

Prevalences of aflatoxin (AFM1) in raw milk: A review

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Abstract. Dairy and dairy products are particularly susceptible to AFM1 contamination, which is thought to pose a number of health risks to consumers. As a result, dairy and dairy products have the most clearly shown potential for the human diet to contain aflatoxin residues. Children, particularly infants, may be more vulnerable and sensitive to AFM1 exposure than adults, and their capacity for carcinogen biotransformation is slower than grownups. The severity of AFM1 in dairy can be significantly reduced by implementing outsourced control strategies like providing livestock with high-quality feed. Onsite monitoring of the occurrence of AFM1 throughout the raw milk supply chain, from the udder of the cow to the factory and to the consumer, is warranted. Likewise, the good control condition framework for AFB1 rations defilement is critical to significant in the event of the nation considering the environmental change situations. There have been some investigations of milk's AFM1 content. Still, the current focus must be creating an effective and sensitive method for determining its presence in dairy and dairy products. This review aimed to assess and review the prevalence of aflatoxin M1 in human-useable raw milk and its potential obstacles in the future food and rations formulations companies.

1 Introduction

Dairy cows are a main source of human being food, especially through the production of dairy and dairy products [1], and they contribute significantly to the global supply of human nutrition. Besides, they give significant wellsprings of nutritious eating regimens, such as protein, calcium, phosphorus, iodine, riboflavin, and B12 constituents [2]. Milk is a good balance, and it seems to be a completely nutritious food that contains a variety of essential

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macronutrients like proteins. These fatty acids, lactose, minerals, antioxidants, and vitamins are basic for human life's growth, development, and safety, particularly in neonates, children, and the elderly [3]. As a result, worldwide perceptions of an increase in this nutritious product's consumption [4-6]. As reported by the Food and Agricultural Organization (FAO), the average annual units consumed of milk by individuals worldwide is approximately 100 kg. However, this number can vary significantly across nations (10–300 kg) [7]. Therefore, it is important to remember that aflatoxin m1 (AFM1) is a heat-resistant material [8]. Moreover, the use of this food has increased worldwide [4-6]. However, the dairy production chain, especially in many developing countries, still faces numerous challenges in meeting consumer demands and laws regarding the safety and hygiene of dairy products [9, 10]. Cleaning milk and dairy products is therefore essential for both producers and consumers. In addition, food hygiene and well-cleaning packages for all products containing animal substances are causing concern in several nations, primarily from a public health standpoint [11]. This entails controlling adulterants and eliminating contamination concentrations, naturally occurring toxins, and other components that can potentially infect humans with foodborne illnesses. Dairy and dairy products require clean, well-controlling environments to maintain general health and provide healthy food for consumers. According to Saitanu [9], it is necessary for the safety of the public's health as well as the products' satisfactory shelf life to produce dairy substances that are lower in pollution levels. Right now, any food product, especially dairy substances, that have genuine cleanliness and acceptable quality degrees are in higher levels of client needs. Consumer health risks from dairy products typically fall into three categories: chemical, physical, and microbiological [12]. As cited by Bahrami et al. [4], about 25% of food materials are reportedly contaminated yearly by secondary harmful compounds produced by fungus or mycotoxins. About 300 kinds of mycotoxins, 90% are aflatoxins. At some stages of harvest and post-harvest processing, a large variety of agricultural foodstuffs, including cottonseeds, peanuts, cereal grains, and dried fruits, can make aflatoxins [13-16]. In temperate (25–30 °C) and wet (80–90%) climate zones, they are mostly produced by a range of toxicogenic filamentous fungi, such as *Aspergillus flavus* and *Aspergillus parasiticus*, with *Aspergillus nomius* producing them to a lesser extent [3, 17-19]. Because even a low concentration of AFs hurts people and livestock [20], their identification and quantification present a significant obstacle to food safety assurance. In the manufacturing of dairy products, it is impossible to be reduced by subject to high heat techniques like pasteurization, sterilization, and ultra-high temperature (UHT) techniques once it has been present in raw milk [14]. AFM1 limit level or maximum level (ML) in dairy products has been established by a number of countries, it differs significantly depending on the economic status and development of the nation. This is due to the severe toxicity of AFM1, its status not to be affected by heat, and the elevate strong market for dairy products. In this regard, maximum limits for AFM1 in liquid milk were created by the US Food and Drug Administration and the European Union (EU) at 0.05 µg/ kg and 0.5 µg/ kg, respectively [14]. Maximum concentrations for aflatoxin B1 (AFB1) have been at 20µg/ kg for all rations, 10 µg/kg for final rations, and 5 µg/kg for dairy animals' final rations. According to Khaneghah et al. [16], twenty kinds of aflatoxins have been recognized. The AFB1 is the more distributed through feed and the most important type of aflatoxins (B1, B2, G1, and G2), and it has the highest carcinogenicity of all the A.F.s prevalence in most food and feed commodities [16]. Consumption of rations contaminated with AFB1 by dairy cow bring about lactating animals using this poison to responsive epoxide transitional, more polar metabolite or 4-monohydroxylated structure in their liver by cytochrome P450 oxidase and hence discharge it out in Milk [18, 21]. It has been reported that between 0.3 and 6.2% of the AFB1 in animal rations changed into AFM1, which appears in milk 12 hours after the first intake and disappears 72 hours after the last intake. Several nutritional factors, such as the kind of feed, the quantity consumed, the rate at which food is digested, and the animal's

physiological factors vis, impact the transfer of AFB1 to AFM1 (carryover). Breed, health, liver's ability to detoxify, duration of lactation, milk production, and ecological elements like the season, weather, place, and region's growth levels [17, 22-24]. AFM1 pollution is most common in dairy and derived products, and it can have negative effects such as teratogenicity, carcinogenicity, neurotoxicity, cytotoxicity, and immunosuppressive effects [3, 19, 21, 25, 26]. As a result, AFM1 was assigned to category 1 by the International Agency for Research on Cancer (IARC) (absolutely human carcinogen compounds) in (2002). Pasteurization and ultrahigh temperature (UHT) processing of milk have not been associated with any significant changes in the concentration of AFM1 [6, 23]. The content of AFM1 does not appear to be affected by freezing contaminated dairy and dairy substances for several months [27, 28]. The state main variables that could affect AFM1 contamination in milk include environmental status, housing, and feeding regime, in addition to cleaning and good practices of food manufacturers [27, 29]. One of the excellent ways to decrease dairy cow exposure to mycotoxin is to prevent mold growth in feed. Decreasing AFB1 contamination in animal materials feed is the most effective strategy for preventing AFM1 contamination and its prevalence in milk and milk substances [30]. The methods of intake of toxins that are effective in dispensing with mycotoxins or lessen the seriousness of their belongings might be useful [31]. The possible and Ideal features for the methods of Intake of toxins, which include physical, chemical, and biological techniques, subjected to products that are ready for dairy rations have been defined by the European Commission in Regulation 2015/786 [34]. Clay enterosorbents added to the rations of milking dairy cows have also been shown to promote mycotoxins' excretion and suppress or reduce AFB1 absorption [33]. Numerous reviews have discussed the presence of AFM1 in dairy and other dairy products, focusing on national and international occurrences for those in high-income and low-income nations [7, 34]. This review sought to evaluate and review the amount of aflatoxin M1 in raw milk that is fit for human consumption as well as its potential obstacles in the food and rations formulations company in the future.

2 Aflatoxin in milk and foods containing milk

Feeding mold metabolites (aflatoxins) made by small species of *Aspergillus parasiticus* and *Aspergillus flavus* causes aflatoxicosis. By increasing the actual protein requirement of dairy cows, AFB1 is the most potent cancer mediator of all aflatoxins.

Mycotoxins introduced into milk and milk-based foods are the primary cause of aflatoxins AFM1, which are hydroxylated of AFB1 and undergo bio-transformation in animal udder before being shed in milk during milking, is one of the various metabolites of aflatoxin B1 that naturally occur in feed [35]. Because of the higher vulnerability and significant levels of aflatoxin contamination of all feed commodities worldwide, groundnuts and maize are the primary sources of aflatoxin for cattle and humans [36]. Furthermore, Prandini et al. [27] proposed that maize and peanuts are the most common causes of dairy animals and people being subjected to aflatoxin. Because milk can biologically contain aflatoxin if animal feeds are contaminated with aflatoxin. As a result, this phenomenon is the most alarming delinquency of all time globally, as cow milk is the most valuable food source and is contaminated everywhere [37]. Nyaga [38], states that the milk shed in and around Addis Ababa is highly contaminated with aflatoxins.

Additionally, milk produced by dairy cows can exceed the conventional limit of 0.05 mg/L of aflatoxins from feeds with more than 5 mg/kg of AFB1. The finding also indicates that contamination of naut cake, primarily used as milking cow feedstuff AFB1, is one of the leading causes of aflatoxin in the rural regions in Addis Ababa's milk supply chain. In addition, as shown in Table 1 below, this variation is due to the unique circumstances of each country, which may influence the percentage of contamination and its levels.

Table 1. AFM1 incidence according to the country.

Country	Type of Milk	Range of AFM1	Reference
Algeria	fresh milk	0.096–0.557 $\mu\text{g L}^{-1}$	[42]
Chile	fresh milk	0.015 $\mu\text{g/kg}$	[43]
Croatia	fresh milk	0.001–0.124 $\mu\text{g L}^{-1}$	[25]
Italy	fresh milk	0.0072–0.0225 $\mu\text{g L}^{-1}$	[32]
Lebanon	fresh milk	0.011–0.440 $\mu\text{g L}^{-1}$	[44]
Pakistan	fresh milk	0.020–3.090 $\mu\text{g L}^{-1}$	[21]
Qatar	fresh milk	5.32–12.73 ng/L	[45]
Serbia	fresh milk	<0.005–1.10 $\mu\text{g L}^{-1}$	[46]
Sudan	fresh milk	0.05–0.1 $\mu\text{g/kg}$	[47]
Turkey	fresh milk	0.011–0.1 $\mu\text{g L}^{-1}$	[48]

3 Aflatoxins in commodities derived from contaminated feedstuff

According to Elzupir and Elhussein [44]. In their opinion, A comparison of various feeds revealed that Maize and groundnuts are tainted with AFB1. In contrast, yeast devoid of water, wheat bran, and corn grain have fewer contamination limits. Moreover, milking animals with drunk aflatoxin B1 defiled rations emitted aflatoxin M1 during milking [46]. Because the presence of significant levels of AFB1 in rations gives high levels of AFM1 contamination in dairy, there was enough quiet and essential relation between AFB1 and AFM1. AFM1 is shed out within 12 hours after ingesting rations contaminated with AFB1 [47].

Table 2. AFM1 incidence (ng/l) in raw milk according to the animal species.

Species	Range of AFMI	Reference
Buffalo	2.20 2.50	[8]
Camel	3.25 29.16	
Cow	77.65 80.32	
Ewe	55.65 86.65	
Goat	18.82 23.48	

Furthermore, Gizachew et al. [48], point out that a plausible link was found between milk containing aflatoxin M1 and the degree of AFB1 contamination in animal rations. According to the authors' findings, the average transfer rate of aflatoxin from lactating dairy cow rations to dairy and dairy substances is approximately 1%. Buffalo and cow milk had less and higher AFM1 concentrations in raw fresh milk, respectively (Table 2). Feeding habits can impact the amount of AFM1 a species produces. The other kinds of animals, like buffalo, are fed by

open grazing; in contrast, milking cows are put in housing farms and fed polluted materials rations or silages. According to Bahrami et al. [4], domestic animal feeding patterns substantially influence the elevated prevalence of AFM1 concentrations in dairy products.

4 Aflatoxins in dairy cow-based foods from contaminated milk

Mycotoxins M1 and M2 are derivatives of dairy aflatoxins, which are hydroxylated, heat-resistant metabolites produced by milking cows that ingested aflatoxin-contaminated feed [46, 49]. In dairy cattle, the ingested AFB1 is converted to AFM1, whereas the consumed AFB2 is converted to AFM2. The carryover rate is about 1-3 AFB1 and AFM1 [50]. Aflatoxin M1 is also the more necessary metabolite that different kinds of dairy excrete in their products [36]. Through hydroxylation at the terminal furan ring of the parent molecule, AFM1 is set during bioconversion in the udder of the milking cow using the liver CYP enzyme mechanism. AFM1 accounts for 95% of the AFs found in milk. Small amounts of substances, such as Aflatoxicol (AFL), M2 (AFM2), and (AFM4), are identified and determined to be of less significance to human health.

5 Effects and prevalence of aflatoxin in dairy

According to Wu and Khlangwiset [51]. Aflatoxin's occurrence, impact, severity, and character vary significantly depending on the prevalent materials, mold type, and ecological status [46, 51]. While *A. flavus* primarily makes aflatoxin B1 and B2 on corn, *Aspergillus parasiticus* makes all types of aflatoxin (AFG1, AFG2, AFB1, and AFB2). Three primary feedstuffs are used in milk production *Aspergillus* species frequently attack cottonseed, corn, and peanuts during growing, yield, loading, and storage [51]. In most cases, storage facilitates colonization; high humidity content, weak placed conditions, kernel damage, heat, and lack of healthy air exchange can all contribute to forming aflatoxin [52]. Additionally, the handling and storage procedures significantly impact Aflatoxin M1 dispersion and stability, as milk and milk-based foods require a variety of processes. Aflatoxin is more likely found in raw milk than in other dairy products such as cheese, yogurt, and skim milk, because of utilizing several physical, chemical, and biological methods used for each type of product [53]. As numerous authors suggested, cheese may contain aflatoxin for various reasons. The introduction of waste AFB1 from contaminated animal rations to dairy is the primary cause of AFM1 in raw fresh milk. The subsequent things here are the creation of AFB1, AFB2, AFG1, and AFG2 by fungi that engender on cheddar, albeit the moment measure of CHO doesn't establish appropriate climate and substrate. The third is the consumption of cheese, which contains aflatoxin M1 and is made from milk powder. In any case, a few creators detailed that expansions in AFM1 focus on cheddar as an element of cheddar assortment hardware to be reused to handle it, as well as the amount of water eliminated throughout [54, 55]. Specifically, hot conditions, adding enzymes, pH, and pressing time can all affect the degree of water excreted and the level of AFM1 in dairy products. Ability of animals to convert AFB1 to AFM1 different from species to another in addition to environment and management system (Figure 1).

Most animals affected by AFM1

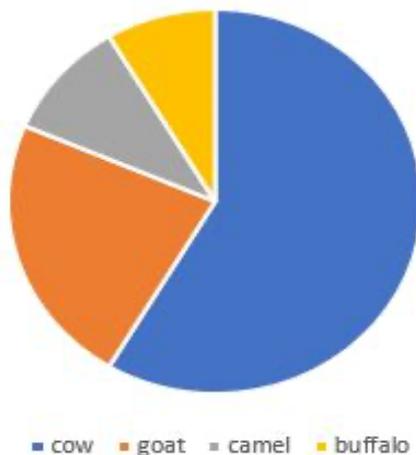


Fig. 1. Animals more vulnerable to AFM1.

6 Harmful farmer practices associated with aflatoxins

Aflatoxins have more factors associated with them, some of them in the field and others inside the farm. These factors include meteorological conditions, agricultural practices, livestock feeding systems, packaging methodologies, transportation logistics, and storage management. Aflatoxins can infiltrate the feed chain from the pre-harvest to the post-harvest phase. Inadequate harvest timing, insect activity, unfavorable storage conditions such as excessive moisture and heat in the barn, high moisture content in feed due to insufficient drying, and crop damage from environmental fluctuations like drought during harvest and heavy rainfall can result in feed contamination by aflatoxins [56]. The farmer's practice of some activities may increase the percentage of aflatoxins B1 in feed and thus aflatoxin M1 in milk. The contamination of the farm is the main reason for the growth of fungi, so it's essential to cure a sanitary cage. Moreover, feed and feedstuff are sometimes stored in inappropriate places with high humidity and poor ventilation, which is very suitable for *Aspergillus* species. So, it is essential to be clear and dry to avoid fungi multiplication.

On the other hand, the wastewater inside the farm causes an increase in humidity, which may lead to the growth of fungi. Hygienic environment and the storage location of food and feed commodities may affect the prevalence and concentration of aflatoxins in foods due to the proliferation of mycotoxins. The increase of aflatoxins during storage is associated with excessive storage practices and insufficient drying conditions for feed, alongside food supply frameworks and poor transportation. The incapacity to desiccate feed materials prior to storage is a significant component of the further development of mycotoxigenic organisms in crops. As usual, sometimes the feed was introduced to the animals without any processing and sometimes cut to particle size; The concentration of AFM1 in milk was elevated, presuming that the feed particle size deviated from the recommendation (the division retained on the upper screen exceeded 8%, indicating a surplus of coarse fiber in the diet). To clarify, during the months when particle size distribution was suboptimal, the cows exhibited a marked preference for smaller particles, resulting in a reduced retention time of feed in the rumen and consequently preventing ruminal microbes from degrading mycotoxins. The diminished perennial feed quality in the rumen may elucidate the increased carry-over rate [57]. Therefore, the feed particle size is crucial for the carryover of aflatoxin, and it is

essential to introduce the feed as it's without any process for cutting to small particle size. The kind of accessible commodities impacts the taking care of Feed managerial ideas and methodologies. Products susceptible to mycotoxigenic contamination, such concentrated feed, maize, cotton and sunflower seed cakes, wheat grain, peanut meal, and soybean, may not be difficult to promote. Simultaneously, maintaining fresh and verdant fodder, grass, and fields proves challenging. The contamination of feedstuff is a pervasive concern. In many nations, especially in South Asia, new feeds are more readily available throughout summer months than to cold ones. Consequently, reduced levels of AFM1 may be transmitted throughout the storage of feed ingredients [57]. More preventive measures concerning sanitary conditions ought to be executed to decrease Contamination with Aflatoxin in milk and dairy products. Despite increasing human demand for milk production, the elevated expenses related to milk and dairy products contribute to inadequate consumption in Africa, Asia, and China, where AFM1 levels are surpassing as far as possible [56].

7 Food safety and risk assessment of aflatoxin M1

Food safety risk assessment is defined for every population group, with an extraordinary consideration for those recognized as possibly more susceptible. Three standard-setting associations drive the One Health international utilization of wording for risk evaluation: The Codex Alimentarius Commission (CAC) corresponding to food safety, the World Organization for Animal Health (OIE) for animal health, and the International Plant Protection Convention (IPPC) for plant health, under the Settlement on the Use of Clean and Phytosanitary Measures (SPS Arrangement) of the World Exchange Association of which the European Association is a part. Guideline (EC) 178/2002, which lays out European Food Safety Authority (EFSA), contains meanings of various gamble-related general terms like those given by CAC. Although the European lawmaker doesn't mandate which of the three systems (and related phrasing) must be utilized, should the significant reason for threat assessment to serve as a global exchange guideline, the EFSA Scientific Committee inferred that specific consideration should be assumed that the standards of CAC, OIE, or IPPC are followed rigorously? EFSA Logical Boards ought to distinguish which explicit methodology is most valuable in managing their orders, perceiving that different risk analysis principles affect the phrasing utilized by various EFSA Scientific Panels [58]. In their turn, EFSA exercises could lead to events and refresh the scientific premise of fundamental OIE, IPPC, and CAC principles. The definition of a toxic peril in pecking order begins from the recognizable evidence of the effects on physical well-being on categories that may have better organic vulnerability, in addition to the connection within degree and seriousness of implications and admission degree. In equal, openness assessment should consider the degree of openness, the weakest food wares, and the most uncovered populace group(s), which may not be equivalent to the naturally vulnerable group or groups. Exact, exhaustive, and similar information on food utilization is necessary for survey hazards. AFM1 contamination of milk can be reduced but not completely eliminated by using good agricultural practices, various heat treatments, and dietary interventions with aflatoxin caps.

8 Effect of aflatoxins on human health

The symptoms of severe mycotoxin toxicity are typically caused by aflatoxins. Fluid retention, headaches, nausea, yellowing of the skin abdominal discomfort, abrupt liver failure, and, finally, passing away are among the adverse symptoms of aflatoxicosis [58]. First reported in Western India in 1974, the severe harm caused by exposure to significant nutritional amounts of AFs (2000–6000 µg/day) resulted in 106 loss of life, or 10% of the

total population. The outbreak occurred after corn that had been severely debased by *A. flavus* and contained up to 15 mg/kg of Afs [60]. Twenty of the 68 instances of aflatoxin infection that were reported in the United Republic of Tanzania in 2016 were fatal. The pandemic was thought to have been caused by local maize that had been contaminated with high levels of aflatoxins (10–51,100 µg/kg). Eight out of ten grain testing were also contaminated with high levels of fumonisins (945–12,630 µg/kg) in addition to aflatoxins [61]. In persistent situations, mycotoxins pose a variety of health risks to humans. The effects of mycotoxicosis on human health depend on a number of variables, including the age, weight, sexual orientation, food type and quantity, interaction with enticing experts, and the existence of various mycotoxin and bioactive material types. For instance, cancer, liver diseases, teratogenic reactions, and genetic abnormalities might result from small-scale exposure to aflatoxins through the mouth, respiratory system, or skin [62]. According to a recent survey, AFs and FBs are the most relevant mycotoxins, having detrimental effects on developing embryos and children. Although contact with FUMs increases the risk of neural tube abnormalities in newborns, contact to AFs throughout embryonic growth is linked to neonatal growth delays [63]. Breast milk (AFM1), child food kinds that contain mycotoxin-contaminated ingredients such as animal milk, rice, oats, and soybean protein, and child recipes are the main ways that newborns are exposed to mycotoxins [63]. According to studies, eating food tainted with AFs was linked to the establishment of liver cancer [62, 64].

Furthermore, when exposed to aflatoxins, people with hepatitis B and C—common diseases in China and Africa—had a greater chance of developing liver cancer than people without liver disease [65, 66]. According to estimates, 40% of the 155,000 instances of aflatoxin-induced liver cancer that occur each year occur in Africa (59,900 out of 155,000) [67]. In China, liver cancer is also one of the most common cancers with a high death rate. Furthermore, even at low doses, liver tumors and aflatoxin (AF) are known to have teratogenic and mutagenic effects on humans and animals, however many aspects of the systems of aflatoxin toxicity are still unclear [70, 69]. It has been shown that AFs are genetically harmful and mutagenic to bacteria. According to a few studies carried out in Ghana and Gambia, they can impair immune function and result in congenital impairments in children, hence reducing defense against infectious diseases like HIV and TB [70].

9 Strategies for increasing safety of food and feed supply chains

Significant efforts were made to ensure animal feed and food safety, protecting humans, livestock, and animal companions from mycotoxicosis. These efforts encompass the management of mold infection and growth in agricultural settings, prevention of mold and mycotoxin contamination during post-harvest processing, detoxification of contaminated products, and regulation of mycotoxin levels in natural ingredients and regulated goods. Nevertheless, not all methods or strategies can achieve sufficient control of mold and mycotoxins regardless of pre- or post-harvest stage. Coordinated administration procedures are frequently expected to lessen mycotoxin exposure. This methodology of preventing openness to mycotoxin targets guarantees that food sources have the least commonsense concentration, to achieve this, specific procedures in the fields of production, collection, storage, transit, marketing, handling, and regulation should be observed.

10 Aflatoxin's effects on the economy

Food-borne illness absenteeism from work and school, a decline in customer satisfaction with the product, and increased costs on past and unwell subsidized care health modeling are all consequences of food safety issues that significantly negatively impact the country's budget

[71]. In addition, deaths caused by aflatoxin contamination of food result in costs associated with treating food intoxication and purchasing medications, in addition to economic losses and expenditures for general care, workers, and animal practices, according to Boutrif [71]. According to reports, mycotoxins are found in approximately 20% of all foods produced worldwide annually, while aflatoxins have a more significant proportion than any other group. Charged with dairy and dairy products in addition to milking cow production include infection and cancer in dairy cattle, an elimination in dairy production and reproductive, and a decline in the immune system of dairy cows. With such large financial losses and public health hazards, it is imperative that aflatoxin be inhibited and frustrated in nursing animal feeds and animal-based food items [43]. Furthermore, Figure 2 shows conceptual framework of causes of prevalence of aflatoxin.

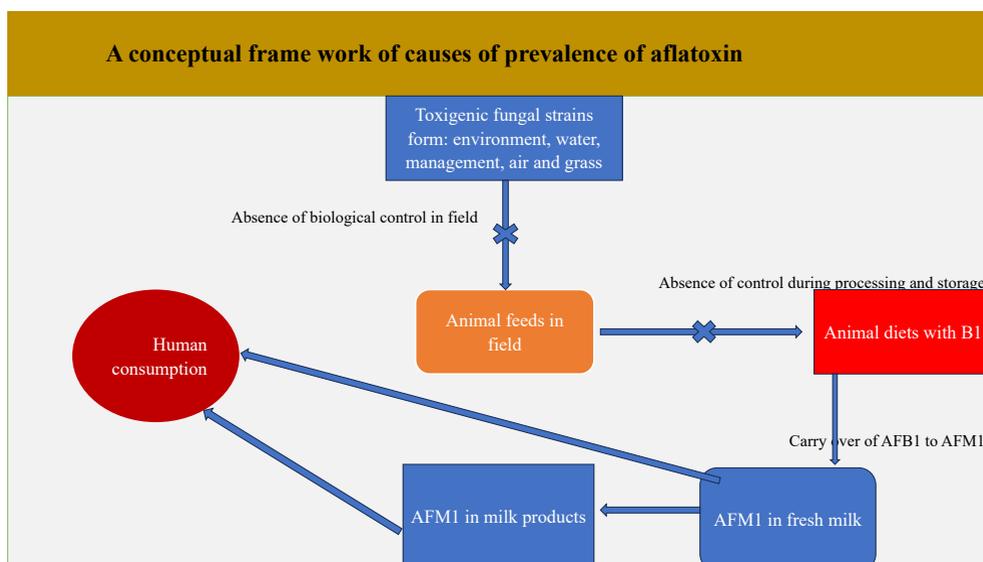


Fig. 2. A conceptual framework of causes of prevalence of aflatoxin.

11 Conclusion

In this review, cow milk had the highest AFM1 percentage in raw fresh milk. Therefore, a higher AFM1 percentage in raw milk indicates that the pasteurization technique will not destroy aflatoxin and limit concentrations to an ideal degree if raw milk is highly contaminated. The concentrations of AFM1 in raw fresh milk might be considerable reduced by implementing outsourced control strategies like providing livestock with high-quality feed. According to our review, onsite monitoring of the prevalence of AFM1 throughout the fresh milk supply chain, from udder of the cow to the factory and to the consumer, is warranted. Likewise, considering the environmental change situation, the excellent cleaning and control framework for AFB1 rations defilement is critical and significant in the nation.

Declaration

The authors declare that we conceptualized this review and collaborated in writing, revising, and made final manuscript.

Conflict of Interest

None.

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