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Research brief

Aflatoxin M1 Causes Minimal Global Cancer Risk

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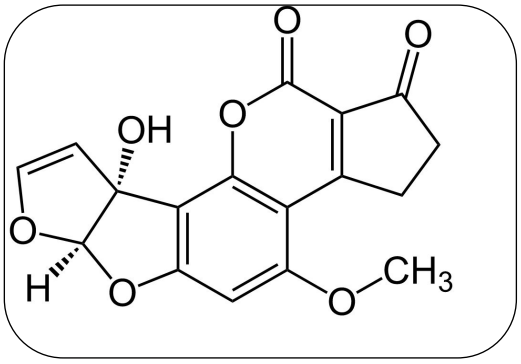

Model of aflatoxin M1
(credit: Dharminderhundal11 on Wikipedia)

A milk vendor in Nairobi, Kenya
(photo credit: ILRI/Shadrack Isingoma)

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Background

Aflatoxins are a group of chemicals produced by the fungi *Aspergillus flavus* and *A. parasiticus* that infect food crops such as maize and peanuts. AFB1, the most toxic of the aflatoxins, which is the form in most foods other than milk, causes liver cancer in humans and other animals. When dairy animals consume feed contaminated with AFB1, they secrete its metabolite, aflatoxin M1 (AFM1), in milk. Much less is known about the human health effects of AFM1, yet it is important to understand these effects, as dairy foods are an important dietary staple worldwide. From a policy standpoint, it is crucial to understand what risk AFM1 may truly pose, as many nations have enacted strict standards for AFM1 in dairy foods based on its perceived carcinogenicity, and these standards are currently impossible for some dairy producers to meet in certain countries. This results in milk being dumped, dairy producers losing business, and populations with low supplies of a critically needed animal-source food with unique and important nutritional benefits. For instance in 2013, various Balkan countries reported widespread milk contamination leading to dumping of milk and suspension of dairies (Andric et al. 2013; Balkan Insight, 2013; Bilandžić et al., 2015; Popovic et al., 2017). In Ethiopia, concerns emanating from misinterpretation of a publication revealing higher levels of AFM1 in Ethiopian milk than the EU threshold (Gizachew et al., 2016) led to social media postings that greatly reduced the demand for milk. This problem occurred even though values for most of the tested milk samples were acceptable based on US FDA guidelines. (Gizachew et al., 2016) and necessitated a government clarification and response (Shiferaw 2015; Alemayu, 2015).

This research brief presents a global cancer risk assessment for AFM1 in milk based on exposure data (levels of AFM1 in milk and consumption of liquid milk), an assessment of the carcinogenicity of AFM1, and a comparison of the risks of AFM1 in milk with the risks of AFB1 in other foods. It summarizes three research papers (Liu et al., 2010, Saha-Turna et al., 2021a, 2021b).

Key messages

- The risk of liver cancer from drinking milk contaminated with aflatoxin M1 is much lower than previously thought.
- There is no evidence for other serious health effects.
- International standards for AFM1 in milk are not risk-based.
- Dumping of milk because international standards for AFM1 are exceeded creates economic and nutritional risks that far outweigh the minimal cancer risk.

Exposure to AFM1 is much lower than exposure to AFB1 across the world

Human exposure to AFM1 and AFB1 were estimated using the same methodology that considered the concentration of the chemical in the food, the amount of food consumed, and the body weight. Data on exposure to both toxins in different regions of the world (Table 1) suggest that the exposure to AFM1 is on average *100-fold lower* than exposure to AFB1. Possible explanations are higher daily consumption of foods containing AFB1 (e.g., maize, peanuts) in many parts of the world, and by lower concentrations of AFM1 in dairy than AFB1 in other foods. Exposure to AFB1 in high-income

countries is at least 10 times lower than in low-and middle-income countries, while the difference for AFM1 exposures between high- and low-income countries is less pronounced.

Table 1. Average daily dose (ADD) of aflatoxin B1 (AFB1) and aflatoxin M1 (AFM1) in global regions

Region	ADD AFB1[#]	ADD AFM1[&]
Africa	10-180	0.02-0.8
North America	0.3-1	No data
Latin America	20-50	0.01-2.6
Eastern Mediterranean	10-80	0.1-1
Southeast Asia	30-100	0.03-0.6
Western Pacific	0.2-50	0-0.09
Europe	0-4	0-0.2

[#] Liu et al., 2010
[&] Saha Turna et al., 2021a

AFM1 may be carcinogenic, but the available evidence is not conclusive

AFM1 is classified as a *possible human carcinogen* (Group 2B) by the International Agency for Research on Cancer. By contrast, "naturally occurring mixes of aflatoxins" (as a group, of which AFB1 is the most toxic) are classified as *known human carcinogens* (Group 1) (IARC, 1993; 2018). AFB1 has been known for over 60 years to cause hepatocellular carcinoma (HCC), or liver cancer. There is much less evidence for AFM1's carcinogenicity. Two main animal studies conducted in the 1980s have shown that AFM1 exposure can produce liver tumors in rodents (Lutz et al. 1980, Cullen et al. 1987); however, AFM1 was considerably less carcinogenic than its parent compound AFB1. On the basis of these studies, the Joint Expert Committee on Food Additives (JECFA) of the Food and Agriculture Organization (FAO) and World Health Organization (WHO) estimated that, at most, *the cancer potency of AFM1 is 10-fold lower than AFB1* (JECFA 1998).

Even under worst case assumptions, AFM1 in liquid milk contributes very little, less than 0.0015%, to global liver cancer incidence

In a risk assessment, a worst-case assumption was made that AFM1 is indeed carcinogenic to humans but at the 10-fold lower cancer potency than that of AFB1. JECFA had estimated AFB1's cancer potency as causing an additional 0.01 cases of liver cancer per year per 100,000 population for every additional 1 ng/kg bw/day consumed of AFB1 (JECFA, 1998). Thus, the risk of developing AFM1-related liver cancer is 0.001 cases/100,000/year/ng/kg body weight/day.

It has been well established that the carcinogenic potency of AFB1 is 30-fold higher in people who have been infected with the hepatitis B virus (HBV) than in those that have not been infected. Similar data are not available for AFM1. In a risk assessment, a worst-case assumption was made that the interaction between AFM1 and HBV is similar to that of AFB1 and HBV.

Based on the worst-case assumptions, we estimate that exposure to AFM1 contributes 12 to 32 hepatocellular carcinoma (HCC) cases per year in the countries for which data are available. These countries together had 5.2 billion inhabitants worldwide. In comparison, the incidence of HCC due to exposure of AFB1 was estimated to be 25,200–155,000 cases per year (data available for countries capturing nearly 6 billion inhabitants; Liu and Wu 2010).

In other words, even under worst case assumptions, the estimated incidence of HCC due to exposure to AFM1 in dairy is negligible, as an absolute number as well as compared to the risk of AFB1.

Table 2. Worst-case estimates of the incidence of hepatocellular carcinoma (HCC) by exposure to aflatoxin B1 (AFB1) and aflatoxin M1 (AFM1) in in different regions of the world

Region	HCC incidence AFB1[#]	HCC incidence AFM1[&]
Africa	2.0-7.4	0.0001-0.003
North America	0.003-0.004	No data
Latin America	0.20-0.80	0.00002-0.004
Eastern Mediterranean	0.35-2.7	0.00004-0.002
Southeast Asia	0.40-2.3	0.000003-0.002
Western Pacific	0.62-1.5	0.00001-0.0001
Europe	0.03-0.09	0.000007-0.002

[#] Liu et al., 2010; [&] Saha Turna et al., 2021b

No data are currently available to estimate the risk of other health outcomes of AFM1 exposure

Assessing AFM1's effects beyond cancer—such as growth impairment in children—has been a challenge in epidemiological studies, because when trying to link health effects to AFM1 found in urine, it is impossible to know whether those effects are caused by ingestion of AFM1 or its parent compound AFB1 (Saha Turna and Wu 2021). Several studies attempted to circumvent this problem by analyzing AFM1 in mothers' breastmilk, to associate it with infant growth outcomes. These studies had mixed results (Mahdavi et al. 2008; Magoha et al. 2014; Memis et al. 2020), possibly because of vastly different AFM1 levels in breastmilk and the confounders included or omitted in the analyses. One study that sampled milk in Kenyan villages (Kiarie et al. 2016) found an inverse association between imputed AFM1 intake and height-for-age Z-score (HAZ) in infants. However, only 13% of the milk samples in this study were taken from the infants' households; the remainder were from nearby markets, so it is unclear that the imputed AFM1 exposures represented what the infants actually consumed.

US and EU standards for AFM1 in milk are not risk based

The US action level for aflatoxin M1 was triggered by high levels of aflatoxin-producing molds in the 1977 corn crop grown in the southeastern United Sates. AFM1 may occur in the milk of dairy cattle exposed to high levels of AFB1 in their feed. At the time, this was considered a potentially serious public health hazard. An action level of 0.5 parts per billion was established without further clarification of the basis for this level[1].

According to the European Food Safety Authority (EFSA Panel on Contaminants in the Food Chain, 2004), the maximum level for aflatoxin M1 in milk in the EU (0.05 parts per billion) is based on the ALARA (As Low As Reasonably Achievable) principle, aiming to reduce human exposure to the lowest achievable level. In Europe, this standard offers a high level of protection, with a margin of exposure estimated to vary between 2,000 to 100,000-fold (EFSA Panel on Contaminants in the Food Chain, 2020). However, the current standards are not truly risk-based.

Dumping milk that exceeds the US or EU AFM1 standards is not recommended, as the nutritional and economic impacts would likely outweigh the health risks.

Compared to the minimal estimated risk associated with AFM1 exposure, there is significant nutritional and economic risk in low-and middle-income countries (LMIC) associated with dumping milk that exceeds US or EU standards. Milk is a nutrient dense food that is well tolerated by infants and young children—a population at high risk for undernutrition and its sequelae. Milk is rich in

[1] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cpg-sec-527400-whole-milk-lowfat-milk-skim-milk-aflatoxin-m1; accessed September 4, 2021

energy, protein, and micro-nutrients, including vitamin B12, vitamin A, riboflavin, folate, and calcium, all of which contribute to proper and full growth and development of children. Consumption of milk can improve cognitive function and poor nutrition in undernourished children, and it can reduce consequent morbidity and mortality (Dror and Allen 2011). Dumping milk that exceeds US or EU standards for AFM1 thus mitigates a *low* risk in exchange for a *high* risk, as milk is an important source of micro- and macronutrients for children. Low consumption of milk and other animal-source foods is associated with increased risk of stunting and undernutrition in LMIC (Herber et al., 2020).

The economic impact of dumping milk is significant when the loss in revenue for dairies and income for families is considered (Popovic et al., 2017). In certain cases, exceeding the accepted AFM1 standards for milk has led to rejection of milk (Radosavljevic et al., 2013) and in certain cases, closure of dairies (Cornall, 2020), which implies loss of employment for staff as well as desperate measures to find new dairies that will accept the cows. Sadly, far reaching consequences like greater infant stunting could occur as well as considerable stress and depression among dairy producers due to low demand for milk, which has led to suicides (Smith, 2018). These grave consequences are an urgent and compelling call to action to rectify the status quo, as the perceived cancer risk from AFM1 has been considerably overstated.

A pebble is almost nothing when compared to a mountain, just as the risk from aflatoxin M1 is minor and does not justify the dumping of milk. (credit: "Pebble Lake" by Alaina McDavid [CC BY-SA 2.0], via Flickr)

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