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Occurrence and Stability of Aflatoxin M_1 in Milk and Milk Products: A Worldwide Review

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ABSTRACT

This paper critically reviews data from the literature since 1980 on the occurrence of aflatoxin M_1 (AFM_1) in human and animal milk, infant formula, dried milk, cheese, and yogurt. Furthermore the influence of storage and processing of milk and milk products on the occurrence and stability of AFM_1 is reviewed. It is concluded that (i) efforts in attempting to harmonize already existing regulatory limits for AF in foods and feed should be made; (ii) further investigations should verify the influence of milk storage and processing on AFM_1 occurrence to avoid uncertainty in actual practice; (iii) the occurrence of AFM_1 in animal milks and milk products is widespread, although, considering the current scientific fund, contamination levels do not seem to be a serious health hazard; however, further studies should provide accurate scientific information concerning the human health hazard related to long-term exposure to subchronic AF levels; (iv) monitoring programs should be more extensive and frequent; and (v) in tropical and subtropical countries, especially in African countries, a particular attention should be used in monitoring milk and milk products other than those from cows, as well as feed. Furthermore, extensive and periodic surveys on the occurrence of AF and their metabolite in human breast milk should be performed, since a serious health hazard to mother, fetus, or infants could occur.

Key words: Aflatoxins, AFM_1, milk, cheese, milk products

Aflatoxins (AF) are a group of highly toxic secondary metabolic products of some *Aspergillus* spp.; they easily occur on feeds and foods during growth, harvest, or storage. As AF are carcinogenic, teratogenic, and mutagenic to animals and humans, contamination of feed and food is a current problem *(107)*.

Mammals who ingest aflatoxin B_1 (AFB_1)-contaminated diets eliminate into milk amounts of the principal 4-hydroxylated metabolite known as "milk toxin" or aflatoxin M_1 (AFM_1). AFB_1 is metabolized by the hepatic microsomal mixed-function oxidase system, but it also can undergo several metabolic conversions depending on species *(90)*. AFM_1 is as toxic as AFB_1 to rats *(112)*, whereas the DL_{50} for 1-day-old ducklings is 0.24 mg of AFB_1/kg and 0.32 mg of AFM_1/kg, *(113)*. According to Barnes *(11)* AFM_1 is not as mutagenic as AFB_1. Sinnhuber et al. *(132)* reported similar carcinogenicities of AFB_1 and AFM_1 for trout livers. Recently Rothschild *(123)* classified AFB_1 and AFM_1 as class 1 and 2B (or probable) human carcinogens, respectively. Lafont et al. *(78)* observed a high genotoxic activity of AFM_1, although it was lower than that of AFB_1.

According to Stoloff *(135)* milk has the greatest demonstrated potential for introducing AF residues from edible animal tissues into the human diet. Moreover, as milk is the main nutrient for growing young, whose vulnerability is noteworthy and potentially more sensitive than that of adults, the occurrence of AFM_1 in human breast milk, commercially available milk, and milk products is one of the most serious problems of food hygiene. To reduce this risk most of the developed countries have regulated the maximum permissible levels of AFB_1 in foods and feeds as well as the levels of AFM_1 in milk and milk products. However, the matter of the legal limits is questionable. Currently the limits are highly variable (Table 1), depending on the degree of development and economic involvement of the countries in setting regulatory limits: according to Pohland and Yess *(110)*, regulatory limits seem to be a practical compromise between the need to have carcinogen-free commodities and the economic consequences of setting regulatory limits. For example, the Swiss legislation (the most restrictive in the world) forbids the use of peanuts, perhaps the most frequently AFB_1-contaminated feed, in dairy cow feeding: would it be possible in countries which are big groundnut producers?

Recently an expert group, charged by the Commission of the European Community to provide it with scientific information concerning legal limits for AF in an attempt to standardize them, proposed a limit of 50 ng of AFM_1/liter of milk and $<$1,000 ng of AFM_1/kg of infant formula.

However, Stoloff et al. *(138)* observed that concerning

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TABLE 1. *Regulatory limits for AFM_1*

Country	Milk (ng/liter)	Infant formula (ng/kg)	Cheese (ng/kg)
Argentina	500[a]	100	
Austria	50	10	250
Brazil	500	10	
France	200		
Germany	50	10	
Italy	50	50	
Netherlands	50	50	200
Switzerland	50	10[b]	250
US FDA	500		

[a] Sum of B_1, B_2, G_1, G_2, and M_1.
[b] Sum of B_1 and M_1.

AF there was little scientific basis, or the available scientific information was not used, in setting legal limits in most countries. Thus, even the low regulatory limits set in developed countries could not prevent chronic effects of AF, especially the carcinogenic effect, due to continued exposure to subacute levels of AF. Furthermore, although most of the references in the literature only report data for AFM_1, it is well known that, despite being in small amounts overall, other mycotoxins such as AFB_1 *(22, 86, 99, 129)*, AFG_1 *(22, 86)*, AFM_2 *(10)*, AFM_4 *(34, 78)*, sterigmatocystin *(153)*, ochratoxin *(94, 153)*, T-2 toxin *(153)*, and fumonisins *(85)* can occur in animal milk and milk products as well as in human milk. The only two countries which consider the additive amounts of some aflatoxins in regulatory limits for milk and milk products are Swiss (10 ng of B_1 plus M_1 per kg of infant formula) and Argentina (500 ng of B_1, B_2, G_1, G_2, and M_1 combined per kg of milk) *(152)* (Table 1). Do the regulatory limits consider possible combined or synergetic toxic, mutagenic and carcinogenic effects among mycotoxins?

Difficulties in estimating dietary intake *(15, 16, 24)*, assessing human exposure levels and health risk based upon animal toxicological studies *(110)*, and detoxifying or removing mycotoxins from human and animal diets *(107)*, make monitoring programs the principal strategy to decrease the risk of exposure for both animals and humans.

This paper is a survey of data from the literature on the occurrence of AFM_1 in animal milk, milk products, and human breast milk since 1980. Furthermore, studies on AFM_1 stability following milk processing are reviewed.

STABILITY AND OCCURRENCE OF AFM_1 IN ANIMAL MILK

Milk is a highly variable product that rapidly loses its homogeneity and spoils if untreated. Since milk may be processed in numerous ways, the effects of storage and processing on stability and distribution of AFM_1 are of great concern.

Variable effects have been reported concerning cold treatments. Kiermeier and Meshaley *(75)* observed that detectable AFM_1 decreases by 11 to 25% after 3 days at 5°C, 40% after 4 days at 0°C and 80% after 6 days at 0°C, whereas McKinney et al. *(92)* revealed that freezing at −18°C for 30 days resulted in an apparent loss of 14%, with 85% lost after 53 days. Stoloff et al. *(141)* suggested less degradation of AFM_1 at −18°C with insignificant loss after 53 days.

As regards the effect of pasteurization, contrasting data on AFM_1 thermoresistance arise from studies revealing no reduction of AFM_1 under various conditions *(7, 41, 48, 98, 139, 140, 155, 167)*, or widely variable effects *(46, 57, 75, 76, 88, 104, 115, 116)*. Allcroft and Carnaghan *(3)* reported no reduction of AFM_1 toxicity by pasteurization or roller drying. According to Wiseman and Marth *(167)*, AFM_1 recovery could be affected by the influence of heat treatment on milk proteins and solubility of salts. Furthermore, contrasting data could be ascribed to the wide range of temperature, different analytical methods, and employment of both naturally and artificially contaminated milk *(147)*.

AFM_1 distribution in milk is not homogeneous: cream separation can affect AFM_1 distribution, since 80% is partitioned in the skim milk portion *(60)* because of AFM_1 binding to casein *(25, 26)*. An amount of 30% of AFM_1 is indeed estimated to be associated with the nonfat milk solids and in particular with casein. According to Van Egmond and Paulsch *(153)* the behavior of AFM_1 in processes which involve fat separation may be explained by its semipolar character, leading to a predominance in the nonfat fraction.

Contrasting data have been reported on the influence of milk concentration on AFM_1. Kiermeier *(73)* and Sabino *(126)* reported no losses of AFM_1, whereas other authors *(44, 96, 114)* observed losses ranging from 60 to 75% following milk concentration.

Data from the literature on the occurrence of AFM_1 in animal milk since 1980 are reported in Table 2. Because of wide differences between and within the countries related to feeding, animal and environmental factors, extraction and analysis procedures, and regulatory limits for AF in feeds and milk, it is quite difficult to compare the literature data.

However, it is possible to point out some topics for consideration, as follows. In recent years the incidence of AFM_1 contamination seems to have been balanced on the one hand by increasing precision of extraction and analysis procedures and on the other hand by the setting of stricter regulatory limits for AF in feeds and milk. According to Visconti et al. *(158)*, most of the negative results reported in the first studies performed in Italy should be attributed to the poor sensitivity of the analytical methods used. Today the high efficiency of immuno-enzymatic extraction and the accuracy of analytical methodology and equipment, such as the latest high-pressure liquid chromatography and fluorescence detectors, allow detection limits to decrease, improving the percentage of positive samples. Moreover, in recent years attention to the concern of AF in feeds as well as in milk has increased in most of the developed countries.

The incidence of AFM_1 contamination is often higher in commercial milk than in raw farm milk, because of the dilution of uncontaminated bulk milk by only a few contaminated samples *(23, 109, 158)*. For the same reason high AFM_1 contamination levels in commercial milk seldom occur.

TABLE 2. *Incidence and level of AFM_1 in animal milks*

Reference	Year	Country	Milk type[a]	No. of samples	No. of positive samples	AFM_1[b] (ng/liter)
Maffeo et al. *(83)*	1980	Italy	C	50	0	NA[c]
Pfleger and Brandle *(106)*	1980	Austria	D	210	8	200–*[c]
			D	837	468	30–690
Stoloff *(137)*	1980	USA	C	302	157	100–4,000
Bartos and Matyas *(12)*	1981	Czechoslovakia	R	77	5	tr–380[c]
Blanc and Karleskind *(17)*	1981	France	C	380	168	50–1,150
			D	222	129	50–5,200
Castelli and Riberzani *(33)*	1981	Italy	C	31	5	30–70
			D	21	4	30–250
Della Rosa and Morales *(38)*	1981	Brazil	C	6	3	25–500
Fremy et al. *(49)*	1981	France	C	102	32	500–5,000
Fritz and Engst *(51)*	1981	Germany	C	60	4	100–6,500
Heschen et al. *(66)*	1981	Germany	C	279	265	0.3–68
Maffeo and Leali *(84)*	1981	Italy	C	160	0	NA
Tripet et al. *(148)*	1981	Switzerland	C	163	16	50–2,000
			C	230	40	50–3,000
Gajek *(55)*	1982	Poland	C	22	11	10–250
Karim et al. *(71)*	1982	Iran	R	52	48	*–23,000
			P	9	9	*–20,100
Van Egmond et al. *(154)*	1982	Netherlands	C	105	84	15–90
Vesela et al. *(157)*	1982	Czechoslovakia	C	67	9	50–100
Amodio et al. *(4)*	1983	Italy	UHT	60	10	100–500
Burdaspal et al. *(32)*	1983	Spain	C	95	7	20–40
Coppedge *(36)*	1983	USA	C	816	554	100–2,000
			C	912	116	100–2,000
			C	624	144	100–2,000
			C	847	107	100–2,000
			C	786	235	100–2,000
			C	168	99	100–2,000
Finoli et al. *(48)*	1983	Italy	D	4	0	NA
Moller and Anderson *(95)*	1983	Sweden	C	84	1	50–100
			C	13	13	5–36
Paul et al. *(105)*	1983	Germany	C	142	0	NA
			D	70	2	500–*
Ranfft *(118)*	1983	Germany	D	95	47	100–2,550
Riberzani et al. *(122)*	1983	Italy	D	13	6	50–100
Schuddeboom *(131)*	1983	Netherlands	C	105	84	15–90
			C	462	83	200–*
Skrinjar et al. *(134)*	1983	Yugoslavia	R	34	0	NA
Gilbert et al. *(58)*	1984	UK	C	409	24	*–10
			D	277	5	*–30
Pompa et al. *(111)*	1984	Italy	C	160	0	NA
Watson *(161)*	1984	UK	C	268	201	100–*
			C	277	13	*–*
Boccia et al. *(23)*	1985	Italy	R	52	9	5–146
			C	18	12	5–30
Quintavalla and Casolari *(117)*	1985	Italy	V	22	22	100–434
Visconti et al. *(158)*	1985	Italy	R	31	8	5–91
			P	66	59	4–150
			D	9	9	10–280
Piva et al. *(108)*	1985	Italy	C	82	34	tr–569
Davoli et al. *(37)*	1986	Italy	C	59	46	tr–378
Gelosa *(56)*	1986	Italy	C	27	24	5–65
			P	68	61	5–50
			UHT	32	28	7–50
Martins and Martins *(87)*	1986	Brazil	C	224	4	tr–2
Gilli et al. *(59)*	1987	Italy	C	107	5	24–94
Oliviero et al. *(101)*	1987	Italy	C	104	0	NA
Parreiras et al. *(102)*	1987	Brazil	C	*	*	tr–790

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TABLE 2. *(Continued)*

Reference	Year	Country	Milk type[a]	No. of samples	No. of positive samples	AFM_1[b] (ng/liter)
Piva et al. *(109)*	1987	Italy	C	276	70	>0.5
		France	C	88	11	*–23
		Germany	C	225	31	*–23
Vittani *(159)*	1987	Italy	P	30	27	3–22
			D	10	10	15–100
Bachner et al. *(9)*	1988	Germany	C	1465	142	*
				1533	35	*
				1697	104	*
Blanco et al. *(20)*	1988	Spain	UHT	47	14	20–100
Fukal *(52)*	1988	Czechoslovakia	C	191	25	50–100
Bachner *(8)*	1989	Germany	C	6445	624	10–>50
Bento et al. *(13)*	1989	Portugal	P	143	7	100–400
			D	30	0	NA
De Natale et al. *(39)*	1989	Italy	R	57	24	100–930
			R	60	3	100–280
Kaaraioannoglu et al. *(70)*	1989	Greece	R	99	4	100–130
Langset and Okland *(80)*	1989	Norway	R	4	4	1.3–6.8
Saad et al. *(124)*	1989	UAE	Ca	20	6	250–800
Sabino et al. *(127)*	1989	Brazil	C	50	9	100–1,680
			C	100	1	*
Sharmanov *(129)*	1989	Kazakhstan	V	750	117	*
Bento et al. *(14)*	1990	Portugal	G	55	0	NA
Bruhn et al. *(31)*	1990	USA	R	393	2	>250
Heeschen et al. *(65)*	1990	Germany	P	473	*	4–10
				*	*	10–14
Fukal et al. *(54)*	1990	Czechoslovakia	R	376	46	<500
			P	314	16	<500
			R	89	27	<500
Macho et al. *(82)*	1990	Spain	R	29	28	<10
					1	25–50
			R	32	24	<10
					8	10–25
			UHT	33	28	<10
					5	10–25
Heeschen and Bluthgen *(64)*	1991	Germany	R	238	*	12†c
			D	*	*	4.2†
Nikov et al. *(99)*	1991	Kazakhstan	C	*	0	NA
Vandana et al. *(150)*	1991	India	V	60	25	*
Anonymus *(5)*	1992	Germany	C	1507	1504	0–50
					3	>50
				388	387	0–10
					1	>10
Margolles et al. *(86)*	1992	Cuba	C	85	22	>500
Mosso et al. *(97)*	1992	Italy	C	176	0	NA
Skrinjar et al. *(133)*	1992	Yugoslavia	R	*	0	NA
Dragacci and Fremy *(42)*	1993	France	C	5489	5284	0–50
			C		200	50–500
			C		5	>500
			R	757	659	0–50
			R		84	50–500
			R		14	>500
Bagni et al. *(10)*	1993	Italy	C	107	66	6–101
			C	107	56	3–60
Tabata et al. *(144)*	1993	Japan	C	37	0	NA
Jalon et al. *(77)*	1994	Spain	R	61	49	<10
					10	10–20
					2	20–40
			R	29	28	<10
					1	20–40
			R	32	21	<10

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TABLE 2. *(Continued)*

Reference	Year	Country	Milk type[a]	No. of samples	No. of positive samples	AFM_1[b] (ng/liter)
Jalon et al.					10	10–20
					1	20–40
			UHT	33	28	<10
					4	10–20
					1	20–40
Kawamura et al. *(72)*	1994	USA	D	10	4	95†
		China	D	28	21	102.8†
		Italy	D	14	0	NA
		New Zealand	D	3	0	NA
		Poland	D	3	1	85†
Rajan et al. *(119)*	1995	India	R	504	89	100–3,500

[a] B, buffalo; C, cow; Ca, camel; D, dried or powder; G, goat; P, pasteurized; R, raw; S, sheep; UHT, ultra high temperature.
[b] Range, minimum to maximum.
[c] NA, not applicable; *, not reported; tr, trace; †, average.

According to numerous authors, a seasonal effect influences AFM_1 occurrence. Some authors reported a higher incidence of AFM_1 contamination during cold seasons than hot ones *(10, 17, 19, 48, 49, 50, 59, 66, 73)* because in winter cows are fed with greater amounts of compound feeds, whereas during spring and summer forage, roughage, and pasture are widely available. In a survey carried out in several regions of Germany, Bachner et al. *(9)* reported that different agricultural systems and feeding types can influence AFM_1 occurrence. In contrast, Rasmussen *(121)* reported no significant seasonal or regional influence on AFM_1 occurrence in Norway.

Within countries a variable geographic distribution of AFM_1 occurrence can occur *(21)*. Thus climatic factors can account for AFM_1 occurrence, especially in countries with wide regional climatic variability. Piva et al. *(109)*, in a survey on dairy products marketed in Italy, observed lower AFM_1 occurrence and contamination level in southern Italy than in central and northern Italy.

Most of the references in the literature report data on cows milk, although it is well known that AFM_1 can readily occur in sheep *(150)*, goat *(14, 150)*, buffalo *(150)*, and camel *(125)* milk. We think that in tropical and subtropical countries much more emphasis should be placed on the control regulations of the presence of AF in feeds, milk other than cow milk, as well as in other human foods, for two reasons: (i) animal milks other than cow are the most produced, processed, and consumed; and (ii) climatic and storage conditions are the most favorable to the development and growth of aflatoxigenic fungi on foodstuffs.

STABILITY AND OCCURRENCE OF AFM_1 IN CHEESE

Occurrence of AF in cheese can be due to three possible causes: AFM_1 present in raw milk as a consequence of carryover of AFB_1 from contaminated cow feed to milk, synthesis of AF (B_1, B_2, G_1, and G_2) by *Aspergillus flavus* and *Aspergillus parasiticus* growing on cheese *(171)*, and occurrence of these toxins in dried milk used to enrich the milk used to make cheese *(20)*.

Contrasting data have been reported on the influence of cheese preparation on AFM_1 recovery. The first studies, performed in the years 1971 to 1974, showed variable losses of AFM_1 during cheese manufacturing: 65%, 47%, 20%, <20% and <15% according to Purchase et al. *(116)*, McKinney et al. *(92)*, Stoloff and Trucksess *(139)*, Grant and Carlson *(60)* and Stubblefield and Shannon *(142)*, respectively. In contrast, later investigations of several authors *(17, 26–28, 98, 108, 153)* reported increases in AFM_1 concentration in cheese as a function of cheese type, technologies, and the amount of water eliminated during processing.

However, the increase in AFM_1 concentration in cheese has been explained by the affinity of AFM_1 for casein *(3, 6, 25, 57, 60)*. Brackett and Marth *(25)* suggested that since is possible to extract AFM_1, it must not be covalently bound but linked by hydrophobic interactions with hydrophobic areas of the casein. Further investigations should better establish whether cheese manufacture influences AFM_1 distribution.

Some tests carried out on several kind of cheese, such as Brick and Limburger *(29)*, Camembert and Tilsit *(74)*, Cheddar *(7, 26)*, Gouda *(155)*, Manchego *(20)*, Parmesan and Mozzarella *(27)* and Swiss *(81)* showed an overall stability of AFM_1 during ripening and storage, whereas Marshaly et al. *(88)* revealed a gradual decrease of AFM_1 in stored Karish cheese.

Several investigations on the partitioning of AFM_1 during cheese manufacture reported a wide range of distribution of AFM_1 between whey and curd, also because of starting with different milk contamination levels. Some authors observed that half or more of the AFM_1 was in the whey: 50%, 50%, 61%, 66%, 86%, and 100%, according to Grant and Carlson *(60)*, Stubblefield and Shannon *(142)*, Wiseman and Marth *(168)*, Blanco et al. *(20)*, Stoloff et al. *(140)* and Purchase et al. *(116)*, respectively. In contrast, others reported that most of AFM_1 was with the curd: ranging from 66% to 72%, from 73% to 77%, 80%, and

TABLE 3. *Incidence and level of AFM_1 in cheese*

Reference	Year	Country	No. of samples	No. of positive samples	AFM_1 (ng/kg)
Saito et al. *(128)*	1980	Japan	*[a]	9	100–4,000
Blanc and Karleskind *(17)*	1981	France	343	102	*–5,200
Castelli and Riberzani *(33)*	1981	Italy	6	5	50–400
Tripet et al. *(148)*	1981	Swiss	91	33	500–*
Parvaneh et al. *(103)*	1982	Iran	8	7	*–*
Brezina et al. *(30)*	1983	Czechoslovakia	29	6	5–66
Finoli et al. *(48)*	1983	Italy	50	4	50–100
Riberzani et al. *(122)*	1983	Italy	4	2	20–40
Hisada et al. *(67)*	1984	Japan	126	56	110–300
			128	111	25–1,060
			32	13	12–2,520
			132	120	10–500
Nishijima *(100)*	1984	Japan	79	17	*–*
Piva et al. *(108)*	1985	Italy	83	70	3–250
Quintavalla and Casolari *(117)*	1985	Italy	10	7	200–1,140
Zerfiridis *(170)*	1985	Greece	94	0	NA[b]
Trucksess and Page *(149)*	1986	USA	118	8	100–1,000
Piva et al. *(109)*	1987	Italy	416	130	*–>250
		Netherlands	43	23	*–>250
		Germany	34	9	*–>250
Tabata et al. *(145)*	1987	Japan	303	44	200–1,200
Vecchio *(156)*	1987	Italy	50	4	50–100
Cirilli and Aldana Cirilli *(33)*	1988	Italy	66	12	280–1,300
			66	6	340–870[c]
Haydar et al. *(63)*	1990	Syria	*	0	NA
Karaioannoglou et al. *(70)*	1989	Greece	127	0	NA
Nikov et al. *(99)*	1991	Kazakhstan	*	*	*
Tabata et al. *(144)*	1993	Japan	37	0	NA
Taguchi et al. *(146)*	1995	Japan	41	0	NA

[a] *Not reported.
[b] Not applicable.
[c] AFM_4.

100% according to Marshaly et al. *(88)*, El Deeb et al. *(46)*, McKinney et al. *(92)*, and Allcroft and Carnaghan *(3)*, respectively. According to Blanco et al. *(20)* these contrasting results can be ascribed to different factors such as extraction technique, methodology, type and degree of milk contamination, differences in milk quality, expression of the results, the presence of a small portion of curd in whey which could influence AFM_1 concentration, and the cheese manufacture process.

The incidence of positive cheese samples for AFM_1 (Table 3) seems to be widely variable. In two surveys performed in Greece, Zerfiridis *(171)* and Karaioannoglou et al. *(70)* did not reveal positive samples. Similarly, Tabata et al. *(144)* and Taguchi et al. *(146)* found no positive samples in imported cheese in Japan, as did Haydar et al. *(63)* in goat and sheep cheese from Syria. Trucksess and Page *(149)* and Vecchio *(156)* detected few positive samples, whereas other authors *(67, 103, 108)* observed a high incidence of positive samples, ranging from 84% to 97.5% of the cheese samples analyzed. As regards the contamination level, several authors *(34, 67, 145, 149)* found a maximum contamination level over 1,000 ng of AFM_1 per kg whereas two authors *(17, 128)* detected over 4,000 ng of AFM_1 per kg. These latter contamination levels could be hazardous; however, since their incidence is quite low, they should not have been a problem.

STABILITY AND OCCURRENCE OF AFM_1 IN YOGURT

Several authors reported no influence of yogurt manufacture on AFM_1 content *(18, 136, 141, 151, 153, 166)*, in agreement with a study by Ismail et al. *(76)* on AFM_1 behavior during kefir manufacture. In contrast Van Egmond et al. *(155)* and Munksgaard et al. *(98)* observed variable increases of AFM_1 content in yogurt related to the milk, as did Wiseman and Marth in kefir *(16)*.

As regards AFM_1 stability during storage of yogurt, Van Egmond et al. *(155)* observed no reduction of AFM_1 in yogurt stored for 7 days at 7°C.

Megalla and Hafez *(93)* observed complete transformation of AFB_1 in its hydroxy derivative AFB_2A caused by the acids present in yogurt, whereas Rasic et al. *(120)* revealed a high reduction (up to 97%) of AFM_1 in yogurt and acidified milk. El Deeb et al. *(46)* observed that enzymic, microbial, and particularly acid coagulation caused degradation of AFM_1 in buffalo milk. Maryamma et al. *(89)* reported a high

reduction of AFM_1 in fermented goat milk. Nevertheless, since it is known that exposure of the AF molecule to strong acid, such as trifluoracetic acid, can cause its acid-catalyzed hydration, leading, for example, from AFB_1 to AFB_2A *(35)*, but not it's degradation or neutralization, the effect of the weak acidity of yogurt on AF should be verified.

Since the nutritional advantages of yogurt consumption are related to the presence and viability of microorganisms, besides altering the healthiness of yogurt AF can cause some negative effects on its nutritive properties. El Deeb et al. *(45)* observed some negative effects of AFM_1 on *Lactobacillus bulgaricus* (cell wall thickening and shortening of cell chain length) and *Staphylococcus thermophilus* (cell wall thickening and cell shape changing from coccoid to oval). Similarly, Sutic and Banina *(143)* and Rasic et al. *(120)* observed changes in the morphology of the latter microbe and curdling delay caused by AFB_1 *(143)*.

Except for a survey performed in Italy by Quintavalla and Casolari *(117)*, who found in 6 out of 8 samples with from 36 to 334 ng of AFM_1 per liter, and a study of Haydar et al. *(63)* which reported 190 ng of AFM_1 per kg of koshk, a blend of yogurt and parboiled wheat, we are aware of no studies on the occurrence of AFM_1 in yogurt. We think that surveys on AF occurrence in commercially marketed yogurt and further studies on its stability and influence on microorganisms should be carried out for the following reasons: (i) in recent years human consumption of yogurt has greatly increased; (ii) there is contradictory data on AFM_1 stability during manufacture and storage in the literature; (iii) and the presence of AF in yogurt could decrease or undo the nutritional benefits of its consumption.

OCCURRENCE OF AFM_1 IN HUMAN BREAST MILK AND IN DRIED MILK FOR INFANT FORMULAE

Humans who ingest AF-contaminated foods eliminate variable amounts of the toxins in body fluids or accumulate them in the tissues. The occurrence of AF in human tissues or fluids is a current problem in either tropical or subtropical countries much more than in cold ones, although Dragsted et al. *(43)* found some aflatoxin-like substances in urine samples of people living in a cold country (Denmark) which were related to consumption of beer, dairy products, and meat. Maxwell et al. *(91)* detected AFM_1 in breast milk (Table 4), cord blood, and maternal blood of Sudanese, Ghanaian, Kenyan, and Nigerian people, recording three unexplained stillbirths, too. Wild et al. *(164)* detected the occurrence of AFM_1 in human milk samples collected in Sudan, Ghana, and Zimbabwe, whereas no AFM_1 was detected in human milk samples from France. An indirect assessment of widespread exposure to AF-contaminated food produced and consumed in tropical and subtropical countries was provided by Wilkinson et al. *(165)*, who found a much higher level of AF metabolites in sera of Nigerian and Nepalese people compared to sera of people in the UK. Further evidence arises from studies which reported the occurrence of AF in food consumed in Gambia (West Africa) *(61, 68, 69, 162)* and in the Chinese Guangxi region *(62)*, and AF metabolites in sera *(163)* and urine *(61, 62, 162)* of people living in these latter countries and in cord and maternal sera from people living in Songkhla (Thailand) *(40)*.

TABLE 4. *Incidence and level of AFM_1 in human breast milk*

Reference	Year	Country	No. of samples	No. of positive samples	AFM_1 (ng/l)
Wild et al. *(164)*	1987	France	42	0	NA[a]
		Zimbabwe	64	6	≤50
Lamplugh et al. *(79)*	1988	Ghana	264	90	20–1,816
Maxwell et al. *(91)*	1989	Sudan	99	37	5–1,379
		Ghana	510	163	5–1,379
		Kenya	191	53	5–1,379
Saad et al. *(124)*	1989	UAE	64	10	300–1,300
Zarba et al. *(170)*	1992	Gambia	5	3	*–*[b]
Saad et al. *(125)*	1995	Algeria	2	2	170–790
		Bahrain	1	1	158[c]
		Bangladesh	6	6	6–174
		Egypt	48	48	4–720
		Holland	1	1	20[c]
		India	48	48	4–600
		Indonesia	2	2	3–51
		Iran	3	3	51–1,600
		Iraq	2	2	8–14
		Jordan	42	42	2–880
		Lebanon	15	15	14–1,000
		Morocco	3	3	7–150
		Oman	6	6	70–978
		Pakistan	44	44	2–1,100
		Palestine	55	54	0–840
		Philippines	2	2	250–580
		Saudi Arabia	2	2	58–395
		Somalia	18	18	2–1,000
		Sudan	44	44	3–2,100
		Syria	36	36	3–800
		UAE	37	37	9–3,000
		Yemen	28	27	0–1,600

[a] NA, not applicable.
[b] *Not reported.
[c] Average.

Indications of serious prenatal health hazards to infants due to the exposure to AF have been reported by several authors. Indeed, Maxwell et al. *(91)*, Denning et al. *(40)*, Wild et al. *(162)*, Wilkinson et al. *(165)* and Lamplugh *(79)* reported that AF can cross the human placental membrane and may be concentrated by the developing fetoplacental unit. Lamplugh et al. *(79)* detected AFM_1, AFM_2, AFB_1, AFB_2 and aflatoxicol at variable concentrations in human milk samples collected in Ghana, in blood cord samples obtained from Ghanaian infants at birth, in samples of venous blood from Nigerian mothers during pregnancy and in cord blood samples from their infants. Zarba et al. *(170)* found both AFM_1 and AFG_1 in human milk from Gambia. Saad et al., in two studies performed in the United Arabs Emirates (UAE) *(124, 125)*, detected up to 100% of human milk samples containing AFM_1 from mothers representing a

TABLE 5. *Incidence and level of AFM_1 in dried milk and infant formulae*

Reference	Year	Country	Milk type[a]	No. of samples	No. of positive samples	AFM_1 (ng/kg)
Quintavalla and Casolari *(117)*	1985	Italy	D	7	7	679–1,960
Riberzani et al. *(122)*	1985	Italy	D	233	58	20–80
Adensam et al. *(1)*	1987	Czechoslovak	D	*[b]	*	*
Finoli and Rondinini *(47)*	1989	Italy	D	*	3	13
Fukal et al. *(54)*	1990	Czechoslovak	R[a]	376	46	*–<500
Nikov et al. *(99)*	1991	Kazakhstan	D	*	3	200–400
Fukal and Brezina *(53)*	1991	Czechoslovak	R[a]	376	2	*–>100
Heeschen and Bluthgen *(64)*	1991	Germany	D	*	*	1.6[c]

[a] D, dry; R, raw milk for infant formulae.
[b] *Not reported.
[c] Average.

wide range of nationalities, ages, and health statuses. Seasonal fluctuations in the level of exposure, higher in wet seasons, have been reported by Lamplugh et al. *(79)*, Denning et al. *(40)*, and Maxwell et al. *(91)*.

Moreover, in tests on rat offspring suckling mothers dosed with AFB_1, Allameh et al. *(2)* reported excretion of AFB_1 metabolites in milk and their transfer, distribution, and binding to many tissues leading to chronic effects; Wakhisi *(160)* observed the development of liver cancer and liver dysplasia.

It is concluded that, although the interaction between dietary AF intake and exposure of the mother, fetus, and newborn infants is very complex, depending on the physiological status of the mother and on food composition *(125)*, the presence of AFB_1 and its metabolites in human blood and breast milk presents serious health hazards. Although it may be difficult, it would be desirable, at least during pregnancy and the lactation period, for mothers to ingest low-content AF or AF-free foods to avoid the undesirable transfer of AF metabolites to the fetus or infant.

Data in the literature on the occurrence of AFM_1 in dried milk and infant formulae milk since 1980 are summarized in Table 5.

In a survey carried out in Czechoslovakia, Fukal et al. *(54)* reported that, although 46 out of 376 samples of raw milk collected from farms in the area of a planned new infant food factory were positive for AFM_1, no sample exceeded the limit of 500 ng of AFM_1/kg (the Czechoslovak legal limit until 1990). In 1991 Fukal and Brezina *(53)* detected no AFM_1 in 330 out of 376 samples of raw milk from a factory producing milk-based baby food, whereas only two samples contained more than 100 ng of AFM_1/kg (the decreased Czechoslovak legal limit).

In Kazakhstan, Nikov et al. *(99)* found from 200 to 400 ng of AFM_1/kg of dried milk. An overall quite low quality of infant foods in that country was attributed largely to poor processing technology and storage conditions, as confirmed by Sharmanov *(130)*, who revealed a high degree of contamination by aflatoxigenic fungi in infant foods.

In Italy, Finoli et al. *(47)* detected up to 13 ng of AFM_1/kg of dried milk infant formula. Riberzani et al. *(122)* reported a contamination level in 25 out of 233 samples of dried milk infant formula which did not exceed the Swiss limit. In contrast, Quintavalla and Casolari *(117)* detected 100% AFM_1 contamination, ranging from 679 to 1960 ng/liter.

In Germany Heschen and Bluthgen *(64)* reported the presence of a quite low average contamination level (1.6 ng of AFM_1/kg) in dried milk for manufacturing baby foods.

Except for data from Kazakhstan, which according to the authors *(99, 130)* feels the effects of particularly inadequate processing technology and storage conditions, altogether the data referred to seldom exceeded the Swiss legal limit.

Although few literature data are available, the incidence and contamination level of AFM_1 in dried milk and infant formulae should not be an health hazard. However, we think that, since infants are more vulnerable and sensitive than adults, monitoring of infant foods should be repeated more frequently and extensively.

CONCLUSIONS

Currently the regulatory limits are widely variable and there has been little scientific basis in their setting. Efforts should be made in attempting to provide further and extensive scientific information on human health hazards related to low-level long-term AF exposure and to standardize the already existing regulatory limits for AF.

Forthcoming studies should verify the influence of milk storage and processing on AFM_1 occurrence to avoid actual uncertainty. However, since it is generally assumed that neither storage nor processing determine reduction of AFM_1 content, further information on possible AFM_1 concentration following milk processing should be furnished.

The occurrence of AFM_1 in cow milk and milk products is widespread, although, considering the current scientific fund of information, contamination levels do not seem to be a serious health hazard. Wide and frequent monitoring programs performed by accurate and reliable analytical techniques still remain the primary strategy to provide protection for milk consumers. In tropical and subtropical countries an appropriate attention should be used to control milk and milk products other than those from cows, as well as foods and feeds.

The occurrence of AF and their metabolites in human breast milk is of great concern especially in tropical and subtropical countries. Since serious health hazards to the mother, fetus, and infant could occur, extensive and periodic surveys should be performed. Although the current incidence and occurrence of AFM_1 in dried milk infant formula does not seem to be a health risk, surveillance should be continuous and accurate.

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