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Research Article

Maternal dietary habits and mycotoxin occurrence in human mature milk

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During 2006, 82 samples of human mature milk were collected at Italian hospitals and checked for aflatoxin M1 (AFM1) and ochratoxin A (OTA) by immunoaffinity column extraction and HPLC. AFM1 was detected in four (5%) of milk samples (ranging from < 7 ng/L to 140 ng/L; mean level: 55.35 ng/L); OTA was detected in 61 (74%) of milk samples (ranging from < 5 ng/L to 405 ng/L; mean level: 30.43 ng/L. OTA levels were significantly higher ($p \leq 0.05$) in milk of habitual consumers of bread, bakery products and cured pork meat. No other statistically significant differences were observed although habitual consumers of pasta ($p = 0.059$), cookies ($p = 0.061$) and juices ($p = 0.063$) had mean contamination values of OTA higher than the moderate consumer. The very few AFB1 positive samples did not allow statistical comparisons. The present study confirms that the occurrence of OTA in human milk is related to maternal dietary habits. The findings support the possibility of dietary recommendations to woman, during pregnancy and lactation, aimed to tentatively reduce the OTA contamination of human milk.

Keywords: Aflatoxin M1 / Cereals / Human milk / Maternal dietary habits / Ochratoxin A

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1 Introduction

The occurrence of mycotoxins in human, animal and milk-formula is one of the most serious problems of food hygiene since milk is an important food for adults, and the unique nutrient for infants. The latter are extremely vulnerable because their diet is much less varied and depends on mother dietary habits. It has been reported that in human milk a variable amount of mycotoxins, ingested by the mother, can be accumulated as intact or metabolized. The major concern about human milk contamination by mycotoxins are substantially limited to aflatoxin M1 (AFM1) and ochratoxin A (OTA) [1]. The former is derived from dietary aflatoxin B1 ingestion, that after liver metabolization is named "milk toxin" or AFM1.

Although AFM1 is considered to be a detoxification product, there is evidence of a putative AFM1 carcinogen role as reported by the International Agency for Research on Cancer [2]. A similar carcinogenic potential role has been established for OTA [2]. Of note, infant exposure to AFM1 and OTA can initiate during prenatal life since the fetoplacental unit can constitute a site of concentration due to their ability to cross the human placenta [3].

Despite the constantly claimed need of frequent surveys on a so delicate public health issue, few studies are available worldwide. Literature data report the detection of AFM1 in breast milk, cord blood and maternal blood in African countries (Sudan, Ghana, Kenya, Nigeria, Sudan, Gambia), in the

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Abbreviations: AFM1, aflatoxin M1; **OTA**, ochratoxin A; **TDI,** tolerable daily intakes

Chinese Guangxi region, (see [3] and references cited therein) as well as in the Arabian peninsula [4, 5], in Australia and Thailand [6] and in Brazil [7]. If AFB1 appears to be a concern mainly in tropical or subtropical countries, diversely OTA residues in human milk appear to be typical of countries in the temperate and cold areas of the Northern hemisphere, such as Italy [8 – 11], Switzerland [12], Sweden [13], and Germany [14]. In this sense, an exception seems to be the data reported by Jonsyn *et al.* [15], who observed high OTA levels in human milk from Sierra Leone.

The aim of the present study was to monitor the presence of AFM1 and OTA in human milk according to mother dietary habits.

2 Materials and methods

2.1 Subjects and sampling

Informed consent was obtained from all women before inclusion in the study, and approval from our local human investigation committees. From January to December 2006 we collected mature human milk samples obtained from 82 singleton physiological pregnancies admitted to our Maternal, Fetal and Neonatal Health Department tertiary level, whose deliveries were at term (Table 1). All newborns had a birth-weight between the 10th and 90th percentile according to gestational age, and a normal clinical examination at sampling time-point.

Exclusion criteria were: multiple pregnancies, gestational hypertension, diabetes and infections, fever, chromosomal abnormalities, metabolic diseases, diseases of the breast or central nervous system, malnutrition, maternal allergy, maternal addiction for tobacco, alcohol and cocaine. Other exclusion criteria were: newborns with any malformation, cardiac or hemolytic disease.

Mature milk samples (5 mL) for AFM1 and OTA assessment were collected on day 30 after birth according to Playford *et al.* criteria [16] and immediately stored at -70°C.

Table 1. Maternal and neonatal characteristcis in the studied group. Values are given as means ±SD.

	Donors ($n = 82$)
Maternal age (year)	25.7 ± 4.1
Gestational age at delivery (wks)	38 ± 1
Mode of delivery-no/total	
caesarean	19/82
vaginal	63/82
Birth weight – no. 10° – 90° centile	82
Born at study hospitals – no.	66
Apgar 1st min < 7-no.	0
Apgar 5th min < 7-no.	0
Sex – Male/Female	43/39
Neurological Examination at Discharge Normal/Suspect/Abnormal	82/0/0

2.2 Analysis

Chemicals and solvents used were of HPLC grade or equivalent (Carlo Erba, Milan, Italy). All water used was distilled and, for HPLC, passed through a Milli-Q purification system (Millipore, London, UK). ACN and acetic acid used for mobile phases were of HPLC grade and provided by Merck, Darmstadt, Germany. The immunoaffinity columns (Ochraprep and Easy-extract Aflatoxin) were purchased from R-Biopharm Rhône LTD (Glasgow, Scotland, UK).

Milk analysis of OTA was performed using a new method of extraction, while AFM1 was analyzed using a standard method [17] slightly adapted to the low available amount of milk sample.

A sample of milk was homogenized and centrifuged two times at $4500 \times g$ and 4°C for 10 min. The defatted milk was conditioned at 37°C, then 2 mL of milk were diluted with 5 mL of phosphate buffered saline (PBS: NaCl 8 g/L, KCl 0.2 g/L, Na_2HPO_4 1.15 g/L, KH_2PO_4 0.2 g/L; pH 7.4) and the homogenized solution was applied to a Ochraprep column. The eluate was collected in a glass vial and then passed through an Easy-extract Aflatoxin column. After washing of both columns with 5 mL of PBS, OTA and AFM1 were slowly eluted into two graduated glass vials with 3 mL of methanol:acetic acid (98:2 v/v) and 2.5 mL of methanol, respectively. Each eluate was concentrated to a small volume by nitrogen flow, brought to 1 mL with the HPLC mobile phase and vortexed for 10 s. The extracts were filtered (Millipore Corporation, Bedford, MA, USA, HV 0.45 μm) before injection.

For both HPLC analyses, a Superspher 100 RP-18 column (4 μm particle size, 125 × 4 mm, Merck) was employed at ambient temperature. For OTA analysis, the mobile phase was ACN:2% acetic acid solution (41:59 v/v) at 1.0 mL/min and the fluorescence detector was set at 333 nm excitation and 470 nm emission wavelengths. For AFM1, the mobile phase was ACN:water (25:75 v/v) at 1.0 mL/min and the fluorescence detector was set at 365 excitation and 440 nm emission wavelengths. The injection volume for both standards and samples was 100 μL. Quantification was on the basis of peak areas using the PC software. Generally, only one analysis per sample was carried out. Figures 1 and 2 report the HPLC run of OTA and AFM1, respectively.

2.3 Equipment

The two HPLC systems consisted: the first of a PU 1580 pump equipped with an AS 1555 sampling system and a FP-1520 fluorescence detector (Jasco Corporation, Tokyo, Japan), governed by a Borwin 1.5 software (Jasco), used for OTA analysis; the second of a Series 200 pump (Perkin Elmer, Norwalk, CT, USA) equipped with an AS2055 sampling system (Jasco) and a FP-920 fluorescence detector (Jasco), governed by a Turbochrom 4 software (Perkin Elmer), used for AFM1 analysis.

Table 2. Ochratoxin A and Aflatoxin M1 (ng/L) occurrence in human milk

Mycotoxin	Samples							
			Frequency distribution				Contamination	
	Tested	Positive	<5 ng/L	5–10 ng/L	>10–50 ng/L	>50 ng/L	Range[a)]	Average[b)]
		n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)		
OTA	82	61 (74)	21 (26)	28 (34)	27 (33)	6 (7)	<5–405	30.43 ± 66.89
AFM1	82	4 (4)	78 (95)[c)]	1 (1)[d)]	2 (2)	1 (1)	<7–140	55.35 ± 58.59

a) min–max.
b) mean of positive samples ± SD.
c) <7 ng/L
d) 7–10 ng/L.

2.4 Standard solutions

OTA and AFM_1 standards were obtained from Sigma-Aldrich (St. Louis, MO, USA). A solution of OTA (40 μg/mL in benzene:acetic acid 99:1 v/v) was calibrated spectrophotometrically at 333 nm using the value 5550 $M^{-1}cm^{-1}$ for the molar extinction coefficient (A.O.A.C., 18th Ed., Gaithersburg, MD, 2005, 49.06.01, method 973.37); for AFM1, a solution (5 μg/mL in benzene:ACN 9:1 v/v) was calibrated spectrophotometrically at 350 nm using the value 18815 $M^{-1}cm^{-1}$ for the molar extinction coefficient (A.O.A.C., 18th Ed., Gaithersburg, MD, 2005, 49.02.03, method 971.22). The stock solutions were stored at −20°C when not in use. Working standards were prepared by evaporating an exact volume under a stream of nitrogen and redissolving the residue in the HPLC mobile phase. Five OTA and AFM1 standards of between 1–50 pg and 1.5–20 pg respectively, were injected.

2.5 Dietary questionnaire

For each woman a questionnaire was completed, reporting diet and eating habits focused on foods more likely to be sources of AFM1 and OTA according to the European Commission Food Science and Techniques indications [18]. Based on questionnaire results, study population was sub-grouped according to the frequency of consumption, in moderate consumers (up to seven times a week), or habitual consumers (more than seven times a week) of foods demonstrated to be likely sources of AFM1 and OTA [1]. The focused foods were: cereals foods (pasta, bread, breakfast cereals, cookies, bakery products), corn, rice, legumes, poultry, bovine meat, pork meat (fresh and cured), milk products (milk, yoghurt, cheese), beverages (white and red wine, beer, black tea, coffee, juices), fruits, dried fruits (peanuts, chestnuts, walnuts) and chocolate.

2.6 Statistical analysis

Perinatal and neonatal parameters, AFM1 and OTA (ng/L) mature milk concentrations are expressed as means ± SD. Comparison between means was evaluated by student t-test and by Mann–Whitney U test, when the data were not normally distributed, using SPSS/PC + V 2.0 statistical Package. A value of $p < 0.05$ was considered significant.

3 Results

3.1 Recoveries, detection and quantification limit

The calibration curves showed good linearity (r^2 >0.996). For the recovery experiments, an uncontaminated sow milk was used; aliquots of the milk were spiked with OTA and AFM1 at two levels, 20 and 50 ng/L. Average recoveries for three replicate samples ranged from 95.6 to 97.8%. The precision was demonstrated by a RSD always below 3.5%. All results were not corrected for recovery. The LOD and LOQ were determined by the S/N approach; the LOD and LOQ were defined at those levels resulting in S/Ns of 3 and 10, respectively. The LOD and LOQ were 2 and 5 ng/L for OTA, 3 and 7 ng/L for AFM1, respectively; accuracy and precision at LOQ levels resulted acceptable (recoveries > 90% and RSD < 8%).

3.2 Occurrence of AFM1 and OTA

AFM1 was found in four samples (5%) whereas OTA was detected in 61 (74%) of the samples (Table 2). The contamination level of AFM1 and OTA in milk ranged from <7 to 140 ng AFM1/L and from <5 to 405 ng OTA/L), respectively.

Differences were observed when comparing OTA levels in subjects grouped according to dietary and drinking habits. Indeed, basing on data collected by the dietary questionnaire, we grouped the subject according to the frequency of consumption in moderate consumers (up to seven times a week), or habitual consumers (more than seven times a week) of foods demonstrated to be likely sources of OTA. We observed that OTA levels were significantly higher ($p \leq 0.05$) in milk of habitual consumers of bread, bakery products and cured pork meat. No other statistically significant

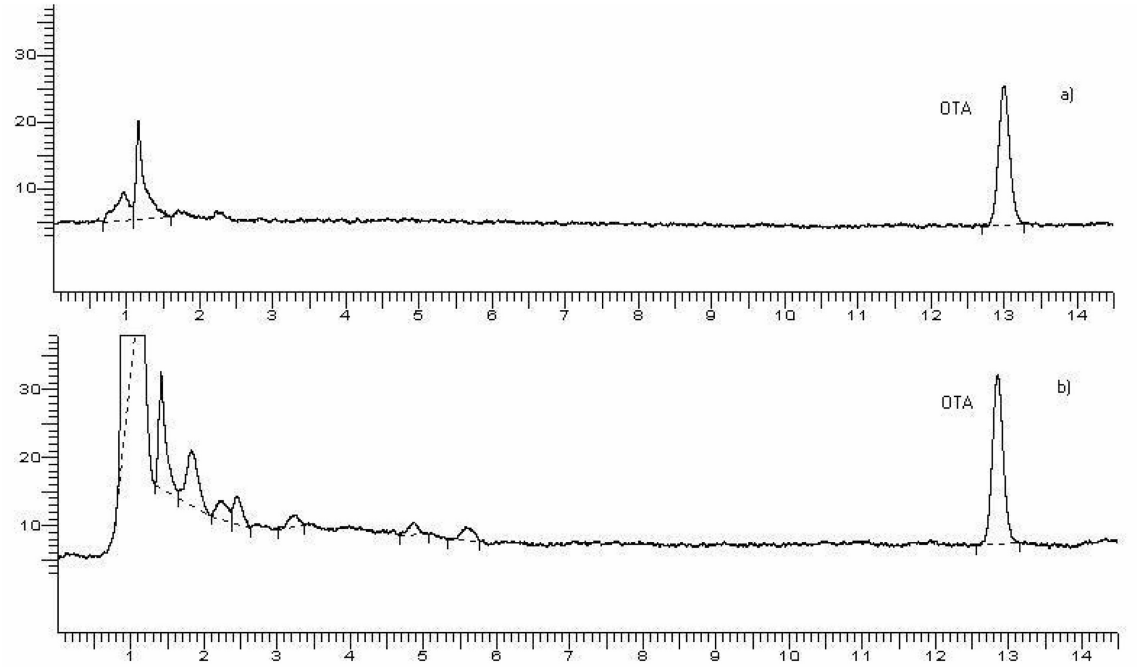

Figure 1. Chromatogram (HPLC; fluorescence detection) of: a) an OTA standard solution (479 ng/L), equivalent to 47.9 pg of OTA injected; b) a naturally-contaminated human milk sample containing 280 ng/L (equivalent to 56 pg of OTA injected).

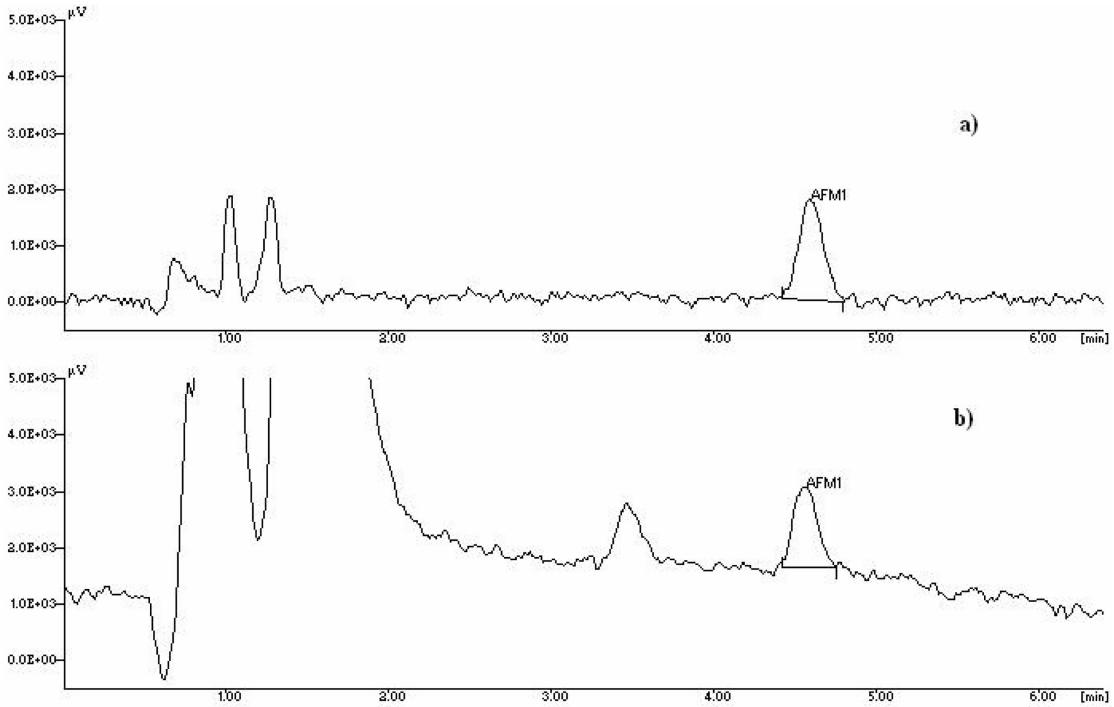

Figure 2. Chromatogram (HPLC; fluorescence detection) of: a) an AFM1 standard solution (62 ng/L), equivalent to 6.2 pg of AFM1 injected; b) a naturally-contaminated human milk sample containing 26 ng/L (equivalent to 5.2 pg of AFM1 injected).

differences were observed although habitual consumers of pasta ($p = 0.059$), cookies ($p = 0.061$) and juices ($p = 0.063$) had mean contamination values of OTA higher than moderate consumer. As specifically regards beverages no comparison was allowed for the alcoholics due to the very occasional consumption of wine and beer during pregnancy, however the frequency of OTA contamination was higher in milk from red wine moderate drinkers respect to non-drinkers. No difference were observed for other beverages such as tea and coffee, despite the latter being another possible source of OTA.

The very few AFM1 positive samples did not allow statistical comparisons. However, the donor whose milk was highly contaminated (140 ng/L) by AFM1 reported to consume largely corn meal based foods in substitution of cereal based food.

No significant seasonal differences were observed for both the mycotoxins when comparing samples collected in the period November – April with those collected in the period May – October.

4 Discussion

Mycotoxins are highly undesirable substances that unavoidably enter the human food chain. The present study provides evidence that human mature milk constitutes a biological fluid of accumulation of OTA. The incidence and the contamination level of OTA were much higher than AFM1 and the findings were clearly correlated with maternal dietary habits. The finding on the presence of AFM1 and OTA in human mature milk is consistent with previous observations and offer additional support on the debate regarding the constant need of monitoring mycotoxins accumulation in different biological fluids as well as in foods.

The different incidence of AFM1 and OTA contamination in breast milk is in agreement with previous observations related with mycotoxins spread according to geographical and climate areas [3 – 15]. A further explanation can be found in the different metabolism of the two mycotoxins. After gastrointestinal absorption, OTA is bound to serum macromolecules which constitutes a mobile reserve that can be made available for excretion for a long time [19], whereas the metabolism/excretion aflatoxins is much more rapid.

In the present study we also found that dietary and drinking habits can somewhat affect the occurrence of mycotoxins in human mature milk. In particular, a high occurrence of OTA was observed in the mothers classified as habitual consumers of bread, bakery products and cured pork meat. Of note, cereals based foods are the major contributors to human exposure to OTA, accounting for 50% to the mean European dietary intake [10], whereas pork meat is the most important dietary source of OTA among animal products [20]. These findings are in overall agreement with previous observations by Turconi *et al.* [21], as specifically concerns bread, and with Skaug *et al.* [22, 23] for what regards cereals based foods and pork products. The possibility that other food groups, such as alcoholic beverages, can trigger the OTA presence in human mature milk is intriguing, however, our data do not allow definitive conclusions. Taken together, the present findings suggest the need to provide mothers few basic dietary recommendations to tentatively reduce the presence of OTA in milk. Reducing the dietary intake of refined cereals-based foods by their partial substitution with legumes, as well as by substituting pork meat by fish or poultry, are not only two simple valid dietary strategies to minimize the occurrence of OTA in breast milk, but also good overall dietary habits suggested by a demonstrated healthy dietary model such as the Mediterranean diet. Bearing in mind that: i) the persistence of OTA in human body is prolonged due to its unfavourable kinetics of elimination [24] ii) the OTA accumulation capability in the fetoplacental unit, and the subsequent exposure to toxicity [25] iii) any dietary modification has to be done largely before the presumed birth period, all together, support the opportunity to extend the above dietary recommendations to pregnant woman.

Our finding of OTA high occurrence in milk offers additional support to the debate on the Tolerable Daily Intakes (TDI) which are aimed at defining threshold levels for adverse effect. TDI represents an estimate of the amount of a contaminant, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risks. Over the last decade, different OTA TDI have been suggested, and an exposure below 5 ng/kg/bw/day has been recommended for European countries [25]. In our series, estimated TDI are in agreement with previous observations [10] showing super imposable incidence of infants at higher (n=11; 13.4%) and close to (n=4; 5%) recommended exposure limits. Moreover, it has to be considered that, during both the breast feeding and the weaning period, other foods are often introduced which are additional sources of mycotoxins, as in the cases of dried or milk formula and cereals based baby foods, which are additional source of AFM1 [1] and OTA [26], respectively. Given that baby foods are severely regulated and controlled low levels of AFM1 and OTA are expected to be present, however it is likely that in the first period of their life infants are exposed to uncontrolled additional and contextual assumption of OTA and AFM1. Additional warnings arise from the following considerations: i) infants should be considered highly susceptible to contaminants exposure; ii) regardless their severity all of the proposed TDI have not been calculated for infants but for adults; iii) toxicological studies leading to TDI calculations are based on a single mycotoxin approach, thus possible additive or synergistic toxic effects among mycotoxins are not considered although preliminarily demonstrated [27]. Besides, even if the toxicological evaluation of OTA is still an open question, recent studies highlight the concrete possibility that OTA would be classified as a direct

genotoxic thus leading, as in the case of AFM1, to the application of the even stricter As Low as Reasonably Achievable (ALARA) principles instead of the TDI safety guidelines. In a so uncertain scenario it appears undoubtedly opportune to adopt any preventing measure aimed to prevent or reduce the risk before that definitive information on the toxicological profile of OTA become available.

In conclusion, the present data offer additional matter of debate in the occurrence of mycotoxins in biological fluids and their putative toxicological impact. The findings open up a new cue on woman dietary recommendations, during pregnancy and lactation, aimed to warrant the unique role of breast milk in infants nutrition. Further investigation for this purpose is needed.

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