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Aflatoxins, Dairy Products Contamination in the Incidence and Development of Diseases in Children Population – A Short Systematic Review

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Authors' contributions

The brief systematic review study was carried out in collaboration among all authors. The authors FJMR, AMJB, VAN and EMR wrote the first draft of the manuscript. The authors FJMR and DGA collected information about the data on the main online platforms. The authors FJMR and EMR finalized the statistical information. All authors read and approved the final manuscript.

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ABSTRACT

Aims: This study aimed to characterize a profile according to a systematic review when addressing the acute effects and side effects on child health and the importance of preventive measures for controlling food in the presence of aflatoxins and mycotoxins.

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Methods: The method used was a systematic review. We conducted a systematic review of the SCOPUS, PUBMED, COCHRANE databases to identify all potential publications between the years 2005 and 2018. At the same time, short and extended abstracts were excluded. The language of the studies was in English and Portuguese. After this process, the selected articles were examined and the data extracted for analysis were 05 articles.
Results: The initial search resulted in 289 randomized experimental articles. the presence of liver cancer is represented as the primary effect of chronic toxicity related to high dose intake in an ordinary matter. The aflatoxins B1 promotes the formation of hepatocellular carcinoma and it can occur with lower doses than the standard established of 30 µg/kg.
Conclusion: This systematic review shows the need for food control regarding aflatoxins contamination, especially food targeting children, once the health damages can occur in both acute and chronic exposures, bringing growth and development impairment due to immune system disorders and frequent infections.

Keywords: Aflatoxin; aflatoxicosis; mycotoxins; incidence; child.

1. INTRODUCTION

It is possible to observe, in the past 30 years, that several fungi produce toxic metabolites known as mycotoxins, that develop during food storage [1-3]. Usually, mycotoxins contamination occurs repeated times in food products, leading to the development of immune system illnesses, especially regarding food consumption, as such, dairy products [4,5]. Besides, aflatoxins (AF) comprise a group of proximate to 20 carcinogenic secondary metabolites, which are metabolized by the "*Aspergillus flavus* and *Aspergillus parasiticus*" species in aliments [6], such as peanuts, corn grains. Cereals and animal feed that is consumed in the human diet [7]. The aflatoxins B1 (AFB1) [6], aflatoxinsB2 (AFB2), aflatoxinsG1 (AFG1) and aflatoxinsG2 (AFG2) are found more often as a direct food contaminant [8,9,10]. Aflatoxins investigation is necessary due to its toxicologic relevance and its relationship with the development of food-related ailments in Brazil and worldwide [11,5]. Among the aflatoxins cited above, the one with the higher carcinogenic potential to the liver in mammals is the aflatoxins B1 [7,10], classified by the International Agency of Research regarding cancer as a Group 1 carcinogenic agent [10]. The contamination with aflatoxins is a world health issue [2,12], especially in Brazil [5], where the aflatoxins contamination is related to 40% of the diseases associated with contaminated food [11,13,14]. The prolonged exposure to aflatoxins may be associated with diverse side effects on health [4], like the dilation of peripheral blood vases, hypotension, hives, immunity loss, and promotion of some kinds of cancer growth, mainly hepatocellular carcinoma [14,15,16].

In this way, the Food and Agriculture Organization of the United Nations (FAO) affirms that, based on the world epidemiologic status, around 25% of the food crops can be affected by mycotoxins each year, mostly from dairy products [9,7]. The aflatoxins contamination in Brazil happens principally in the states with the milk industry and in 2018 dairy production was around 24.450 million liters, with a large part directed to the dairy products industry [1,8,11].

Some Brazilian states such as Minas Gerais, Rio Grande do Sul, Paraná, São Paulo, Santa Catarina, and Goiás held 84% of Brazil's national dairy production in the year of 2018 [12], with Minas Gerais alone being responsible for 24.8% for the nationwide output. In Brazil, the National Health Surveillance Agency (ANVISA) conducts dairy surveillance [5], which follows the international recommendations set by the European Union (EU) for daily acceptable upper levels [11], of 3,5 ng/day per person of aflatoxins in Latin America, once this compound group belongs to human carcinogenic Group 1 [11,17].

This study aimed to characterize a profile according to a systematic review when addressing the acute effects and side effects on child health and the importance of preventive measures for controlling food in the presence of aflatoxins and mycotoxins.

2. METHODS

We performed a systematic review when searching for data in the SCOPUS, PUBMED, COCHRANE and PubMed databases to identify all publications with the potential to be included in this study between the years 2005 and 2018. Two sets of commands were used: the first

Table 1. Identification and selection for a short systematic review

Authors	Article identification	Year
Jovita MC, Michael NR, Shona W, David WD, Joseph KM, Kimani G, Christopher PW, Yun YG. Aflatoxin exposure is inversely associated with IGF1 and IGFBP3 levels in vitro and in Kenyan school children. Mol. Nutr Food Res. v.59. p.574–581. 2015.	Article 1 (A1)	2015
Oliveira CAF, Rosmaninho J, Rosim R. Aflatoxin M1 and Cyclopiazonic acid in fluid milk traded in São Paulo, Brazil. Food Additives and Contaminants. v. 23. n. 2. p. 196-201. 2006.	Article 2 (A2)	2006
Sacramento TR. Importância da Contaminação de Alimentos por Aflatoxinas para a Incidência de Cancer Hepático. Revista Ciências Exatas e Naturais. v.18. n.1. Jan/Jun. 2016.	Article 3 (A3)	2016
Santilia ABN, Camargo, Nunesa SR, Gloria EM, Machado PF, Casso LD, Santos CT, Domingues MAC. Aflatoxin M1 in raw milk from different regions of São Paulo state – Brazil. Food Additives & Contaminants: Part B. v.8. n.3. p.207–214. 2015.	Article 4 (A4)	2015
Kata K, Paolo B, Andrea S, Federica G, Silvia P, Vittorio Z, Alessandra C, Zsuzsa F, Árpád A. An effective self-control strategy for the reduction of aflatoxin M1 content in milk and to decrease the exposure of consumers. Food Additives and Contaminants. Part A. 2016.	Article 5 (A5)	2016

searched for terms related to exposure to interest [aflatoxin, mycotoxin aflatoxicosis, incidence, disease and child]; in the second command, we look for words related to the primary outcome of interest [cancer, neoplasia, seizure, mutagenic and teratogenic]. The combination to perform the search on each data platform occurred by adding the Boolean operators "OR", "AND" and "AND NOT". The criteria for the articles to be included in this systematic review were, in this case, all studies carried out a randomized clinical trial with humans, with results on the effects of aflatoxin on the health of children in dairy products. and studies such as short and extended abstracts or doctoral theses or master's dissertations were excluded. The studies included were in Portuguese and English. The selection process of the articles to be included was in two stages, that is, in the first stage the two independent researchers read the title and the summary of the articles in order to select the study to form the basis of the research. Articles that did not contain a summary and without adequate information were excluded from this systematic review. All disagreements were directed to a third reviewer. After this process, the selected articles were examined and the data extracted for analysis (Table 1).

Table 1 shows the articles selected, naming the authors with the respective publication year used in the systematic review.

Fig. 1 represents the process selection flow to include in the systematic review. The initial search resulted in 289 randomized experimental articles (Fig. 1). After refining the results, only five articles complied with the inclusion criteria and therefore used in the systematic review (Fig. 1).

3. RESULTS AND DISCUSSION

3.1 Critical Analysis of the Impact Caused by Micotoxin Contaminated Dairy Products in Children Population

Aflatoxins: The aflatoxins are mycotoxins produced by the fungi *Aspergillus flavus* and *Aspergillus parasiticus* [14]. The fungus from the genera *Aspergillus* is classified as a *Deuteromycotina*, with the presence of mycelium, septa hypha with asexual reproduction, being defined by the different terminal shapes in the structure known as conidiophores [17]. The mycotoxin has been studied mainly due to the mutagenic and carcinogenic activities [6,13]. Animals show different degrees of toxic effects; where in the same species, it is possible to verify a dose-response according to breed, gender, age, and other environmental factors [7,18]. The aflatoxins B1 belongs to the substituted coumarins group and has an anticoagulant factor in several animal species [11,19].

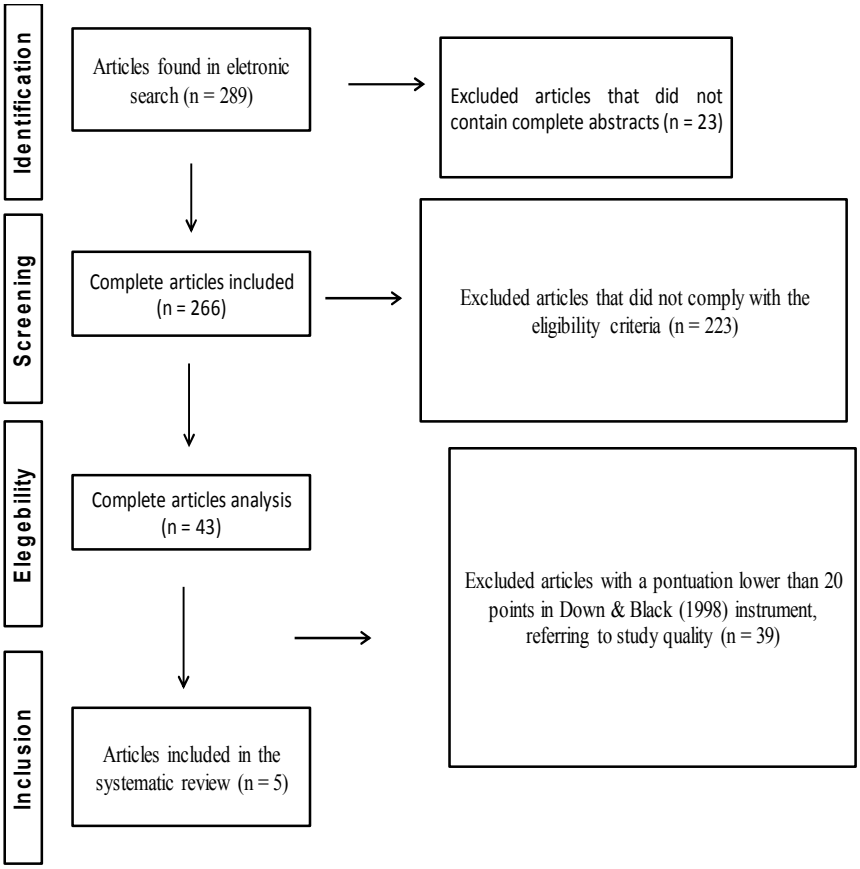

Fig. 1. Selection flow process to the inclusion of articles in the systematic review

The aflatoxins B1 has no color, no smell and it is soluble in organic solvents such as methanol and ethanol, it is resistant to the high intensity of light, to the cold and the heat; and usually does not alter the flavor of foods, being degraded only in the liver metabolism [20]. Although the aflatoxins can resist temperatures over 100°C, they are not stable to the ultraviolet light [1,20].

The aflatoxin M1 is identified as the principal metabolite of AFB1 in animals, with excretion in the milk and urine of dairy cows and other mammal's species that consumed food contaminated with aflatoxins [8]. The chronic effect, manifested by the liver carcinoma is some worry [9,17].

Aflatoxins considered natural substances that may lead to cancer [14,17,20-22]. Due to its essential correlation to human health, 99 countries established acceptable upper limits to its content in food, such as dairy [17,18]. The presence of aflatoxins in food for children's consumption is associated with adverse acute and chronic side effects, with economic and public health relevance [22]. The results in the health status can worsen according to exposure time, dosage, diet, nutritional status, gender, and age of the individual [21] in Fig. 2 presents the chemical structure of aflatoxins.

Among the aflatoxins, the aflatoxins B1 has the highest toxigenic potential, followed by the aflatoxins G1, aflatoxins B2, and aflatoxins G2 [5,22], once it has carcinogenic, teratogenic, and mutagenic properties [22]. The liver is the primary target organ to these compounds, where even a short exposure will produce necrosis and lipidic degeneration, with this condition named aflatoxicosis [14]. Even low levels of these mycotoxins, with a certain frequency and long exposure may result in liver carcinoma [23]. It can be observed in Fig. 2 that the structures are similar and belong to the difuran-coumarins family, differing in a double bond and a ring of 5 or 6 carbons, including oxygen. They are

chemically stable and resistant to regular cooking degrading procedures [22].

Mycotoxins: Mycotoxins are found in all planet regions, mostly in tropical and subtropical weather areas [23], where their development is favored by humidity and temperature [18]. The production of mycotoxins thrives when food is stored under inadequate conditions, such as high humidity and elevated temperature, which are the ideal conditions for fungi development [14,17]. In this way, mycotoxin contamination in food can vary according to weather, processing method and production, and storage conditions [17,23].

The type of food is a factor related to food contamination process [22], once some food is more susceptible as a substrate than others for fungi growth [20]. According to scientific evidence, knowing food quality is of great utility to the problem exposure and also provides the development of methods as preventive measures applied in public health [4,15,24], once it would be possible to know and avoid said foods [15].

In this matter, the European Union introduced measures to minimize the presence of aflatoxins in several foods and the Regulation (CE) number 1881/2006 of Official Journal of the European Union**,** from December 19, emphasizes the aflatoxins total content limitation in food (sum of aflatoxins B1, B2, G1, and G2) [5], as well as the specific amount of aflatoxin B1 in Brazilian territory in the ANVISA resolution RDC 07/2011 [5].

Exogenous intoxication with aflatoxin: The aflatoxin intoxication is a mycotoxicosis that may lead to human organism impairment during development, affecting the organism functions and favoring the growth of tumors with lethal characteristics [21,25]. The aflatoxins are considered highly carcinogenic in the human species, and the liver is the primary target of aflatoxins B1 [26,25,27]. Some countries as Uganda, Taiwan, Thailand, India, and Kenya reported the death of some individual due to the ingestion of lethal doses of aflatoxins, despite there is no consensus regarding which could be a deadly dosage establish for humans [9,2,22].

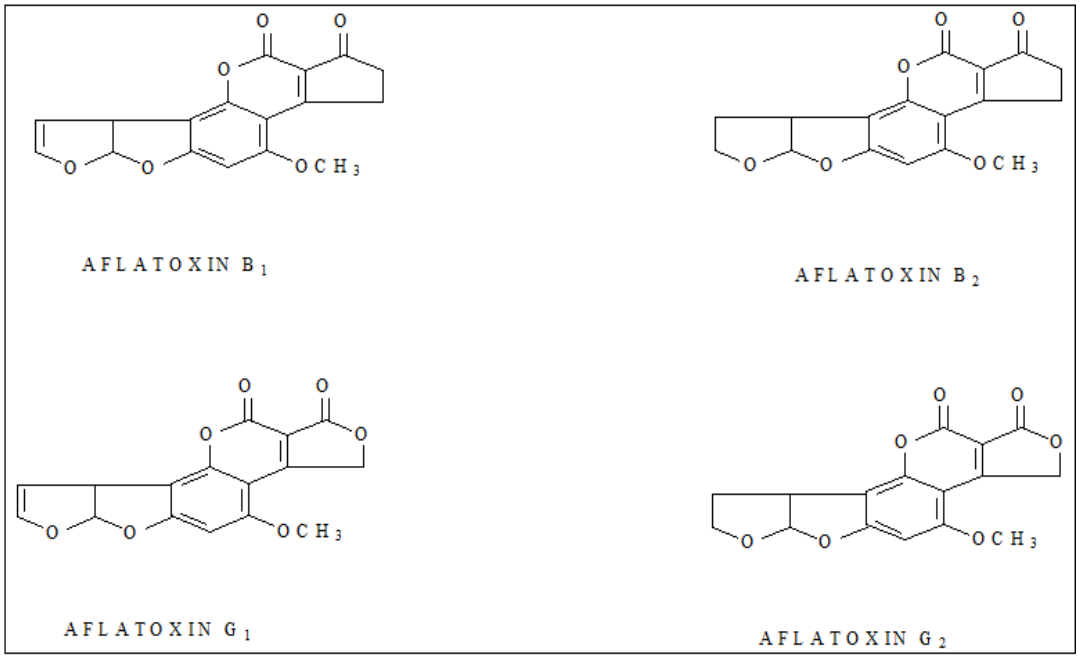

Fig. 2. Aflatoxins chemical structure

A- Aflatoxin B1 (AFB1) - (2.3. 6a á 9a á-Tetrahydro- 4-Metoxyciclopent (C) Furo (3',2': 4,5) Furo (2.3-h) (I) Benzopyran-1.11-Dione; B) Aflatoxin B2 (AFB2) -2.3. 6a, 8, 9a á--hexahydro-4-methoxy-cyclopent a (c) furo (3',2':4,5) furo (2.3-h) (I) benzopyran-1,11-dione;C) Aflatoxin G1 (AFG1) 3,4,7a,10a-tetrahydro-5-methoxy-1H,12H-furo(3',2':4,5)furo(2,3-h)pyrano(3,4-c)chromene-1,12-dione;D) Aflatoxin G2 (AFG2) 3,4,7a,9,10,10a-hexahydro-5-methoxy-1H,12H-furo[3',2':4,5]furo[2,3-h]pyrano[3,4-c]chromene-1,12-dione

Cancer development is related to two distinct phases when approaching experimental research, namely cancer start, and cancer promotion [15,22]. In cancer start, it is verified a mutagenic change response in the cell, and cancer promotion is directly related to the phenotypic expression of the modifications that occurred in the first phase of cancer development [6,21].

Usually, the aflatoxins B1 is transformed into aflatoxicol [23], known as the toxic metabolic reservoir of aflatoxins B1 [27]. The aflatoxins oxidates and becomes a radical of high covalence, so it is possible to determine its binding to nucleic acids [4], resulting in genetic altering, characterizing the carcinogenic action [15]. The definition of aflatoxicol is a carcinogenic element, as such aflatoxin B1, however, less mutagenic, and being able to order DNA lines in the same way as aflatoxins B1 [3].

The presence of aflatoxicol in the carcinogenesis is evidenced by the tumor suppressor gene p5, known as the "Genoma Keeper," which plays a major role in the control, once it is triggered in response to cellular damage signals provoked by viral exposure, as in the viruses E1B, PPV16, HPV 18, and aflatoxins [3,22].

The mutagenic process occurs in the G1 cell division [3], before the genic duplication with the finality of DNA repair. When there is cell damage that is not repaired, the cell will suffer apoptosis [22]. If the p53 gene mutates, the damaged DNA cells will give rise to a defective and malignant clone [4,22,27]. Patients with hepatocellular carcinoma exposed to an elevated aflatoxins concentration in food with a high transversion prevalence [AGG→AGT (Arg→Ser)] that usually happens in the third codon base 249 from the gene p53 (mutation 249ser) [17,20,23].

The knowledge regarding the mutagenic process enabled to develop biomarkers mechanisms, as such, biotransformation products and macromolecules adducts. The adducts AFB-N7-guanine and AFB-albumin are known biomarkers and often used in epidemiologic studies to assess the exposure to the Aflatoxins B1 [22], with diagnosis importance, once they are direct products of the damage caused to a macromolecular cellular critical target [21,22]. Typically, the AFB-N7-guanine adducts are a product of the binding of the aflatoxin-exo-8,9-epoxide, a highly active Aflatoxins B1 metabolite, with the liver cells DNA, and it is always excreted via urine [20,22].

This binding complex blocks protein synthesis and interferes with the production of enzymes that are necessary to energy metabolism and fat mobilization [21,22,23]. The enzyme amount reduction results in the minimized formation of structural proteins, the malformation on antibodies, decreased fat digestion, and incomplete synthesis of clotting factors [17].

The lack of the formation of the lipid-accepting protein in the liver promotes liver steatosis, and the diminution of cellulose digestion, the reduction in the volatile fatty acid formation, and the proteolysis inhibition result in a low feed conversion [22]. The clinical signs of acute aflatoxicosis in experimental studies with swine initiate 6 hours after ingestion, with severe depression, in appetence, and blood in the stool [21,22], muscle tremors, motor in coordination with fever (up to 41°C), and it can lead to death in between 12-24 hours [22].

The intoxication or their toxic effects in health can happen in an acute or chronic matter, mostly influenced by the dose and duration of the exposure [22]. In the subacute intoxications, the clinical signs are slower, presented by bristly hair, low appetite, lethargy, and depression [22,27]. Some animals can show jaundice, dehydration, and malnutrition, with red areas in the skin, with a progressive weight loss [14]. Chronic intoxication presents itself with a reduction in weight gain and feeds conversion, in appetence, general bad appearance, and sometimes diarrhea [4].

The aflatoxins B1 can cause severe liver damage, including hemorrhagic necrosis, fatty infiltration in the liver, and biliary duct proliferation [15]. The acute effects of AFB1 among species show that a variation up to 10-fold in the susceptibility and that no specie can be considered entirely resistant to AFB1 liver injury induction [24].

Experiment studies in children for aflatoxin carcinogenesis: The Table 2 presents the relationship between the average aflatoxin and mycotoxins contaminated milk and dairy intake frequency in the analyzed studies with carcinogenic results.

The principal negative effect was the high presence of aflatoxins in milk and dairy in the

included studies (Table 2), which as related to AFB1 aflatoxin chronic toxicity (Table 2) [3,4, 14,22]. The aflatoxins B1 induces hepatocellular carcinoma even when ingested in low quantities (Table 3) [3], so, according to scientific evidence [13] the higher the aflatoxins content in milk, greater the risk for it to be a potent natural liver carcinogenic in children, according to environmental characteristics [3,23], such as exposure time, dose, diet, nutrition status, gender and age of each individual [22].

Generally, the liver is the primary target of tumor development, but it can occur tumor development in secondary organs such as the pancreas and intestine. These data are verified in studies that determined food contamination with aflatoxin (Table 2) [4,15,22].

The results obtained in this systematic review are in agreement with other epidemiologic studies and emphasizes that mycotoxins human exposure happens mainly by the ingestion of contaminated dairy foods [3,4]. The presence of mycotoxins in milk and dairy products used by children entails concerns about infant health [3,4,22] once these products are often the only source of food in children and the continuous exposure, even in low doses may have as an effect the liver cancer [3,4,22].

Considering the high incidence of liver cancer in Brazil, it is possible to demonstrate that human exposure to mycotoxins in contaminated food is a worldwide health concern as a negative indicator [4,5]. So, Brazil is adopting strict limits in mycotoxin legislation in food, depict in RDC n 07 from February 18, 2011 [3,5]. The ANVISA establishment sets tolerable upper limits for aflatoxins B1, B2, G1, and G2 in infant formulas of 1 µg/kg [5].

In Table 3, we show the relationship between the aflatoxin B1 (AFB1), excluded other causes and liver cancer incidence.

In Table 3, the presence of liver cancer is represented as the primary effect of chronic toxicity related to high dose intake in an ordinary matter. The aflatoxins B1 promotes the formation of hepatocellular carcinoma [3,4,21,22] and it can occur with lower doses than the standard established of 30 µg/kg [13].

Elevated levels of aflatoxins B1 are present in milk and dairy products, according to the review conducted [11,14,23]. These high levels of aflatoxins B1 may happen due to the dilution factor of samples, where samples with higher contaminated mycotoxin levels are blended with other samples from farms with low contamination levels to produce one batch of milk [13,22,27]. In this way, the need for a better milk quality selection and dairy production is imperative once this dilution of high contaminated milk can bring future hazards in public health (Table 3) [4,22]. The hepatoma induction dose is between 10 to 30 µg/kg of aflatoxins B1 in the daily diet. [3,4,22]. The studies considered in this research are prone to liver cancer induction due to their elevated content and regular milk and dairy product intake [4,15,22,27].

The grand endemic incidence of liver cancer in the studied areas of dairy production has hindered the scientific corroboration of aflatoxins role in liver cancer in areas with an elevated HBV infection [4,25,22]. However, we found that in some Brazilian regions, the relationship and mortality from liver cancer and the intake of aflatoxins are contrary to the prevalence of patients that carry the surface antigen for hepatitis, which is strongly related to liver cancer (Table 3) [4,23,27]. Despite the Brazilian legislation to prevent complications regarding the high exposure to aflatoxins B1, the presence of aflatoxins is commonly found in the dairy industry in several states [14].

The contamination of dairy products by mycotoxins takes on relevance to public health, once children are one of the major milk consumers in Brazil [13]. It is critical to note that the aflatoxins B1 is highly carcinogenic and mutagenic, showing a genotoxic activity of great consequence and, therefore, a health hazard due to its possible accumulation in the organism and DNA binding [13,22,28].

The ingestion of milk and dairy products have the potential to introduce the aflatoxins B1 in the human diet, and the consumption of these products by children occur in a high amount [28, 29]. Children are a susceptible population to the mycotoxin infections side effects (Tables 2 and 3) [3] once they have smaller body weight, higher metabolic rate, lower detoxification capacity, and the incomplete development of some organs and tissues, such as the central nervous system [3,4,5,17,23].

Table 2. Probably aflatoxin and mycotoxins contaminated milk and dairy average consumption in the analyzed studies with carcinogenic results

Main substracts	Main toxins			
	Aflatoxin		Mycotoxin	
	N	%	n	%
Pasteurized Milk (A1)	09	01	03	0.3
Pasteurized Milk (A2)	300	35.7	335	39.9
Pasteurized Milk (A3)	11	1.3	04	4.7
Pasteurized Milk (A4)	03	0.3	02	0.2
Yogurt (A5)	97	11.5	75	8.9
Total	**839**			

Table 3. Relationship between aflatoxin B1 (AFB1), excluded other causes and liver cancer incidence

Article	AFB1 intake(µg/kg/day)	Hepatocellular cancer incidence (100.000/hab)
A 1	86,8	4,2
A 2	35,7	2,5
A 3	29,6	5,9
A 4	39,5	5,0
A 5	36,4	4,5

4. CONCLUSIONS

The results presented in this systematic review showed that due to the high consumption of milk and derivatives such as yogurt, it was possible to prove an increased exposure to aflatoxins B1 and other mycotoxins, since the samples used for this analysis exceeded the limits established by the Brazilian normative legislation limit dose. This systematic review shows the need for food control in relation to contamination by aflatoxins and mycotoxins, especially in children's diets directed to foods derived from milk, since damage to health can occur both in relation to overdose due to acute and chronic exposures, and these exposures bring intoxications with damage to child growth and development mainly related to disorders of the immune system and the presence of frequent infections due to recurrent intestinal changes caused by aflatoxin toxicity. This systematic review concludes that there is a need to conduct other randomized studies related to toxicity, mutagenesis and major immunological changes related to aflatoxins and mycotoxins.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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