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CLIMATE CHANGE: IMPACT ON MYCOTOXINS INCIDENCE AND FOOD SAFETY

Dragan Milicevic*, Brankica Lakicevic, Radivoj Petronijevic, Zoran Petrovic, Jelena Jovanovic, Srdjan Stefanovic, Sasa Jankovic
Institute of Meat Hygiene and Technology, Belgrade, Serbia

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Abstract
Climate change may have an impact on the occurrence of food safety hazards along the entire agri-food chain, from farm to fork. The interactions between environmental factors and food contamination, food safety and foodborne diseases are very complex, dynamic and difficult to predict. Extreme weather conditions such as floods and droughts which have not occurred previously in Serbia, may be supporting factors to contamination of crops by various species of toxigenic fungi and related mycotoxins. Mycotoxins are a group of naturally occurring toxic chemical substances, produced mainly by microscopic filamentous fungal species that commonly grow on a number of crops and that cause adverse health effects when consumed by humans and animals. Recent drought and then flooding confirmed that Serbia is one of the few European countries with very high risk exposure to natural hazards, as well as that mycotoxins are one of the foodborne hazards most susceptible to climate change.

Introduction

Serbia is one of the leading agriculture producing countries in the region, which has made agricultural production traditionally an important part of the national economy. According to the Statistical Office of the Republic of Serbia [1], the agriculture accounts for about 15,9 % of Gross Domestic Product (GDP) in - 3rdQuarter 2018. Climate change is a current global concern due to the continuing controversy about the magnitude of its effects on the food production systems and food supply chain. The impact of climate change on agriculture is particularly high in undeveloped and developing countries such as Serbia, due to the difficult economic situation and small investments in the improvement, particularly of primary production. The FAO/UN [2] Convention on Climate Change defines climate change as "a change of climate which is attributed directly or indirectly to human activity that alters the composition of the global atmosphere and which is in addition to natural climate variability observed over comparable time periods." The impacts of climate change on food, environmental and agriculture are interrelated across public health, social and economic dimensions. Therefore, the Convention defines adverse effects of climate change as changes that have deleterious effects on ecosystems, socio-economic systems, and human and animal welfare. One of the main objectives of the Convention is to predict how climate change could affect food safety and quality and to establish generic model risk management policies for mycotoxins contamination, because all of the factors involved in climate change will vary depending on the region or the country. This study review: 1) the potential impacts of predicted changes in climate on mycotoxins contamination 2) to discuss their implications on the food supply chain and possible consequences for public health and finally to 3) identifies adaptation strategies and research priorities to address food safety implications of climate change from the Serbian perspective.

An overview of the country profile

Serbia is a country situated at the crossroads between Central and Southern Europe on the Balkan Peninsula. In 2017 the total population was 7 million. The climate of Serbia can be classified as a warm-humid continental or humid subtropical climate, with more or less pronounced local characteristics (Figure 1). The hottest month is July with a apsolulte maximum air temperature ranging from 37.1 to 42.3 °C. Most of Serbia has a continental rainfall regime, with larger quantities in the warmer half of the year, except in the southwestern regions where the highest precipitation is measured in autumn. The worst is June, when an average of 12 % to 13 % of the total annual rainfall drops on average. The least precipitation occurs in February and October [3]. The country's economy is dominated by the industrial sector and agriculture. Serbia is one of the main grain producers and exporters in Europe (wheat, maize) [4].

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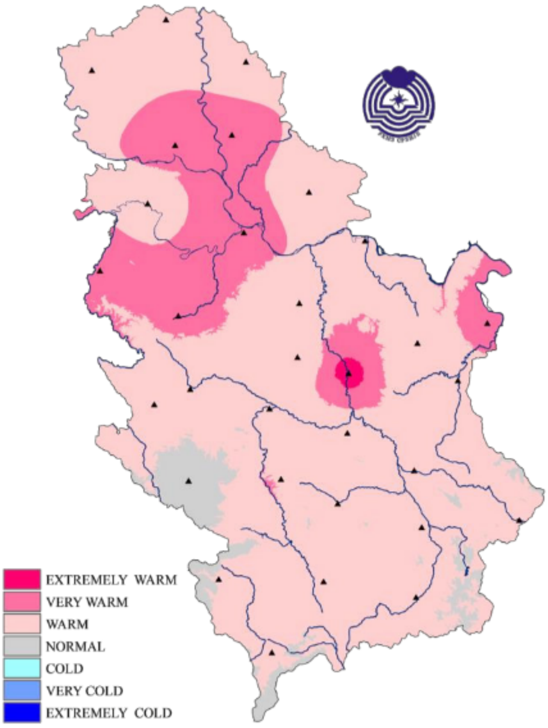

Figure 1. Spatial distribution of the mean annual air temperature based on the percentile method [3]

Food control management

Depending on the purpose, food control management could be defined as "the mandatory regulatory activity of the enforcement of food laws and regulations by national or local authorities to provide consumer protection and ensure that all foods during production, handling, storage, processing and distribution are safe, wholesome and fit for human consumption; conform to safety and quality requirements; and are honestly and accurately labelled as prescribed by law" [5]. In addition to this, food control managementhas been defined as "a continuous process of planning, organizing, monitoring, coordinating and communicating, in an integrated way, a broad range of risk-based decisions and actions to ensure the safety and quality of domestically produced, imported and exported food for national consumers and export markets as appropriate" According to Codex Alimentarius Commission [6] working principles food safety should be based on risk analysis with an integrated-longitudinale from farm to table approach. In Serbia, competences for food and feed safety, animal health, animal welfare and plant health are assigned at national level to Ministries and their related agencies. The Ministry of Agriculture is the leading ministry involved in the food chain. Within the Ministry, Veterinary Directorate, Plant Protection Administration and Directorate for National Reference Laboratories has overall responsibility for food and feed safety. The Ministry's of Health (Sector for Inspection) role, in the context of the food safety system, is limited and responsible for the official controls of food contact materials, food supplements and food for particular nutritional uses.

Official food control laboratories

According to international agencies responsible for food safety and quality, laboratories are an essential component of a food control system and require considerable resources to set up, maintain and operate. Official food control laboratories are accredited by the Serbian accreditation body (ATS) according to ISO 17025, and participating in the inter-laboratory proficiency testing schemes. However, the regulatory laboratories are managed by different ministries, thus the lack of effective coordination among the different laboratories causes duplication in the work and a waste of resources. Harmonization of methods and techniques is one of the challenges in the official laboratories in Serbia, where each individual laboratory often follows its own analytical methods. However, food standards and limits published by the Institute for Standardization of Serbia are followed by most laboratories unless international requirements apply.

Impact of climate change factors in Serbia on growth and mycotoxin production

Over the last three decades a lot of works has been focused on the environmental impact on growth and mycotoxin production by a wide range of mycotoxigenic fungi. Most of them revealed that climate changes have a great impact on growth of many mycotoxigenic fungi. As mentioned, temperature and water activity (aw) is a primary determining factor that modulates fungal growth and mycotoxin production [7]. Therefore, drought is a modulator of mycotoxin contamination that is expected to be more frequent, depending on geography. Serbia has a continental to moderate continental climate. The country often has heavy rainfall. The temperatures (up to 40 °C) and relative humidity (up to 80 %) are high throughout the year. According to a report by the Republic Hydrometeorological Service of Serbia, climatic changes resulted in specific extreme conditions, which have not occurred previously in Serbia in the period from 2011 to 2013 and 2015 producion years. Prolonged periods of extremely high air temperatures during summer of 2012 (daily temperatures near 40 °C) (Figure 2), as well as precipitation deficit, resulted in highest average frequency of *Aspergillus spp.* particularly *A. flavus* and *A. niger* on the analyzed grain [8]. In addition, after high air temperatures during summer, heavy total rainfall was recorded during the winter of 2011/2012 and 2012/2013, thus in most of Serbia location precipitation was on the historical maximum. This consequently induced a high average moisture content in harvested maize kernels (>12 %), followed by *Fusarium* and *Penicillium* growth and production of related mycotoxins. Diseases produced by *Fusarium* toxins are one of the major threats to farmers in Serbia [9]. Under such climate conditions a high presence of mycotoxins can be expected, as well as the co-occurrence of multiple mycotoxins in cereals [10]. Since the presence of mycotoxins may potentially affect human and animal health, maximum levels (ML) have been established for

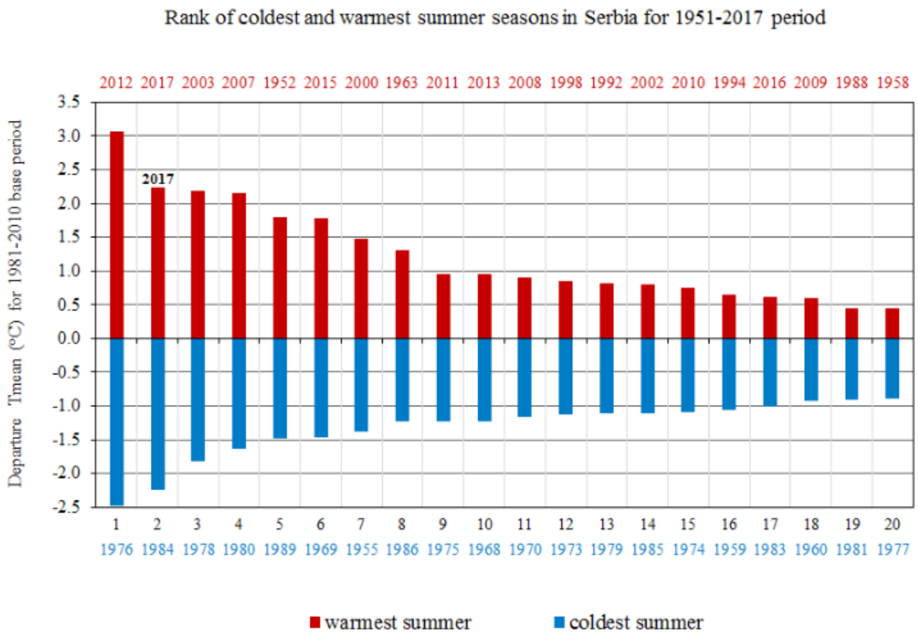

Figure 2. Rank of coldest and warmest summer seasons in Serbia for 1951-2017 period [3]

11 mycotoxins in food: AFTs (the sum of AFB1, B2, G1, and G2) as well as AFB1 alone and AFM1, the sum of FUMs (FB1, FB), OTA, patulin, DON and ZEA [11]. The MLs for feedstuffs were set as mentioned above mycotoxins, except for patulin and FUMs [12].

Maize is one of the major feedingstuffs in the world because of its importance as a main source of energy and protein in animal feeding. In relation to the previous year in Serbia crop production decreased by 23.5 % however, maize is one of the most important agricultural products, both by its production and by the profit it generates in foreign trade. During the 2015–2017 season was 5,4 t/ha, 7,3 t/ha and 4,0 t/ha, respectively [4]. Damage in the production and export of animal feed and dairy products from Serbia caused by contamination of milk and corn by aflatoxins during 2012-2013. are estimated at around 100 and 125 million euros. Costs arising from increased sampling and analysis, as well as investing in additional research can not be estimated. On the basis of rough indicators, economic damage due to lack of adaptatione strategies of Serbian agriculture on the resulting climatic changes, it can be concluded how important is the development of preventive models for preventing food contamination of molds and mycotoxins [10]. Knowledge of environmental factors which support fungi to colonize, growth, and interact with plants is important in order to better understand the variation in the population structures of mycotoxigenic fungi and their ability to produce mycotoxins. Thus, climate change has the potential to increase the risks of new fungal genotypes, usualy involved in food and feed safety.

Occurrence, significance, and toxicity of mycotoxins

The most important agro-economic and public health classes of mycotoxins are aflatoxins (AFTs), ochratoxin A (OTA), zearalenone (ZEA), trichothecenes (TCT), and fumonisins (FUMs) produced by species of *Aspergillus*, *Penicillium* and *Fusarium* [13,14]. In this section we tries to briefly review the important classes of mycotoxins, incidence related to climate changes and discuss to their role in public health risk assessment. Considering that AFTs, DON, FUMs, ZEA, TCT, and OTA are the most frequently studied mycotoxins, on which there are more data, in Tables 1 to 5 an overview of mycotoxins occurrence in different commodities in Serbia since 2010 is presented.

Aflatoxins

Mycological examination of barley, maize, soybean, sunflower, and wheat from different environments in Serbia during 2008–2012 showed that themost frequently isolated genus was *Aspergillus*, particularly *A. flavus* and *A. niger*, although other *Aspergillus spp.* were very rarely detected. Depending on environmental conditions, the highest average frequency of *A. flavus* on the analyzed grain occurred in 2012, then in 2010, and was much lower, and with similar levels in 2008, 2009, and 2011. Before 2008, *Aspergillus spp.* in Serbian grain occurred mostly at low frequency and incidence, but the very high temperatures and extreme drought in 2012 caused *A. flavus* to occur in epidemic proportions [8]. Table 1 and Figure 3 summarizes studies on the incidence of aflatoxins in food groups and milk in Serbia.

Aflatoxins (AFTs) are difuranocoumarin derivatives primarily produced by *Aspergillus flavus* and *A. parasiticus fungi*, which contaminate agricultural commodities [15]. To date, nearly 18 different types of aflatoxins have been identified the five predominant ones being aflatoxin B1 (AFB1), aflatoxin B2 (AFB2), aflatoxin G1 (AFG1), aflatoxin G2 (AFG2) and AFM1 (based on their fluorescence under UV light, blue or green). AFM1 is transformed at the hepatic level by cytochrome P450 enzymes and excreted into the milk in the mammary glands of both humans and lactating animals after the animals have ingested feeds contaminated with AFB1. AFM1 is relatively stable during pasteurization, sterilization, and storage of milk and milk-based products. Among these toxins, AFB1 is the most predominant and the most potent hepatocarcinogen and has been classified as a Group 1, known human carcinogen [16,17], while other compounds have lower toxicity, carcinogenic, mutogenic, and teratogenic effects. For this type of carcinogen, it is generally felt that there is no threshold dose below which no tumour formation would occur. In other words, only a zero level of exposure will result in no risk.

Recent results support hypothesis that some species might shift their geographical distribution in response to global warming, leading to changes in the pattern of mycotoxin occurrence. Developing crops are usualy resistant to infection by *Aspergillus spp* and related mycotoxins, unless environmental conditions favour fungal growth and crop susceptibility. Periods of drought combining with high temperatures significantly increases AFs production in the field. Recent report [18,19] predicted that, within the next 100 years, aflatoxin B1 will become a food safety issue in maize in Eastern Europe, Balkan Peninsula and the Mediterranean regions, especially under a +2 °C scenario. Since weather conditions in 2012 were favorable for *Aspergillus* mold growth, a larger percentage (68.5 %) of maize harbored AFs at levels 1µg/kg. According to Serbian and EU regulation only 46.5 % of maize could be used for human consumption, while maize (24 %) with AFs in the range of 10–50 µg/kg could be used only for animal feed, according to Serbian regulation. Due to the severity of the corn contamination, elevated concentrations of AFM1 were found in milk [20]. Elevated temperatures and extreme weather events, mentioned above, have directly and indirectly impact on the dairy industry. In such climate conditions as a consequence, the contamination risk for maize-derived products and for milk will be higher than in the past, particularly under inadequate storage conditions [21].

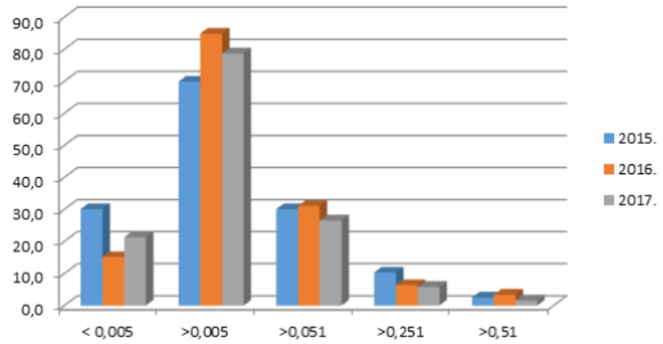

Figure 3. Incidence (%) of aflatoksin M1 contamination during three years period of investigation [21].

Fumonisins

A number of *Fusarium* species particularly *Fusarium verticilliodies* and *F. proliferatum* produces fumonisins (FUMs), a group of some 28 compounds. These compounds are predominantly produced in maize and other cereal grains. Due the similarities in favorable fungal growth conditions (high temperatures in humid climates), fumonisins often co-occur with AFs especially in corn [30]. Although 28 FUM analogs have been identified, fumonisin B1 (FB1) is the most predominant and well-studied isoform which have a longchain hydrocarbon unit (similar to that of sphingosine and sphinganine) playing a role in their toxicity. FB1 exposure has been associated with liver and esophageal cancers in high-risk populations therefore has been classified as a Group 2B, possible human carcinogen [31]. FBs have also been implicated as a risk factor for neural tube defects (NTDs), while in animals FUM scause equine leuko encephalomalacia and porcine pulmonary edema. Last report indicates that Serbia is one of the few regions in Europe with proven cases of ELEM [32]. The mechanism of action of FB1 induced neurotoxicity is the inhibition of the enzyme ceramide synthase an enzyme responsible for the acylation of sphinganine and

Table 1. The incidence of AFT in food and feed samples

Commodity	Region	N (%)	Range (µg/kg)	Mean (µg/kg)	Ref.
Maize	All regions		0.33-2.40		[22]
			1.01-86.1	363	[23]
			Up to 560	33,21	[20]
			2.31-3.34 (harvested)		[24]
			1.03-4.11 (stored)		
			1.98-7.01	1,33	[25]
	West Backa	57.2	1.3–88.8		[26]
	North Banat	13.9	0.60–2.8		
	South Banat	5.6	1.8–28.5		
	Central Serbia	2.8	2.1–7.5		
	Vojvodina	5	2.28-4.31	3.22	[27]
		5-72.3	1.0–111.2		[28]
Flours of various cereals	Serbian market	5.2	1.59–4.76	2,13	[29]
Maize flour		48.2	max. 9.14	0.55	

N-number of positive samles (%-percentage of positive samples)

Table 2. The incidence of FUMs in food and feed samples

Commodity	N (%)	Range (µg/kg)	Mean (µg/kg)	Ref.
Wheat		750–2465		[36]
Corn		30–1520	176	[37]
		880–2950		[38]
		520–5800	1730	[30]
		1519–9780		[24]
		760–35760		
Hors feeds		1680-6050	7,73	[32]
Corn	83	Up to 20340	1009	[39]
Pig feed	3 (100)	350-1061		[10]
Corn	74	540.1-5076	2750	[27]
Corn flours	96.4	15-1468.5	205.5	[40]
Corn flake	73.3	15-579.4	87.3	

N-number of positive samles (%-percentage of positive samples) sphingosine [33]. The World Health Organization [34] established a provisional maximum tolerable daily intake (PMTDI) of 2 µg/kg of b.w. for fumonisins B1, B2 and B3, alone or in combination. Agri-climatic conditions (cool and wet summers) in Serbian farming, including among others conditions influence occurrence of *Fusarium spp.* and related mycotoxins. Incidence and distribution of FUMs concentration in examined samples during period of investigation are presented in Table 2. The overall prevalence of FUMs in Serbia, for the investigated period, was slightly higher compared to the prevalence of FUMs in samples collected between 2000 and 2010 [35].

Zearalenone

Zearalenone (ZEA) is a phenolic resorcyclic acid lactone with potent estrogenic properties, produced by several species of *Fusarium* mainly occurs in wet temperate weather associated with improper storage condition (high moisture) [41]. Among the cereals in which ZEN can occur, maize has been shown to have the highest contamination levels, particularly in central European countries such as Serbia (Table 3). Hence ZEA is one of the most common contaminants of feed and its components. It is also the most prevalent of the mycotoxicoses in domestic animals. These results can be explained by the heavy total rainfall during the maize harvest in 2014 and 2016, mild winter during 2015 as well as uncontrolled conditions of temperature and relative humidity during the storage, which caused the intensive development of mold and increased the content, particularly of *Fusarium* mycotoxins in stored maize [35]. ZEA and its major alcohol metabolites α-zearalenol and β-zearalenol share structural similarity with the human sex hormone 17b-estradiol. Therefore, exposure to this mycotoxin has been linked to estrogenic activity in human and animals likely due to the estrogenic activity exerted by ZEN and its metabolites upon interaction with the hepatic, uterine, mammary, and hypothalamic estrogen receptors. Pigs and cows are very sensitive to ZEA whereas poultry are very tolerant. Although IARC found limited evidence of ZEA carcinogenicity in animal models, classifying it mycotoxin as non carcinogen to humans-Group 3 [42], the SCF [43] established a tolerable daily intake (TDI) of 0.25 µg/kg b.w based on recent data in the most sensitive animal species.

Table 3. The incidence of ZEA in food and feed samples

Commodity	N (%)	Range (µg/kg)	Mean (µg/kg)	Ref.
Wheat		10–1000		[36]
Corn		1.79–3.39		[37]
Wheat flour		1.9–21.1	4.6	[44]
Corn		15.44–188.05		[38]
	15	35.6-183.5	83	[27]
Corn flours	66,1	1-242.1	15	[40]
Corn flake	86,7	max. 121.6	13.6	

N-number of positive samles (%-percentage of positive samples)

Trichothecenes

Trichothecenes are toxic metabolites majorly produced by *Fusarium spp.* The TCT mycotoxins comprise a vast group of more than 100 fungal metabolites classified based on the substitution pattern of the tricyclic 12,13-epoxytrichothec-9-ene (EPT) in four groups, A, B, C and D. Although the group of TCTs has been thoroughly studied worldwide, in Serbia, more intensive studies on DON were initiated after 2005 [45]. In a study recently carried out in Serbia (Table 4), DON was affecting several major cereal crops including oats, barley, corn, and wheat. The overall prevalence of TCT toxins in Serbian cereals for the investigated period was slightly higher compared to the prevalence of these mycotoxins in samples collected between 2005 and 2010. Weather conditions recorded in 2010 and 2014, in terms of air temperature and the amount of precipitation, had a significant influence on TCT occurrence [46]. The EPT structure is considered essential for toxicity. At the cellular level TCT cause protein synthesis inhibition by affecting the 60S subunit of the ribosome interfering with the peptidyl transferase activity [47]. Despite IARC in 1993 designated DONas a Group 3 (not classifiable) human carcinogen due to inadequate evidence of animal carcinogenicity, and lack of investigation in humans, TCT are known to cause neurotoxicity, immunosuppression and renal toxicity. The Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives established PMTDI for DON and its acetylated derivatives (3-ADON and 15ADON) of 1 µg/kg-1 b.w., whereas for NIV and the sum of T-2 and HT-2 toxins the SCF proposed a temporary tolerable daily intake TDI of 0.7 and 0.06 µg/kg^{-1} b.w., respectively [48]. Recently, the SCF [50] concluded that a full TDI of 0.1 µg/kg^{-1} b.w. for the sum of T-2 and HT-2 toxins can be now established, based on recent data.

Table 4. The incidence of TCT in food and feed samples

Commodity	N (%)	Range (µg/kg)	Mean (µg/kg)	Ref.
Wheat	14 (82.4)	68–1572		[50]
		50–5000		[36]
		25–135.6		
Wheat flour		17.5–976	325	[44]
		9.8–26.9	4.1	
Crop maize	52.0	25.3–200	154.1	[51]
Corn		41–226		[38]
		600–700	650	[30]
		25.09–209	50.93	
		380–10.684		[33]
		42–238		
Crop wheat	100	175.0–1440.0	762.5	[52]
Corn	52	275.2-882.1	541	[27]
Crop maize	96.0	264.4–9050.0	3063.3	[53]
	15.5	252.3–6280.0	921.1	
Corn flour	42,9	25-931.8	101.3	[40]
Corn flake	40	25-878.6	255.1	

N-number of positive samles (%-percentage of positive samples)

Ochratoxin

The ochratoxins are a group of related pentaketide metabolites comprises a dihydrocoumarin moiety linked to a molecule of L-β-phenylalanine via an amide bond, mainly produced fungi of the genera *Aspergillus* and *Penicillium* [13]. Ochratoxins A have been isolated from a wide range of commodities all over the world, in both warm and cool climates, and are common contaminants of staple food crops, and beverages such as beer and wine and foods from animal origin, particularly pork or dry-cured meat products [14,54]. OTA is a potent nephrotoxin and based on animal evidence has been causative agent of porcine nephropathy [55]. Historically, OTA has been implicated in several nephropathies, most noticeably Balkan Endemic Nephropathy in the former Yugoslavia, chronic disease, and endemic nephropathy associated with urothelial-cancer. OTA is classified as a possible human carcinogen (group 2B) by IARC (1993) on the basis of sufficient evidence of carcinogenicity in animal models, but insufficient evidence from human studies. OTA was last evaluated by the Scientific Committee on Food (SCF) in 1998 when it concluded that OTA possesses carcinogenic, nephrotoxic, teratogenic, immunotoxic, and possibly neurotoxic properties. The mechanism of action seems to be related to the formation of DNA adducts [56]. Based on this assessment, a tolerable weekly intake of 120 ng/kg b.w. was derived for OTA. Due to the high health risks of OTAs, they have been studied more often than other mycotoxins in our region. Results found in study by Milicevic et al., [57] suggest that in general, OTA contamination in pork and chicken meat originating from different part of Serbia is low and hence for the consumer the contribution to the total intake of OTA from pig and chicken products is very small compared with other sources. The values are far below the Acceptable Daily Intake (ADI) of these toxins (Table 5).

Table 5. The incidence of OTA in food and feed samples

Commodity		N (%)	Range (μg/kg)	Mean (μg/kg)	Ref.
Blood plasma (pigs)		**38 (30)**	**0.24-228**	**3.70**	[57]
Liver	**pigs**	**24 (26,6)**	**0.18-14.4**	**0.64**	
	chicken	**23 (38.33)**	**0.14-3.90**	**0.41**	
Kidney	**pigs**	**40 (33.3)**	**0.17-52.5**	**1.24**	
	chicken	**17 (28.33)**	**0.10-7.02**	**0.36**	
Chicken gizzard		**16 (26.6)**	**0.25-9.94**	**0.36**	
Chickens feed		**100**	**19.04–51.30**	**34.40**	[58]
Hens feed		**100**	**28.34–65.30**	**43.89**	
Breakfast cereals		**20.7**	**0.07–11.81**	**1.76**	[30]

N-number of positive samles (%-percentage of positive samples)

Other important mycotoxins with fewer occurrences

Other important mycotoxins that can be found as contaminants of foods include patulin, citreoviridin, gliotoxin, griseofulvin, mycophenolic acid, b-nitropropionic acid, Kojic acid, penitrems, penicillic acid, viomellein, vioxantin and xanthomegnin and walleminols. Also, emerging mycotoxins such as fusaproliferin, beauvericin, enniatins and moniliformincan be contaminants of foods. In Serbia, there are not current study on the presence of these mycotoxins in foods, likely due to the lack of research to determine their occurrences as well as potential human and animal health effects.

Current and future outlook

Although the emphasis over the past decade has been on microbial food safety issues, in this new global environment chemical hazars has made the headlines over the past several years. The impact of mycotoxins on public health program can be assessed by multiple criteria, such as the health and veterinary care costs, economical losses of livestock production, forage crops and feeds, regulatory costs, and research costs. Despite that developing countries are usually susceptible to mycotoxin outbreaks or interventions, developed nations are also at risk of exposure due to contaminated food imports. In a global climate changing we must also consider that fungal growth and consequently contamination of commodities by mycotoxins in uncommon places is likely to be occur. Temperature and rainfall are the climatic factors that are most likely to affect Serbia in future. These can be expected to have a wide range of impacts on plants and plant pathogens and to affect mycotoxin contamination in various commodities. Furthermore, the identification of climate factors on mycotoxins occurrence is central to risk management. From the Serbian perspective, further research should be focused on:

- the development of predictive models for mycotoxin occurrence based on regional weather data in order to estimate the risk of contamination after agiven growing season,
- continuous monitoring of mycotoxins level in animal feed, particularly in regions where milk samples were previously contaminated by AFM1 above the legal limit,
- improving analytical facilities, and implementing strict regulations, would avoid or reduce these natural contaminants in food and feeds and ensure the safety of food chain.

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AUTHOR INFORMATION

Dragan Milicevic – DVM, MSc, PhD, Senior Research Associate, Adviser of Director for scientific research. Institute of meat hygiene and technology, 11040 Belgrade, Kacanskog 13 Serbia. Tel.: +381112650655. E-mail:dragan.milicevic@inmes.rs. *corresponding author
Brankica Lakicevic – MSc, PhD, Senior Research Associate, Department of microbiological and molecular - biological research. Institute of meat hygiene and technology, 11040 Belgrade, Kacanskog 13 Serbia.Tel.: +381112650655. E-mail: brankica.lakicevic@inmes.rs
Radivoj Petronijevic – MSc, PhD, Research associate, Department of chemical and physical-chemical analyses. Institute of meat hygiene and technology, 11040 Belgrade, Kacanskog 13 Serbia. Tel.: +381112650655. E-mail: radivoj.petronijevic@inmes.rs
Zoran Petrovic – MSc, Phd, Research associate, Coordinator of the Institute's Management System. Institute of meat hygiene and technology, 11040 Belgrade, Kacanskog 13 Serbia. Tel.: +381112650655. E-mail: zoran.petrovic@inmes.rs
Jelena Jovanovic – DVM, Research assistant, Department of sensory and physical testing and parasitology. Institute of meat hygiene and technology, 11040 Belgrade, Kacanskog 13 Serbia.Tel.: +381112650655. E-mail: jelena.jovanovic@inmes.rs
Srdjan Stefanovic – PhD, Research associate, Department for residues testing. Institute of meat hygiene and technology, 11040 Belgrade, Kacanskog 13 Serbia.Tel.: +381112650655. E-mail:srdjan.stefanovic@inmes.rs
Sasa Jankovic – PhD, Research associate, Department for residues testing. Institute of meat hygiene and technology, 11040 Belgrade, Kacanskog 13 Serbia. Tel.: +381112650655. E-mail:sasa.jankovic@inmes.rs

Contribution

Authors equally contributed to the writing of the manuscript and are equally responsible for plagiarism

Conflict of interest

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