25]. The significant increase in scientific research on stingless bees in recent years and the active participation of these researchers in experimental studies are contributing to this field [50].

It can be inferred that *Tetragonisca angustula* and its honey are less exposed to pesticides. This fact can be attributed to the preference of these bees for foraging in areas of native vegetation, less exposed to pesticides [51] and to the stimulus for their breeding within urban locations [52]. Furthermore, the literature on this species is limited, and other research has sought to explore possible seasonal and geographic variations [53].

Just like the *Apis Mellifera*, Jataí bees are also affected by neonicotinoids. These problems related to bee mortality are related to the systemic property of these insecticides, being absorbed and translocated throughout the plant, including pollen, on which bees feed [54]. Being used against insect pests, they can also affect insects that are not the target, such as bees.

Nitro-substitute neonicotinoids (imidacloprid and thiamethoxam) applied topically are the most toxic to bees, with contact LD50 (lethal dose) values in nanograms per bee [55]. As a result of this and their widespread use, there is great concern that neonicotinoids play a harmful role in favoring the decline of pollinators.

IV. Honey

The food produced by honey bees (honey) originates from flower nectar or secretions from living parts of plants, in addition to excretions from sucking insects that remain on these living parts [56]. Bees collect these substances, transform them, combine them with their own substances, store them and let them mature in the hive's combs [56].

Beekeeping is characterized by the management of the *Apis mellifera species*, being widely practiced in society with advanced technology and well-established production standards. Traditional beekeeping products, such as honey, pollen, propolis and royal jelly, are well known, and there are specific laws to control their quality [56], [57] Meliponiculture, in turn, refers to the management of stingless indigenous bees, such as *Tetragonisca angustula,* with the main objective of obtaining honey or for the interest in management [49]. The honey production of this species in a strong colony can reach up to 1.5 L per year [49]. The Jataí bee, although it produces less honey compared to Africanized bees (15 L per year), is easy to manage due to the absence of a sting and its good adaptation to different environments [58]. These characteristics make Jataí ideal for numerous studies. However, honey produced by meliponiculture does not have a pre-defined quality standard in terms of composition, which makes comparisons difficult [49].

In general, honey is recognized for its numerous beneficial effects in various pathological conditions, in addition to being a highly energetic and nutritionally rich food in several complementary elements [59], it is a powerful antimicrobial agent with a wide range of effects [60], [61]and a natural antioxidant [60]

FAO statistical reports from 2021 show that China is the world's largest producer of honey, with 458 thousand tons recorded in 2020, Turkey comes next, with 104 thousand tons, followed by Iran with seventy-nine thousand tons and Argentina with 74 thousand tons [62]. According to the IBGE [63], the value of honey production in Brazil reached R$957,811,000.00 in 2022 and the quantity produced was 60,966,305 kilograms

[63]. In the same year, the state of Paraná ranked second among the largest producers, with a quantity produced of 8,638,089 kilograms, just behind Rio Grande do Sul, with 9,014,249 kilograms [63].

Paraná stands out among the main honey exporting states. In the first half of 2020, it exported 4,987 tons, an increase of 57% over the volume exported in the same period of the previous year, which had totaled 3,174 tons, State Secretariat for Agriculture and Supply [65].

According to data released by Efficienza [65] honey consumption in Brazil is significantly low. While the global average consumption of honey per person is 240 grams per year, in Brazil consumption is only sixty grams per person, one of the lowest rates in the world. This is equivalent to approximately 15 thousand tons of honey consumed annually in the country, of which 53% is destined for table honey (used to sweeten drinks, fruits or for fresh consumption), 35% is consumed by the food industry as an ingredient, and the last 11% is used by the cosmetics, tobacco and animal feed industries [65].

Contamination of honey by pesticides and neonicotinoids

Due to the idea of honey as a natural product, the truth that it can be contaminated with agricultural products is too hidden. Although it is widely used in foods, pharmaceutical formulations and cosmetics, general health legislation regarding this product is scarce in the country. In Brazil, regulations are limited to definitions, labeling requirements [66] and physical and chemical specifications [56], with the National Health Surveillance Agency (ANVISA) classification restricted to table honey, which meets all criteria established for this category [67].

For some pesticides, there are no limits established in Brazil [68]. Normative Instruction No. 233, of July 5, 2023 [67], provides limits for pesticide residues, such as imidacloprid and thiamethoxam, in foods, but there is nothing about limits in honey. So, to meet this need, the reference basis for developing analytical research are European Union (EU) standards, in which these two insecticides must not be present in quantities greater than 0.05 mg/kg in honey and other bee products [69],[70].

Despite more than 30 years of global trade in this class of insecticides, there have been few studies aimed at determining them in brazilian honey. The research by Júnior et al. presents the determination of several pesticides, including imidacloprid, in honey produced by *Apis Mellifera* from canola flowers sown in the state of Rio Grande do Sul; Of 26 samples, nine showed the presence of neonicotinoid [71].

Ligor et al. sampled honey from several countries to determine pesticides [72]. They detected a high concentration of acetamiprid in the honey sample from Brazil. Although in most samples the detected levels of insecticides were not higher than those established by legislation for human ingestion, they nevertheless represent a risk to the health of bees and other pollinators [72].

In the study by Cham et al. [25], they pointed out the main routes of exposure of bees to pesticides and placed risk assessment as gaps to be examined, highlighting the demand for more research to adequately evaluate the toxic effects of pesticides on stingless bees and the determination of these substances in honey.

Marcolin et al. emphasized the importance of monitoring these contaminants to ensure food safety and protect consumer health. The research results demonstrated that honey from *Meliponinae* and *Apis mellifera* , even though distinct in their characteristics, pesticide residues were detected in some samples [1].

Few studies are published on the presence of neonicotinoids in brazilian honeys, especially honeys from stingless bees, which may demonstrate a lack of knowledge, and even encouragement, considering such a relevant topic. A consequence of this can be reflected in the scarcity of brazilian legislation on bee products.

V. Conclusions And Future Perspectives

Neonicotinoids, despite their initial advantages compared to traditional pesticides, present serious risks to both human health and environmental sustainability. Frequent and intensified exposure to these insecticides has caused significant adverse impacts, including contamination of honey and mortality of bees, which are crucial pollinators. These toxic effects are not just limited to bees, but also affect other non-target organisms such as humans, resulting in a range of health problems. Implementing strict regulations and more sustainable agricultural practices is essential to mitigate these risks and protect public health and biodiversity.

Finally, there is still little research on the contamination of brazilian honeys by neonicotinoids, especially from stingless bees. It is important to highlight the urgent need for continuous monitoring and in-depth studies on the incidence and effects of neonicotinoids in the environment. The adoption of sustainable solutions, including alternatives to neonicotinoids and the review of food safety legislation, is essential to guarantee the quality of brazilian honey, ensuring the health of those who consume it and the protection of the bee populations that produce it.

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