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Second order probabilistic assessment of chronic dietary exposure to aflatoxin M1 in Serbia

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ABSTRACT

Considering the genotoxic and cancerogenic nature of aflatoxin M1 (AFM1), its presence in milk and dairy products may pose health risks for consumers. The chronic exposure was calculated using a two-dimensional (second order) Monte Carlo model. Results of 13 722 milk and dairy product samples analysed in the 2015–2022 period were used. Milk and dairy products intake information was collected with a Food Frequency Questionnaire (FFQ) validated by a 24-h recall-based method. Risk characterization was done by calculation of the Margin of Exposure (MOE) and by calculation of AFM1 induced number of hepatocellular carcinoma (HCC) cases. Mean AFM1 Estimated Daily Intake (EDI) was highest in children at 0.336 (CI: 0.294–0.385) ng kg^{-1} bw day^{-1}, followed by adolescents with 0.183 (CI: 0.164–0.204), then adult females with 0.161 (CI: 0.146–0.179) and finally adult males with lowest EDI of 0.126 (CI: 0.115–0.139) ng kg^{-1} bw day^{-1}. MOE values based on mean EDI for all population groups were above risk associated threshold and the number of possible HCC cases was in the range of 0.0002–0.0021 cases per year for 10^5 individuals. The results suggest low health risks due to AFM1 exposure for the whole population. Still, this risk is not non-existent, especially for children as they have a higher ratio of the population exposed to risk associated AFM1 levels, with MOE values below risk indicating threshold starting at 77.5th percentile.

1. Introduction

As secondary metabolites of some *Aspergillus* spp. members, aflatoxins (AFs) present a group of potent carcinogenic, genotoxic, and teratogenic substances that occur in various agricultural commodities. Next to the carcinogenic, genotoxic, and teratogenic effects AFs cause neurological damage, have immunosuppressive characteristics and affect early growth (IARC, 2012; Williams et al., 2004). Most health concerns for AFs are related to hepatocellular carcinoma (HCC) development. It is estimated that AFs are responsible for 4.6–28.2% of all global HCC cases (Liu and Wu, 2010) which classifies them as one of the most significant food safety and public health concerns. Aflatoxin B1 (AFB1), considered as most prevalent and most potent of all AFs, is metabolized in the liver by the action of the CYP450 superfamily of enzymes leading to the formation of, among others products, his hydroxylated form aflatoxin M1 (AFM1) which is easily secreted through milk (Battacone et al., 2005; Cullen and Newberne, 1994; Marchese et al., 2018).

As with all AFs, AFM1 is stable and resistant to heat and most of the processing treatments, therefore it is present not only in milk but also in dairy products (Farkas et al., 2022). Moreover, as it is bound to casein fractions, in some dairy products such as cottage cheese and cheese, their concentration is even higher than in milk (Farkas et al., 2022). The presence of AFM1 in milk and dairy products, even in small amounts, represents a concern, as milk represents a nutritionally complete food with especially high consumption in children who are more susceptible to the negative effects, due to their underdeveloped metabolic and immune systems (Fakhri et al., 2019; Kunter et al., 2017) and consume more milk and dairy products relative to their weight. Most countries have set permissible limits for maximum levels (ML) of AFM1 in milk and/or dairy products. The European Commission had set an ML value of 0.05 μg kg^{-1} for raw milk, heat-treated milk and milk for the

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production of milk-based products (European Commission, 2006). While Serbian regulation was initially synchronized regarding AFM1 with the European Union, a 2012/13 aflatoxin crisis has led to several changes in ML of AFM1 for Serbian milk and until the end of this year it is set at 0.25 μg kg^{-1} for raw milk, heat-treated milk and milk for the production of milk-based products (Serbian Regulation, 2022).

In recent years, there has been growing attention internationally regarding the application of probabilistic techniques for the estimation of exposure to chemicals via food (EFSA, 2012). In contrast to the deterministic methodology, probabilistic techniques allow the distribution of intakes amongst multiple individuals in a specified population to be estimated, taking into consideration the variability in food consumption between and within individuals, as well as the occurrence of chemicals in food commodities (EFSA, 2012). While deterministic methods have a high uncertainty level (arising from parameters uncertainty and variability) and first-order Monte Carlo simulation deals with parameters variability, a two-dimensional (or second-order) Monte Carlo simulation was proposed to estimate the uncertainty in the risk estimates arising from parameter uncertainty (Cullen and Frey, 1999; Pouillot and Delignette-Muller, 2010). A two-dimensional (second--order) Monte-Carlo simulation is a simulation where the distributions reflecting variability and uncertainty are sampled separately in the Monte-Carlo simulation framework, so that variability and uncertainty in the output may be estimated separately (Pouillot and Delignette-Muller, 2010). However, as the implementation of two-dimensional simulations remains difficult this approach is hardly ever used. Programming code for the two-dimensional Monte-Carlo developed by Pouillot and Delignette-Muller (2010) has successfully bridged these difficulties and recently was used in the field of mycotoxin risk assessment (Farkas et al., 2022; Gilbert-Sandoval et al., 2020).

The objective of the present study is to evaluate chronic exposure to AFM1 and to characterize the respective risk in targeted population groups in Serbia, with the use of second-order Monte-Carlo simulation to account for the variability of the used parameters and to consider associated uncertainties.

2. Materials and methods

2.1. Occurrence of aflatoxin M1

A total of 14 308 milk and dairy product samples were analysed for AFM1 between 2015 and 2022 (Table 1). Most of the samples were from local small, medium, and large producers and processing plants, effectively covering the whole territory of the Republic of Serbia, while some of the samples were imported (<1%). AFM1 was determined by an Enzyme-Linked Immuno-Sorbent Assay (ELISA) method using standard validated commercial kits (Ridascreen, R-Biopharm, Darmstadt, Germany, and I 'screen Afla M1, Tecna S.r.l., Mirandola, Italy). Samples were prepared and analysed according to the manufacturer's instructions as explained elsewhere (Milićević et al., 2021; Miocinovic et al., 2017). The analytical quality of the ELISA method was confirmed with the use of certified reference material (RealCheck AFLAM1 Milk Medium-Level MI211, Matrix Reference Material for AFM1 in bovine milk, Test Veritas S.r.l., 35 127 Padova, Italy, rev.118/06/2014). Additional quality assurance was confirmed by participation in a proficiency test of lyophilized milk organized by Test Veritas (Padova, Italy). Test results were satisfactory with the calculated z-score values in the acceptable range of −2 to 2.

From the results presented in Table 1, a total of 13 722 data points were used in the exposure assessment as 586 samples of various miscellaneous products were excluded from the exposure assessment (powdered milk, powdered yoghurt, caseinate etc.). Considering the stability of AFM1 to heat treatment (Deveci and Sezgin, 2006), values of raw and heat-treated milk samples were used as a single data group for exposure assessment. From the full set of data points four samples of raw milk, which exceeded ML values posted by Serbian regulation, were removed, following the assumption that these highly contaminated samples will not reach the final consumer due to rigorous control set by Serbian authorities following the 2012 aflatoxin crisis.

2.2. Food consumption

2.2.1. Consumer survey

Consumption surveys were performed across the territory of the Republic of Serbia in over a hundred large, medium, and small cities, and villages during the 2021–2022 period and in line with a previously published procedure (Udovicki et al., 2021). Surveys consisted of the collection of basic information about the respondents, followed by the Food Frequency Questionnaire (FFQ) and 24-h recall-based food consumption survey. Milk and dairy products intake information gathered by FFQ was used as inputs in the exposure assessment, while the 24-h recall-based food consumption questionnaire was used as an internal, validation study (Freedman et al., 2011). Both methods were based on fourteen food categories (single products or composite foods) allowing the respondents to report consumption of the products as well as the quantity of consumed products (one-half of the portion, whole portion, two or more portions). From the initial fourteen food categories (Supplementary material) nine categories were formatted for AFM1 exposure

Table 1
The occurrence of AFM1 in analysed products (n = 14 308).

Product	N (Np)	Mean (LB-UB) ng kg^{1}	Mean ± SD[a] ng kg^{-1}	Median[a] ng kg^{-1}	Quartiles[a] (Q1-Q3) ng kg^{1}	Range ng kg^{-1}	Above EU MLs
Raw milk	8181(6341)	25.5–26.6	32.9 ± 32.7	20.1	10.7–42.2	5.1–554.8	1341
Heat treated milk	1864 (1541)	18.5–19.4	22.4 ± 17.5	19.8	11.1–27.3	5.5–192.9	82
Yoghurt	1985 (1457)	17.5–20.1	23.8 ± 14.0	20.1	14.4–28.7	10.0–136.5	63
Chocolate milk and milkshakes	570 (402)	8.6–10.1	12.3 ± 6.9	10.1	7.4–14.8	5.3–44.9	0
Fermented (sour) milk	409 (320)	17.9–20.2	23.0 ± 11.8	19.8	14.4–29.2	10.0–104.1	4
Fermented cream	449 (243)	11.8–16.5	21.9 ± 24.3	16.1	11.8–25.3	10.0–294.4	7
Butter and clotted cream	141 (3)	2.5-na	116.9 ± 9.8	113.9	111.5–120.9	108.9–127.8	3
Cheese	73 (58)	129.9–140.2	163.5 ± 92.1	187.6	73.5–240.8	50.8–390.1	5[b]
Cream	50 (21)	7.4–13.2	17.7 ± 6.6	15.6	12.0–21.1	11.2–33.3	0
Various products (not included in the exposure assessment)	586 (428)	17.9–19.2	24.5 ± 21.3	19.3	10.2–29.0	5.1–131.4	40
Total	14308 (10814)						1545

N - number of samples; Np - number of positive samples;

[a] - out of positive samples; Q1-Q3 – Quartiles 1–3; LB (Lower bound) – non-detects are replaced with 0; UB (Upper bound) – non-detects were replaced with the value of Limit of Detection (LOD); LOD was 5 ng kg-1 for milk, chocolate milk and milkshakes, 10 ng kg^{1} for yoghurt, fermented milk/cream and cream; 50 ng kg^{1} for cheese and 100 ng kg^{1} for butter and clotted cream; na – not applicable;

[b] based on the value of 0.25 μg kg^{1} (Skrbic et al., 2015).

assessment, since consumption of milk, yoghurt and cheese from multiple sources were summed in single data points. Portions were defined based on the size of the products available on the market (e.g., cups of yoghurt or fermented cream, Tetra Pak of chocolate milk etc.), common household measurements (glass of milk, tablespoon of butter) and as predetermined or average portions (a portion of cooked meal, piece of cheese etc.) and for the latter one's visual aids in terms of photographs of products and defined portions were provided to the respondents. A full list of used portion sizes and quantity of products of interest in composite foods is presented in Supplementary material. FFQ provided the following responses on food consumption: 2 or more times per day, daily, 3–4 times per week, 2 times per week, weekly, 2–3 times per month, monthly, 1–6 times per year and never. 24 h-recall-based interview was based upon a simple food list approach and formatted as 24 h Food List (24hFL) as explained previously (Udovicki et al., 2021).

The tested population represents a convenient sample, and it was stratified by age according to EFSA guidelines (EFSA, 2009). Further stratification by gender was performed for the adult male and female population groups. Population groups included children (3–10 years), adolescents (11–17 years), adult females (18–64 years) and adult males (18–64 years). Finally, 220 adult females, 169 adult males, 135 adolescents and 135 children were interviewed. Data collection was mostly performed through personal interviews with respondents to avoid uncertain answers and when possible, in the respondents' homes. The recruitment of the respondents was performed outdoors, in front of various food retailers, randomly selecting citizens, as well as using an existing professional and family network, and by further dissemination of the questionnaire through their networks. Consumption surveys were performed in line with the Belgrade University Code of Professional Ethics (Belgrade University Senate, 2016). Brief explanations about the aim of the research were given to the respondents before interviewing. For children and younger adolescents, the parents of the respondents were involved (to various extents) in data collection. For those categories' parents have signed a consent form allowing the interview and subsequent use of data obtained.

2.2.2. Simulation of variability in food consumption

To simulate the variability of day-to-day food consumption, which arises from the use/consumption of different sizes of commercial packages, household items and composite foods recipes, portion sizes and quantities of products of interest (when applicable) were set as distributions within the Monte Carlo simulation. Depending on the frequency of certain size portions occurring uniform or triangular distribution was used (Supplementary material). The number of simulations was set at ten giving a tenfold increase in consumption data values for each population group. This second set was used for later distribution fitting and exposure assessment.

2.3. Probabilistic exposure assessment

2.3.1. Exposure assessment model

Two main parameters of the exposure assessment are the amount of food consumed through a specific period and food contamination data. The exposure to AFM1 was calculated as estimated daily intake (EDI) in ng per kg of body weight (bw) per day using the following formula:

$$\text{EDI (ng kg}^{-1}\text{ bw day}^{-1}) = \Sigma\ \{\text{consumption (kg day}^{-1}) \text{ x contamination (ng kg}^{-1}\text{)/bw (kg)}\} \quad (1)$$

Each of these datasets was parameterized to reflect variability and uncertainty and to create a two-dimensional (second-order) Monte-Carlo simulation framework within the R environment using "fitdistrplus" and "mc2d" packages (Delignette-Muller and Dutang, 2015; Gilbert-Sandoval et al., 2020; Pouillot and Delignette-Muller, 2010).

2.3.2. Fitting distributions to quantitative and censored data

Fitting distributions to data is a common task in statistics and consists in choosing a probability distribution modelling the random variable, as well as finding parameter estimates for that distribution (Delignette-Muller and Dutang, 2015). The package "fitdistrplus" provides functions for fitting univariate distributions to different types of data (continuous censored or non-censored data and discrete data) and allowing different estimation methods (maximum likelihood, moment matching, quantile matching and maximum goodness-of-fit estimation), giving the assessors opportunity to characterize and visualize a dataset to help choose distribution(s) (Delignette-Muller and Dutang, 2015).

When fitting non-censored data, the "descdist" function provides classical descriptive statistics, skewness, kurtosis, and a skewness–kurtosis plot as proposed by Cullen and Frey (1999), as skewness and kurtosis are often useful when selecting appropriate distribution candidates for specific dataset (Fig. 1) (Delignette-Muller and Dutang, 2015). After the selection of the most appropriate distributions, a function "fitdist" is used to estimate the parameters using the maximum likelihood estimation. Distribution is chosen based on the graphs representing empirical and theoretical distributions plot in density and cumulative density function, P–P plot and Q–Q plot or using classical goodness-of-fit statistics (Chi-squared, Kolmogorov–Smirnov and Anderson–Darling statistics) (Delignette-Muller and Dutang, 2015; Pouillot and Delignette-Muller, 2010). When choosing a distribution, an Anderson-Darling statistic is of special importance when it matters to equally emphasize the tails as well as the main body of a distribution, which is often the case in the risk assessment (Cullen and Frey, 1999). Analytical data frequently contain values that are below LOD which are referred to as no detected or censored values. This kind of data can be fitted using the function "fitdistcens" of the "fitdistrplus" package. Before their use, such data must be transferred into a data frame with two columns, respectively named left and right. The left column contains NA for non-detects and the right column contains the limit value for non-detects. During distribution fitting samples are drawn by nonparametric bootstrap (resampling with replacement from the data set) and when the function fails to converge, the value from NA range is returned (Delignette-Muller, 2022). Computations of goodness-of-fit statistics have not yet been developed for the use of censored data, but the quality of the fit can be judged using Akaike and Schwarz's Bayesian information criteria or using "cdfcompcens" function to compare the fit of various distributions to the same censored data set (Fig. 1)) (Delignette-Muller and Dutang, 2015).

Table 2 shows the fitted distribution for used data sets. Next to AFM1 concentration data, censored fitting was used for food consumption data for products with a higher number of reported non-consumers, but the right column contained values close to zero. In that manner, non-consumers were included in distribution fitting without actual influence on the outcome of the exposure assessment.

2.3.3. Modelling of uncertainty on distribution parameters and integrating uncertainty and variability in a two-dimensional Monte-Carlo simulation framework

The functions "bootdist" and "bootdistcens" was used for bootstrap resampling of estimated parameters of a fitted distribution (Pouillot and Delignette-Muller, 2010). Parametric or non-parametric bootstrap resampling is used to evaluate and simulate the uncertainty in parameters estimated from a distribution and to quantify the uncertainty on parameter estimates. The bootstrap procedures allow modelling of the uncertainty around the parameters of distributions and transfer of this information into a quantitative risk assessment model. In the following step, these bootstrap samples were transformed in the "mcnode" class of objects by using the function "mcdata" of the "mc2d" package (Pouillot and Delignette-Muller, 2010). To create a two-dimensional simulation framework, in which the estimation of variability and uncertainty in the risk estimates is separated, the function „mcstoc" is used to sample "mcnode" variability conditionally to uncertainty (Gilbert-Sandoval

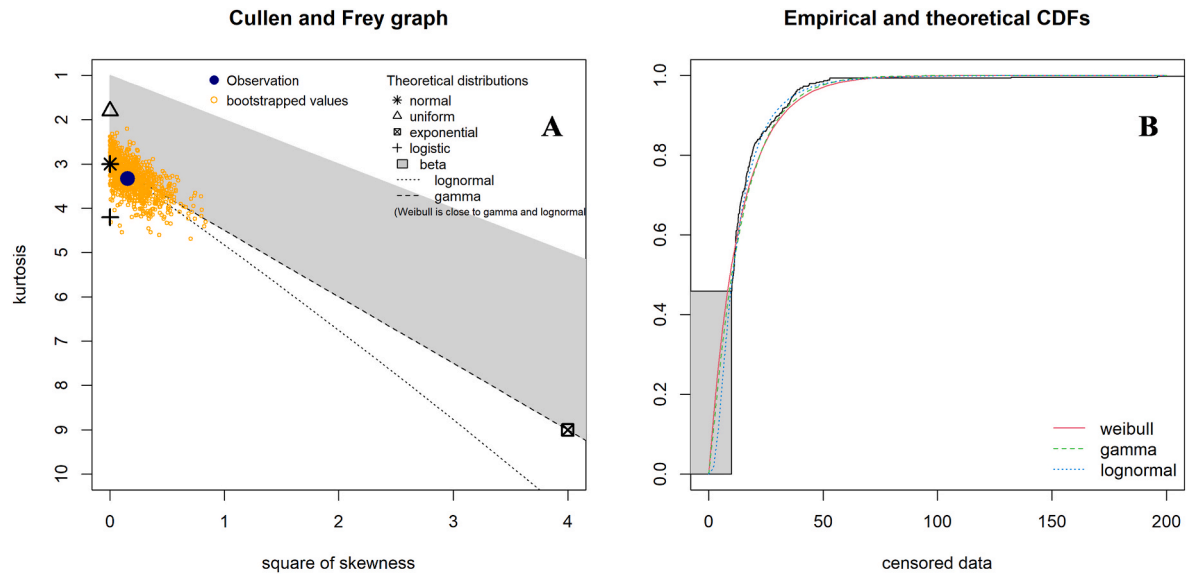

Fig. 1. The output of the (A) "descdist" function: skewness–kurtosis plot for the bodyweight of adult males; (B) output of the "cdfcompcens" function: CDF plot for the fit of a Lognormal, Gamma and a Weibull distribution to censored data of AFM1 concentration in fermented cream.

Table 2
Best fit distributions on body weight, AFM1 concentration, and food consumption.

	AFM1	Food intake			
		Adult males	Adult females	Adolescents	Children
Milk	Lognormal (censored)	Gamma	Gamma	Gamma	Weibull
Chocolate milk and milkshakes	Gamma (censored)	Gamma (censored)	Gamma (censored)	Gamma (censored)	Gamma (censored)
Yoghurt	Lognormal (censored)	Weibull	Weibull	Gamma	Weibull
Fermented (sour) milk	Gamma (censored)	Gamma (censored)	Gamma (censored)	Gamma (censored)	Gamma (censored)
Fermented cream	Lognormal (censored)	Gamma	Gamma	Gamma	Gamma
Butter and clotted cream	Deterministic (mean of all samples)[a]	Weibull	Weibull	Lognormal	Gamma (censored)
Desserts	Milk data - lognormal (censored)	Gamma (censored)	Gamma (censored)	Gamma (censored)	Gamma (censored)
Cheese	Weibull (censored)	Weibull	Weibull	Weibull	Weibull
Cream	Gamma (censored)	Gamma (censored)	Gamma (censored)	Gamma (censored)	Gamma (censored)
Body weight		Lognormal	Lognormal	Lognormal	Lognormal[b]

[a] Due to high LOD.
[b] Best fit was gamma which produced a range of body weight below/above physiological values for the population group.

et al., 2020; Pouillot and Delignette-Muller, 2010). As uncertainty and variability are automatically transferred to the outputs of the model, EDI was obtained using standard arithmetic operations. The code for all the steps is included in Appendix A of this paper.

2.4. Risk characterisation

Risk characterization was done by two approaches: an HCC risk calculation proposed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (1999) and a Margin of Exposure (MOE) calculation proposed by EFSA (2005), for substances that are both genotoxic and carcinogenic.

The HCC risk approach is based on the carcinogenic potency of AFB1 resulting from synergistic hepato-carcinogenic effects of AFB1 and hepatitis B virus infection (FAO/WHO, 1999). As AFM1 is a metabolite of AFB1, it is presumed that AFM1 induces liver cancer by a similar mechanism. Using the comparative data for carcinogenic potency JECFA assumed that the potency of AFM1 is 2–10% that of AFB1. Therefore, the carcinogenic potency of AFM1, based on the model estimate mean (UB) for AFB1 (FAO/WHO, 2018), was estimated to be 0.0269 (0.0562) additional cancer cases per year for 10^5 individuals per 1 ng kg $^{-1}$ bw day $^{-1}$ for hepatitis B virus surface antigen positive ($HBsAg^+$) population group and 0.0017 (0.0049) additional cancer cases per 100 000/year additional cancer cases per year for10^5 individuals per 1 ng kg $^{-1}$ bw day $^{-1}$ for hepatitis B virus surface antigen negative (HBsAg) population group. Taking into regard the prevalence of $HBsAg^+$ individuals in a certain population the carcinogenic potency of AFM1 is calculated as follows:

$$\text{Carcinogenic potency} = 0.0269\ (0.0562) \times \%HBsAg^+ + 0.0017\ (0.0049) \times \%\ HBsAg^- \quad (2)$$

For the calculation of carcinogenic potency lower estimate of 1.2% HBsAg+, reported for the European region (WHO, 2017), was used for this study. The risk of the yearly occurrence of new HCC cases resulting from exposure to AFM1 was calculated as follows:

$$\text{HCC risk} = \text{EDI} \times \text{Carcinogenic potency} \quad (3)$$

The MOE is defined as the ratio between a toxicological reference point, corresponding to a dose that causes a low but measurable response, and the estimated intake. EFSA recommended the use of the $BMDL_{10}$ (benchmark dose lower confidence limit 10%) as a reference point (EFSA, 2005). $BMDL_{10}$ is an estimate of the lowest dose which is 95% certain to cause no more than a 10% cancer incidence in rodents. The $BMDL_{10}$ value for AFM1 is based on the $BMDL_{10}$ of 0.4 μg kg $^{-1}$ bw day $^{-1}$ day derived for AFB1 and a potency reduction factor of 0.1 (EFSA, 2020). If the MOE value is less than 10 000 the EDI is considered of concern from a public health point of view. While MOE values cannot directly be linked to the measure of risk, a smaller MOE indicates a

higher concern.

2.5. Statistical analysis

Basic descriptive statistical processing was performed using MS Excel (MS Office 365, Redmond, WA, USA). Paired samples *t*-Test and Wilcoxon Signed Ranks Test for testing the difference between consumption data obtained by two methods and after Monte Carlo simulation were performed with the SPSS Statistic software package (SPSS 17.0, SPSS Inc., Chicago, IL, USA). Monte Carlo simulation of variability in food consumption was performed with free ARGO Monte Carlo simulation software (ARGO, 2016). Two-dimensional Monte Carlo analysis along with fitting distribution sets and graph plotting was performed in R: A language and environment for statistical computing (R Core Team, 2022).

3. Results and discussion

3.1. Food consumption

Milk and dairy product consumption information was mathematically processed to represent the average amount (g) of milk and dairy products consumed per day for the entire population. Table 3 shows the mean values of the initial food consumption survey and mean values after the Monte Carlo simulation (in brackets {}).

Results presented in Table 3 indicated a high level of agreement for the consumption data obtained by the two methods. For significantly different groups, in most cases, FFQ data were higher compared to 24hFL data, except for cream intake by adult females and cheese intake by children where 24hFL data were higher. Considering both relatively low food intake and lower AFM1 concentration levels, for most of these product/population group combinations, the overall impact on the exposure was assumed as low. Only cheese intake for the children population group could lead to a certain level of underestimation of AFM1 exposure.

Also, only one product/population group combination (cream intake in the children population group) has shown a significant difference between estimated mean food intake before and after the Monte Carlo simulation, thus showing the validity of the approach to simulate variability in food consumption. Changes were observed in both the low and the high end of the range of the possible consumption values, which was expected (and intended) as these variations were included within distributions of Monte Carlo simulation (Supplementary material).

3.2. Exposure assessment and risk characterization

As the final output (Table 4, Fig. 2), EDI is displayed in the variability dimension. The mean, median or specific percentile may be used as a point estimate of this statistic (Pouillot and Delignette-Muller, 2010). The uncertainty dimension of the statistic is evaluated by the 2.5th and the 97.5th percentiles (and median) of each statistic which is used to establish a 95% credible interval (CI95) (Pouillot and Delignette-Muller, 2010).

The highest exposure was observed in children with mean AFM1 EDI of 0.336 (CI: 0.294–0.385) ng kg^{-1} bw day^{-1}, followed by adolescents with 0.183 (CI: 0.164–0.204) ng kg^{-1} bw day^{-1}, then adult females with mean EDI of 0.161 (CI: 0.146–0.179) ng kg^{-1} bw day^{-1} and finally adult males with 0.126 (CI: 0.115–0.139) ng kg^{-1} bw day^{-1}. Maximum EDI could reach a value of 9.100, 4.350, 3.510 and 2.187 ng kg^{-1} bw day^{-1} for children, adolescents, adult females, and adult males, respectively. However, for children, and arguably for adolescents, this is an unlikely scenario.

The main contributors to the total AFM1 exposure were milk, yoghurt, and cheese for all population groups. Milk contribution was in the range of 32% (adult males) to 52% (children), yoghurt contributed to a range of 18% (adolescents) to 24% (adult males) and cheese contributed to the total exposure with AFM1 in the range of 14% (children) to 31% (adult males). All fermented dairy products contributed to the total AFM1 exposure in a range of 24% (adolescents) to 31% (adult males). Details on the contribution of specific categories to the total AFM1 intake are presented in Fig. 3.

MOE values based on mean EDI for all population groups were above risk associated threshold (Table 5) indicating low or no risk to public health. Higher exposure and lower MOE values related to the presence of risk were observed in the higher percentiles of exposure. Only the children population group had a higher ratio of the population exposed to risk associated AFM1 levels with MOE values below 10 000 starts at 77.5th percentile of exposure, while these values start at 91.5th, 93.5th and 97th percentile of exposure for adolescents, adult females, and adult males, respectively. The estimated number of additional cancer cases attributed to the AFM1 is seemingly low (Table 5), but an excess lifetime cancer risk higher than 10^{-5} is considered to be of risk for health concern (EFSA, 2020). Compared to the estimation of AFB1-induced cancer risk for the same population groups (Udovicki et al., 2021), AFM1 will generally make a low contribution to the total number of AFs-induced HCC cases.

Reported EDIs from this study are far lower than initial exposure assessments on AFM1 in Serbia. Kos et al. (2014) estimated mean AFM1 exposure in the range of 0.42–2.34 ng kg^{-1} bw day^{-1} for corresponding

Table 3
The mean intake of milk and dairy products by population groups (g day^{-1}).

Product	Food intake {modelled food intake} (g day^{-1})							
	Adult female		Adult male		Adolescents		Children	
	Mean intake	Median (Q1-Q3)	Mean intake	Median (Q1-Q3)	Mean intake	Median (Q1-Q3)	Mean intake	Median (Q1-Q3)
Milk	159.6 {160.1}	103.3 (32.8–227.7)	129.7 {131.2}	78.9 (28.2–188.5)	178.0 {181.3}	115.9 (57.2–210.5)	148.5 {157.1}	100.0 (47.6–201.5)
Chocolate milk and milkshakes	16.4 {16.0}	0.9 (0.0–10.7)	19.7 {19.6}	0.9 (0.0–16.1)	29.4 {29.3}	7.4 (1.4–32.2)	24.1 {24.3}	7.4 (0.9–32.2)
Yoghurt	102.2 {107.1}	90.0 (25.7–115.8)	113.1 {130.9}	90.0 (29.5–180.0)	86.0 {93.3}	51.5 (25.7–108.7)	80.5 {84.9}	51.5 (25.7–90.9)
Fermented (sour) milk	18.0 {17.7}	5.9 (1.5–25.7)	27.4 {27.1}	12.9 (1.5–25.7)	13.3 {12.9}	3.0 (0.7–20.3)	19.5 {19.0}	7.5 (0.7–25.7)
Fermented cream	18.7[a] {19.1}	12.9 (3.7–22.5)	20.9[a] {22.5}	12.9 (3.7–22.5)	26.7[a] {27.5}	12.9 (6.4–45.0)	17.4 {18.0}	12.9 (3.0–22.5)
Butter and clotted cream	3.7 {4.0}	1.2 (0.2–4.0)	5.7[a] {5.8}	2.1 (0.5–7.5)	3.8 {4.1}	0.5 (0.1–3.2)	1.6 {1.8}	0.5 (0.0–2.0)
Desserts	12.8 {9.6}	3.1 (0.4–13.4)	15.7 {12.8}	1.5 (0.0–7.8)	13.2 {12.3}	3.1 (0.4–10.6)	7.3 {6.3}	0.8 (0.0–7.8)
Cheese	20.9 {20.2}	12.9 (5.5–26.5)	23.1 {22.5}	17.6 (7.5–30.7)	16.2 {16.5}	9.3 (3.7–20.5)	8.6[a] {8.3}	5.2 (2.4–12.1)
Cream	8.6[a] {8.4}	2.9 (0.4–12.5)	9.6 {9.1}	2.9 (0.7–12.5)	6.6[a] {7.2}	2.9 (0.7–7.3)	2.7 {2.4}[b]	1.4 (0.0–3.6)

Q1-Q3 – Quartiles 1-3.
a – Significantly different (α = 0.05) compared to 24hFL data (not shown).
b - Significantly different (α = 0.05) after Monte Carlo simulation.

Table 4
Chronic Estimated Daily Intake of AFM1 (ng kg^{-1} bw day^{-1}) in variability and uncertainty dimensions.

	Mean	SD	Min	2.5th	25th	50th	75th	90th	95th	99th
Adult females										
Median	0.161	0.204	0.005	0.018	0.059	0.106	0.190	0.325	0.457	0.914
Mean	0.161	0.216	0.005	0.018	0.059	0.106	0.190	0.325	0.457	0.928
2.5th	0.146	0.156	0.002	0.015	0.053	0.097	0.172	0.288	0.399	0.721
97.5th	0.179	0.345	0.009	0.022	0.066	0.116	0.208	0.362	0.522	1.222
Adult males										
Median	0.126	0.131	0.006	0.019	0.056	0.093	0.151	0.238	0.319	0.612
Mean	0.126	0.140	0.006	0.019	0.056	0.093	0.151	0.238	0.321	0.623
2.5th	0.115	0.104	0.002	0.016	0.050	0.084	0.136	0.212	0.283	0.491
97.5th	0.139	0.228	0.010	0.023	0.063	0.103	0.167	0.264	0.363	0.820
Adolescents										
Median	0.183	0.248	0.006	0.020	0.064	0.116	0.211	0.368	0.524	1.119
Mean	0.183	0.264	0.006	0.020	0.064	0.116	0.211	0.368	0.526	1.132
2.5th	0.164	0.182	0.002	0.017	0.058	0.105	0.190	0.326	0.453	0.849
97.5th	0.204	0.434	0.010	0.024	0.071	0.128	0.233	0.418	0.605	1.504
Children										
Median	0.335	0.508	0.008	0.032	0.107	0.200	0.374	0.682	1.003	2.240
Mean	0.336	0.540	0.008	0.031	0.107	0.200	0.375	0.684	1.009	2.280
2.5th	0.294	0.362	0.003	0.026	0.094	0.180	0.332	0.595	0.851	1.700
97.5th	0.385	0.918	0.015	0.038	0.119	0.223	0.419	0.784	1.192	3.070

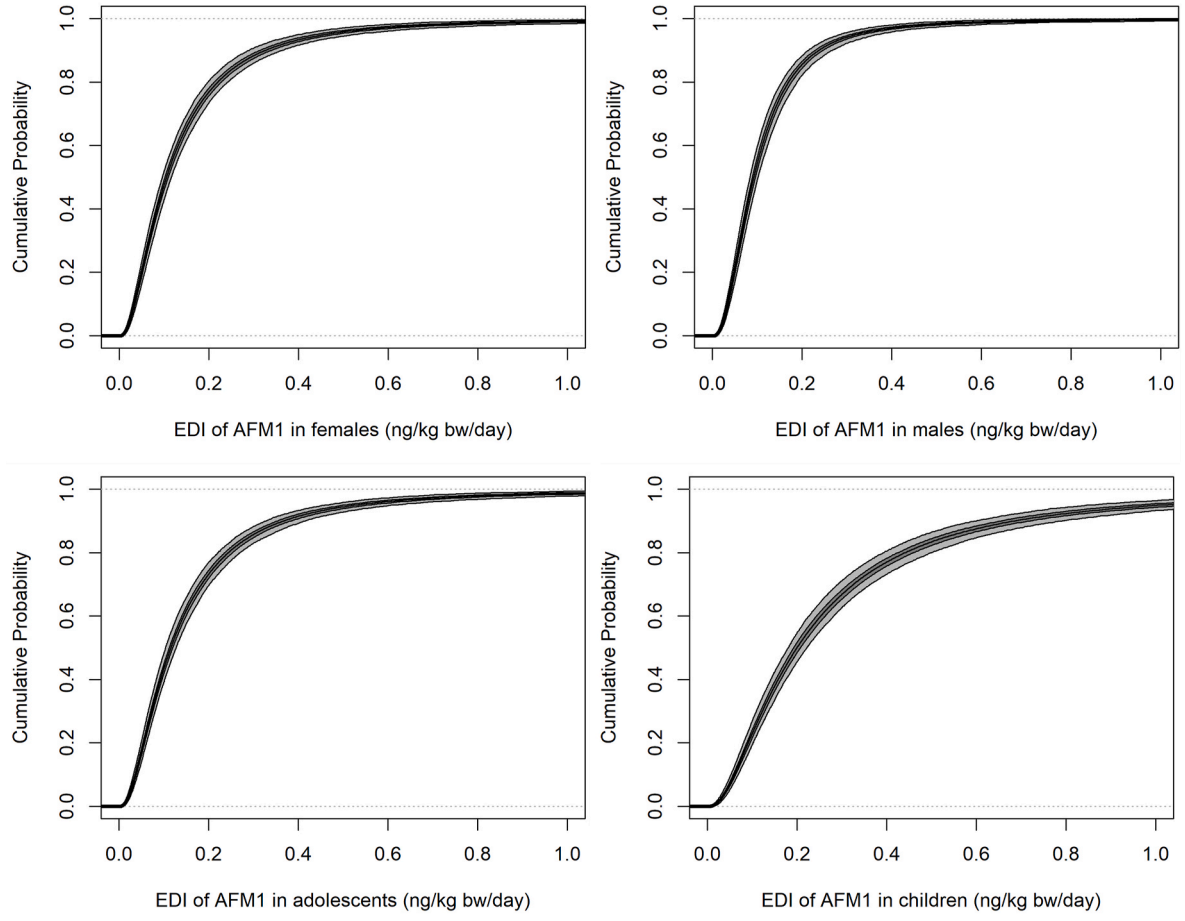

Fig. 2. Cumulative distribution plots of the output of the AFM1 exposure model, with uncertainty indicated: light grey band corresponds to the 95% uncertainty range on each quantile of variability and the dark grey band corresponds to the 50% uncertainty range on each quantile of variability (Pouillot and Delignette-Muller, 2010).

age/gender categories, while Torovic (2015) estimated mean AFM1 exposure in adults at 0.54–0.60 ng kg^{-1} bw day^{-1} using 2013 AFM1 concentration data, and at 0.06 ng kg^{-1} bw day^{-1} using 2014 AFM1 concentration data. Udovicki et al. (2019) estimated exposure of the student population in the range of 1.238–2.674 ng kg^{-1} bw day^{-1}. These researches were based on the occurrence and concentration data exclusively or mostly from the years during and following AFs crisis i.e. years with high occurrence and high levels of AFM1 in milk and dairy products (Kos et al., 2014; Skrbic et al., 2014; Torović, 2015). On the other hand, Milicevic et al. (2021) estimated mean exposure of the

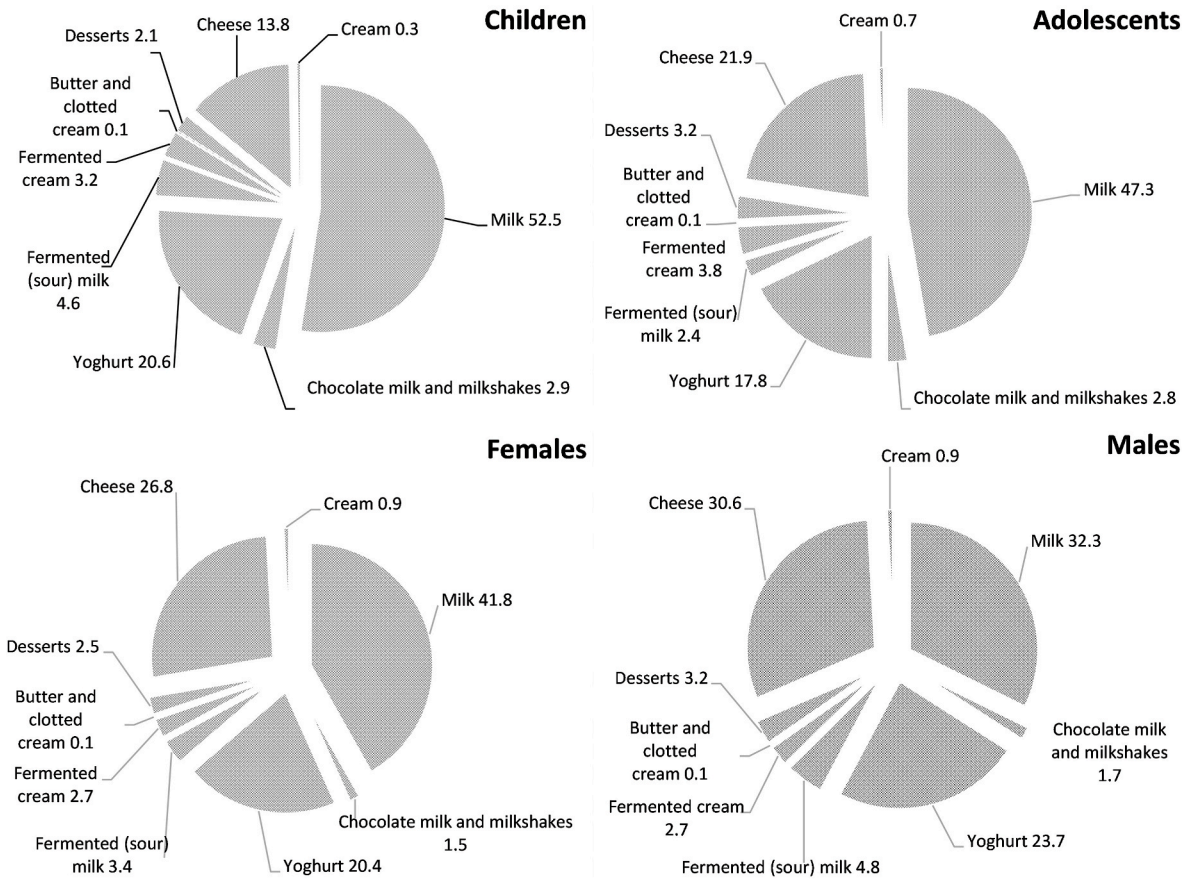

Fig. 3. The relative contribution (%) of specific food categories to total AFM1 intake.

Table 5
Risk characterizations based on mean values of AFM1 Estimated Daily Intakes.

		MOE	HCC risk	
			Mean AFM1 potency	Upper-bound AFM1 potency
Adult females	**Mean**	24845	0.0003	0.0009
	2.5th	27397	0.0003	0.0008
	97.5th	22346	0.0004	0.0010
Adult males	**Mean**	31746	0.0003	0.0007
	2.5th	34783	0.0002	0.0006
	97.5th	28777	0.0003	0.0008
Adolescents	**Mean**	21858	0.0004	0.0010
	2.5th	24390	0.0003	0.0009
	97.5th	19608	0.0004	0.0011
Children	**Mean**	11905	0.0007	0.0019
	2.5th	13605	0.0006	0.0016
	97.5th	10390	0.0008	0.0021

MOE – Margin of Exposure; HCC risk - cases per year for10^5 individuals; Mean potency - 0.0017 (HBsAg-)/0.0269 (HBsAg$^+$) cases/year/10^5 individuals per 1 ng kg^{-1} bw day^{-1}; 95th potency - 0.0049 (HBsAg-)/0.0562 (HBsAg+) cases/year/10^5 individuals per 1 ng kg^{-1} bw day^{-1}.

children population group (3–9 years) in the range of 0.190–0.277 ng kg^{-1} bw day^{-1} with the use of AFM1 concentration data from the 2017–2019 period which were, for some of the products, lower than data sets used in this study. While the results of our study are far from alarming, and exposure is most likely reduced in recent years, precautions should be made as recent climate patterns and estimated effects of climate change impact on the presence of mycotoxins in food and feed (Battilani et al., 2012).

Comparable exposures for the populations of the European countries are usually lower, as European Union food safety standards are the highest in an international comparison. An early study by Leblanc et al. (2005) estimated the average intake of AFM1 in the adult French population at 0.09 ng kg^{-1} bw day^{-1}, while Cano-Sancho et al. (2010) estimated the mean exposure of the Catalonian population to be in average 0.209, 0.74 and 0.039 ng kg^{-1} bw day^{-1} for children, adolescents and adults, respectively. Serraino et al. (2019) estimated exposure among Italian adults in the range of 0.02 and 0.08 ng kg^{-1} bw day^{-1}. Roila et al. (2021) estimated mean chronic AFM1 exposure in the range of 0.05–0.15 ng kg^{-1} bw day^{-1} for corresponding age categories in Italy, with the main contributor represented by drinking milk, followed by the consumption of soft cheeses. Probabilistic exposure assessment of the Hungarian consumers has shown that the median exposure of children is 0.073 ng kg^{-1} bw day^{-1} (CI: 0.046–0.141), of adolescents 0.037 ng kg^{-1} bw day^{-1} (CI: 0.022–0.071) and for adults 0.031 ng kg^{-1} bw day^{-1} (Farkas et al., 2022). The estimated mean number of HCC cases in this study was in the range of 0.000005 and 0.00014 cases per year for 10^5 individuals for corresponding age categories.

On the other hand, many countries have an increased risk of exposure to AFM1 and AFs in general, especially those in African and Asian regions. These regions usually have an increased risk of HCC occurrence as HBV prevalence is, in most cases, increased compared to the European region (Schweitzer et al., 2015). Exposure to AFM1 in Kenia ranged from 3.5 ng kg^{-1} bw day^{-1} in the children population group to 0.8 ng kg^{-1} bw day^{-1} for the adult population group and with an average of 0.004 additional cases of HCC per 10^5 individuals yearly (Ahlberg et al., 2018). Probable mean daily exposure to AFM1 in Malawi was 8.28 ng kg^{-1} bw day^{-1} for children and 4.98 ng kg^{-1} bw day^{-1} for adults, with the estimated HCC case in the range of 0.038 and 0.023 cases per year

for10^5 individuals, respectively (Njombwa et al., 2021). Kaur et al. (2021) estimated the daily intake of AFM1 in the 1–9 years age group at the 7.3 ng kg^{-1} bw day^{-1}, in the 10–20 years old age group at the 2.4 ng kg^{-1} bw day^{-1}, and in the age group of 21–60 years old at 1.3 ng kg^{-1} bw day^{-1} for the population of Ludhiana, Punjab.

While uncertainties related to the lower number of samples for some products and consumption variations were reduced using second-order Monte Carlo simulation, estimated exposure may be higher as milk and dairy products are part of the other composite foods not included in this study. Also, some level of uncertainty could be attributed to the negative trend in the consumption of milk and dairy products in recent years (Milićević et al., 2021).

4. Conclusions

The results of this study suggest low health risks due to AFM1 exposure in all population groups. Still, this risk is not non-existing, especially for children population group, considering the continuous exposure to AFM1, as milk and dairy product are frequently consumed during their entire life, which may have a cumulative effect on the cancer risk. Exposure of the Serbian population was distinctively higher than exposure reported for some European countries in recent periods indicating the need for stricter regulation regarding the presence of AFM1 in milk and dairy products along with their continuous monitoring. This monitoring should include the presence of AFB1 in dairy animal feed, along with the implementation of good agricultural practices and good storage practices as a means of preventing AFM1 occurrence in milk.

Author contributions

B.U.: Conceptualization, Data curation, Formal analysis, Software, Investigation, Methodology, Visualization, Writing – original draft. T.K.: Investigation, Writing – review & editing. B.A.: Investigation, Writing – review & editing. N.S.: Visualization, Writing – review & editing. A.R.: Methodology, Validation, Writing – review & editing.

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

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Appendix A. Supplementary data

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