



OCCURRENCE OF MONILIFORMIN IN CEREALS

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ABSTRACT: In many parts of the world, the major cereal crops (maize, wheat, barley, rye and oats) are particularly susceptible to infection by *Fusarium* species. Moniliformin (MON) is a mycotoxin produced by *Fusarium* species, most often *F. proliferatum*, *F. avenaceum* and *F. subglutinans*. The occurrence of MON has been recorded worldwide, with the highest detected value of 530 mg/kg in maize intended for human consumption. Limited information on toxicity in experimental and farm animals indicates haematotoxicity and cardiotoxicity as the main damaging effects of MON on human health. Its stability and fate during processing has also been poorly studied, so the degree of consumer's exposure to MON is still uncertain.

This review summarizes available information on the MON chemistry, toxicity, its worldwide occurrence in cereals, methods of analysis and the potential methods for its decontamination in food and feed.

Key words: moniliformin, toxicity, food, feed, decontamination

INTRODUCTION

Food and feed monitoring for the appearance of mycotoxins from the genus *Fusarium* continues to attract world attention and in recent years has been a subject of extensive research (Summerell, 2019; Bertero et al., 2018; Bryła et al., 2018; Fraeyman et al., 2017). Factors that contribute to the development of *Fusarium* include humidity, temperature, aeration and substrate type (Stanciu et al., 2015). The genus *Fusarium* involves several species which are important pathogens of maize and small grains. Two main diseases of grains caused by *Fusarium* are

Fusarium head blight of small grains (primarily wheat, barley, and oats) and *Fusarium* ear rot of maize (Jestoi, 2008). Although data on *Fusarium* mycotoxins, such as trihotecene and zearalenone are very well documented, there are limited data on toxicity, occurrence and levels of contamination of other metabolites of *Fusarium* species, such as moniliformin (MON).

MON is a mycotoxin produced by nearly 40 different *Fusarium* species, mainly *F. proliferatum*, *F. avenaceum*, *F. subgluti-*

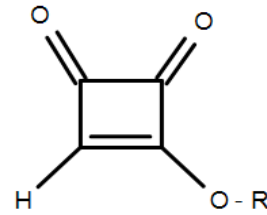
nans, *F. tricinctum*, *F. verticillioides*, *F. anthropophilum* (Peltonen et al., 2010) and one *Penicillium* species (*Penicillium melanoconidium*) (Hallas-Møller et al., 2016). Among the most powerful producers of MON, *F. subglutinans* and *F. proliferatum* prevail in maize typically grown in warm climatic areas of Europe, while *F. avenaceum* and *F. tricinctum* are mainly occurring in small-grain cereals, primarily in moderate regions as Scandinavia (Peltonen et al., 2010). The optimal conditions for moniliformin biosynthesis by *F. subglutinans* and *F. avenaceum* are temperatures between 25-30 °C and water activity (a_w) of minimum 0.90 (Kostecki et al., 1999). MON was found in cereals such as wheat, oats, rice, rye, barley, and triticale, while the greatest contamination was found in maize samples (Jestoi, 2008). In the recent European Food Safety Authority (EFSA) report (2018) it was concluded that there is a large uncertainty about risk assessment of MON in human and farm animals. Furthermore, only several experiments indicate moderate heat stability of MON during thermal food processing (Scott and Lawrence, 1987; Pineda-Valdes and Bullerman, 2000; Pineda-Valdes et al., 2002; Pineda-Valdes et al., 2003). Given the lack of data related to MON, further researches of its toxicity, occurrence and behavior under different food processing conditions are necessary (EFSA, 2018).

Chemical structure and physicochemical properties of MON

MON (Fig. 1) is a polyketide mycotoxin with low molecular weight [$C_4H_2O_3$, IUPAC: 3-hydroxycyclobut-3-ene-1,2-dione]. It is a polar, strong acid with a pKa value of 0.88, also known as semisquaric acid. Because of the low pKa of the free acid, in the nature MON occurs as the sodium or potassium salt (EFSA, 2018).

MON is soluble in water and polar solvents. The UV absorbance of MON has a maximum at 227 nm and a shoulder at 258 nm in distilled water, with extinction coefficients of $19,900 M^{-1}cm^{-1}$ and $5,400 M^{-1}cm^{-1}$, respectively (Sydenham et al., 1996). The melting point for the free acid is 158°C and for the sodium and potas-

sium salts above 320 °C (Cole and Cox, 1981).



R: H (free acid, 98 g/mol), Na (sodium salt, 120 g/mol), K (potassium salt, 136 g/mol)

Figure 1. Chemical structure of MON

TOXICITY OF MON

The mode of action of MON is associated with inhibition of the incorporation of pyruvate into the tricarboxylic acid cycle (TCA). Apart from that, MON inhibits the oxidation of intermediates of the TCA (Thiel, 1978).

Acute toxicity - MON has an acute toxicity at a level comparable to other mycotoxins derived from the *Fusarium* genus, such as T-2 toxin and diacetoxyscirpenol - type A trichothecenes (Sørensen et al., 2007). The specific symptoms of acute toxicity of MON are respiratory stress, muscle weakness, myocardial degeneration and certain evidence of histopathological changes in organs such as pancreas, lungs and kidneys accompanied by vomiting and death (Jonsson et al., 2013). Cardiac changes induced by MON have also been reported in several earlier studies (Kriek et al., 1977; Thiel, 1978; Morgan et al., 1999). Table 1 gives the results of some MON acute toxicity studies (LD_{50}) in different animals. LD_{50} values are defined as lethal doses of moniliformin that kill 50% of the test animals during the observation period.

Subacute, subchronic and chronic toxicity - Subacute toxicity study (Jonsson et al., 2015) in rats predicted LOAEL (lowest-observed-adverse-effect level) of 3 mg/kg BW. Indications of cardiotoxicity were observed at 9 mg MON/kg BW per day and cardiotoxicity was observed at 15 mg MON/kg BW per day. Furthermore, to date only one study (Kriek et al., 1977) has been published regarding subchronical toxicity of MON on rats. According to this study MON showed MON

Table 1.
Acute toxicity (LD₅₀)^{*} of MON in different animal models

Species	Route of exposure	LD ₅₀ (mg/kg BW)	Reference
Broiler chicken	Oral	1.38	Allen et al. (1981)
1-day old chicken	Crop intubation	5.4	Burmeister et al. (1979)
Duckling	Intubation	3.7	Kriek et al. (1977)
Mice (F/M)	Intraperitoneal	20.9/29.1	Bryden et al. (2001)
Mice	Oral	47.6	Burmeister et al. (1980)
Mink	Intraperitoneal	2.2-2.8	Morgan et al. (1999)
Rats (F/M)	Oral	41.6/50.0	Kriek et al. (1977)
Rats	Oral	25.0	Jonsson et al. (2013)

*Lethal dose 50%
F - female; M - male
BW - body weight

indications of cardio toxicity at 17 mg BW per day, while mortality was observed at 32.5 mg MON/kg BW per day. Until today, there are no reports related to chronic effects of MON.

Carcinogenicity and genotoxicity – According to the last available information for the carcinogenicity of MON, the International Agency for Research on Cancer (IARC) classified it in the 3rd group of carcinogenic compounds, due to the insufficient relevant studies (IARC, 2006). As far as genotoxicity is concerned, *in vitro* study shows that MON causes chromosomal damage (Knasmüller et al., 1997). However, there is no genotoxicity data *in vivo*, up to date.

Reproductive and developmental toxicity - Morgan et al. (1998) reported that long-term exposure to *F. fujikuroi* culture material containing 17 mg MON/kg was not lethal to adult female mink, but resulted in significant neonatal mortality and reduced offspring body weight. There is no teratogenic effects of MON in experimental animals (mouse and 1-day old chicken) (Hayes and Hood, 1974; Burmeister et al., 1979).

Human studies - MON has been suggested as one of the etiological factors of Keshan disease, even if a clear correlation is lacking. Keshan disease is a dilated cardiomyopathy closely related to a diet deficient in the mineral selenium (Sørensen et al., 2007).

OCCURRENCE OF MON IN CEREALS

The numerous European countries (Table 2) reported the incidence of MON in cereals, and furthermore the greatest numbers of published data are related to the occurrence of MON in maize samples. The maximum level of MON recorded in maize (530 mg/kg) was detected in *Fusarium*-damaged maize in Poland (Chelkowski et al., 1987).

In 1991, Sharman et al. published an overview of the data on the occurrence of MON in cereal samples from worldwide sources, including some European countries (Italy, Poland, Netherlands and UK). This paper reported the contamination of maize, oats, wheat, rye and triticale with MON (the maximum concentration of 0.847 mg/kg). In addition to cereals, MON was also detected in asparagus spears (Knaflewski et al., 2008) and apples with signs of wet apple core rot in Poland (Sørensen et al., 2009).

In the recent study, Herrera et al. (2017) published an overview on data about the occurrence of MON in cereal-based food samples collected in the Netherlands and Germany. MON was not detected in bread samples (n=32). Of all analyzed wheat flour samples (n=22), only one was contaminated with MON at level of 0.011 mg/kg. Seven of 25 examined pasta samples contained MON at levels around 0.010 mg/kg. MON occurred in eight out of

23 maize products at the levels of 0.012-0.207 mg/kg. Barthel et al. (2018) analyzed 39 samples of popcorn maize kernels (n=21), maize meal (n=14) and semolina (n=4) from the Bavarian market (Germany). The samples originated from Germany (n=8), Italy (n=3), Turkey (n=2), France (n=2) and other European countries (n=6). The origin of 18 samples was not indicated. The rate of contamination with MON was very high (97%) with concentrations ranging from 0.002 to 0.847 mg/kg.

In the recent Serbian study, 190 maize samples were analyzed. Samples were collected during harvest in the Northern Serbian province of Vojvodina over three years period (Jajić et al., 2019). MON was present in more than 90% of the 2016 maize harvest samples (n=73), except in the West-Bačka region (50%). Mean levels of MON ranged from 0.19 (West-Bačka) to 0.920 mg/kg (Srem). The maize samples (n=72) from the 2017 harvest had more than 57% of samples contaminated with MON. The mean levels ranged from 0.179 (South-Bačka) to 0.499 mg/kg (West-Bačka). Furthermore, MON was detected in more than 47% of the maize samples (n=45) harvested in 2018. The mean levels ranged from 0.034 (North-Bačka) to 0.199 mg/kg (South-Bačka). The authors came to the conclusion that high precipitation levels during June 2018 in the South-Bačka and South-Banat regions and during July 2018 in South-Bačka resulted in obtaining the highest mean levels of MON. Further, stepwise regression showed (with 95% confidence level) that air temperatures from May to August resulted in statistically significant differences in MON levels.

Environmental factors such as rain and temperature greatly affected the prevalence of MON in analyzed cereals from Finland (Jestoi and Kokkonen, 2008), Norway (Uhlig et al., 2004) and Italy (Scarpino et al., 2013). Lindblad et al. (2013) investigated the effect of vegetation season period on the MON contamination in wheat from Sweden. Higher levels of MON were detected in spring wheat in relation to winter wheat. However, MON was recorded at lower concentrations in organic wheat

from Norway compared to conventional (Bernhoft et al., 2010). Although there are several species able to produce MON on a wide variety of hosts, the main problem in Europe is strongly linked to the presence of *F. subglutinans* in the maize ear rot complex and *F. avenaceum* in *Fusarium* head blight of wheat (Jestoi, 2008).

MON levels were also analyzed in feed ingredients and compound feeds (Table 2). Scudamore et al. (1998) examined 67 samples of maize gluten and milled maize products, destined for incorporation into animal feedstuffs in the United Kingdom. Analysis showed that 61% of samples contained MON in concentrations higher than 4.6 mg/kg. Results from Slovakia indicate that 52% of poultry feed samples (n=50) were contaminated with MON (concentration range from 0.042 to 1.214 mg/kg) (Labuda et al., 2005).

Several studies carried out in Africa, America, Asia and Oceania reported the incidence of MON in cereals (Table 2).

Thiel et al. (1982) first recorded the natural occurrence of MON at very high level of 25 mg/kg in visibly infected maize kernels in Transkei, South Africa. Although most African countries have a climate characterized by high humidity and high temperature, MON has been considered as an important maize contaminant in the cooler production areas of South Africa (Thiel et al., 1982). Boutigny et al. (2012) reported that *Fusarium subglutinans* is the *Fusarium* species most commonly associated with maize, especially in colder areas of South Africa and that MON was detected in 62% of maize samples collected in 2008-2009, with a maximum level of 1.53 mg/kg. The first report of the natural occurrence of MON in maize in the United States was conducted by Thiel et al. (1986) and detected MON concentrations were up to 2.82 mg/kg. Gutema et al. (2000) conducted a survey in commercial maize samples from different regions of the United States and detected MON concentrations were up to 0.77 mg/kg. In the same study, levels up to 0.86 mg/kg were observed in maize-based retail food products, including maize meal, maize grits, maize masa mix, muffin mix, maize bread

mix, self-rising maize mix, easy mix and maize flour. The first report from Brazil shows that MON is not a common contaminant of maize planted within the state (Leoni and Soares, 2003). New data reported contamination of sorghum grains

intended for animal consumption in Argentina, with MON at levels ranging from 0.363 to 0.914 mg/kg (Pena et al, 2019). There is a lack/shortage of research in Asian and Oceanian countries on the occurrence of MON in cereals.

Table 2.
Worldwide contamination of cereals with MON

Country	Food/ Feed	Commodity	Concentration range (mg/kg)	References
Europe				
Austria	Food	Maize	n.a./0.02	Lew et al. (1991)
	Food	Maize crops	n.a./0.8	Lew et al. (2001)
	Feed	Maize	0.16/1.03	Parich et al. (2003)
Denmark	Feed	Maize	0.001/0.01	Sørensen et al. (2007)
Finland	Food	Cereal samples	<0.02/0.81	Jestoi et al. (2004)
	-	Cereal samples	<0.02/0.85	Jestoi and Kokkonen (2008)
Germany	Food	Maize	<0.08/0.65	Thalmann et al. (1985)
	Food	Cereal samples	<0.0007/0.13	Von Bargaen et al. (2012)
	Feed	Maize	n.a./3.33	Goertz et al. (2010)
Italy	Feed	Maize	<0.001/2.61	Scarpino et al. (2013)
Netherlands	Feed	Winter wheat – preharvest	0.005/0.1	Van der Fels-Klerx et al. (2012)
	Feed	Winter wheat – at harvest	0.007/0.33	Van der Fels-Klerx et al. (2012)
	Feed	Maize cobs	<0.05/0.33	Van Asselt et al. (2012)
Norway	Feed	Cereal samples	<0.13/0.95	Uhlig et al. (2004)
	Food	Organic wheat	<0.04/0.25	Bernhoft et al. (2010)
	Food	Conventional wheat	<0.04/0.34	Bernhoft et al. (2010)
	Food	Cereal samples	n.a./0.52	Uhlig et al. (2013)
	Food	Oats	n.a./0.17	Ivanova et al. (2017)
Poland	Food	Maize	30/530	Chelkowski et al. (1987)
	Food	Wheat	0.5/17	Sharman et al. (1991)
	Food	Rye	6.1/12	Sharman et al. (1991)
	Food	Triticale	2.6-16	Sharman et al. (1991)
	Food	Oats	16/38	Sharman et al. (1991)
	Food	Maize	4.2/399	Sharman et al. (1991)
	Food	Maize	17/425	Logrieco et al. (1993)
	Food	Wheat	7.200/25.2	Lew et al. (1993)
	Food	Triticale	2.4/5.1	Lew et al. (1993)
	Feed	Wheat	n.a./0.198	Grabarkiewicz-Szczesna et al. (2001)
-	Wheat with scab symptoms	<0.010/1.72	Tomczak et al. (2002)	
Food	Wheat	n.a./0.3	Kulik (2008)	
Serbia	-	Maize	0.002/3.86	Jajić et al. (2019)
Slovakia	Feed	Poultry feed	<0.04/1.21	Labuda et al. (2005)
Sweden	Food	Oats	<0.02/0.22	Fredlund et al. (2013)
	Food	Winter wheat	<0.02/0.5	Lindblad et al. (2013)
	Food	Spring wheat	<0.02/2.08	Lindblad et al. (2013)
Switzerland	Food	Maize-based	<0.2/1.35	Noser et al. (2001)

Country	Food/ Feed	Commodity	Concentration range (mg/kg)	References
United Kingdom		products		
	Food	Ethnic food	<0,01/0.03	FSA (2013)
	Feed	Maize gluten	<0.05/0.32	Scudamore et al. (1998)
	Feed	Maize products	<0.05/4.6	Scudamore et al. (1998)
	Feed	Barley	n.a./0.045	Edwards (2007)
	Feed	Oats	n.a./<0.010	Edwards (2007)
Africa				
South Africa	Food	Maize	16/25	Thiel et al. (1982)
	Food	Maize	0.35/11.57	Sydenham et al. (1990)
	Food	Maize	0.32/0.39	Rheeder et al. (1994)
	-	Maize	<0.02/1.53	Boutigny et al. (2012)
America				
Argentina	Feed	Sorghum grains	0.36/0.91	Pena et al. (2019)
Arizona, California, Nebraska, and Ohio	Food	Maize	<0.03/0.77	Gutema et al. (2000)
		Maize-based products	<0.03/0.86	Gutema et al. (2000)
Brazil	Food	Maize	-	Leoni and Soares (2003)
Canada	Food	Maize	0.05/0.2	Scott and Lawrence (1987)
Not specified	Feed	Maize	n.a./2.82	Thiel et al. (1986)
Asia				
China	Food	Rice	n.a./0.25	Ji (1991)
	Food	Maize	n.a./0.26	Ji (1991)
	Food	Rice	0.07/0.27	Yu et al. (1995)
	Food	Maize	0.05/1.12	Yu et al. (1995)
Oceania				
New Zealand	-	Maize	n.a./64	Hussein et al. (1991)

n.a. - not available

DETERMINATION OF MON CONTENT IN CEREALS

Analytical methods commonly consist of MON extraction from the samples with an extraction solvent, usually followed by a sample purification step and a final detection/quantification step of MON by convenient techniques (Scarpino et al., 2013).

Extraction of MON is generally carried out with acetonitrile-water solutions (84–95% acetonitrile). Purification steps may include the use of strong anion exchange columns or other solid-phase extraction columns including MycoSep™ columns (EFSA, 2018).

Several analytical methods for the quantification of MON have been published so far: ion-pair high-performance liquid chromatography (HPLC) with UV detection,

fluorescence detection or detection by atmospheric pressure chemical ionization-mass spectrometry, ion chromatography (IC), thin-layer chromatography (TLC), capillary electrophoresis coupled to diode array detector (CE-DAD), gas chromatography-mass spectrometry after derivatization (GC-MS), liquid chromatography coupled to ultraviolet detection (LC-UV) and currently used method: liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). Besides methods specifically developed for MON analysis (single analyte methods), MON has also been a part of multi-methods for mycotoxin analysis by LC-MS/MS. However, none of the mentioned analytical methods for MON have been validated in interlaboratory studies. Also, certified reference materials are not available for MON, but calibrants are commercially available (EFSA, 2018).

DECONTAMINATION OF MON

Physical methods – MON is stable in food processing that occurs in neutral or acidic conditions, but is unstable in food processing in alkali conditions (Pineda-Valdes and Bullerman, 2000). In ground maize and ground wheat with the addition of MON at 1 mg/kg levels, a moderate degradation was observed by heating at 50, 100 and 150 °C for 0.5-2 h, e.g. at 150 °C about 38% and about 15% of MON remained in maize and wheat, respectively (Scott and Lawrence, 1987). Autoclaving at 121 °C for 65 min of creamed maize for infants and cream style maize and roasting at 218 °C for 15 min of maize meal, all three spiked with 5 mg MON/kg, showed MON reductions of 10%, 23% and 45%, respectively (Pineda-Valdes et al., 2003). However, heating of naturally contaminated maize sample with a MON content of 1.4 mg/kg at pH 10 for 1 h at 175 °C showed complete reduction of MON (Pineda-Valdes et al., 2002). Overall, under the conditions tested for baking, autoclaving, frying, roasting and extrusion, MON showed thermal stability similar to or greater than other *Fusarium* mycotoxins such as deoxynivalenol and fumonisin B1 (Pineda-Valdes et al., 2003).

Chemical methods – As with many other toxins, ozonization is also an effective method in detoxification of MON due to opening the 4-C structure (Zhang and Li, 1994). Zhang and Li (1997) also examined the detoxification of MON in grains and water. To reduce the content of MON in water, chlorinated lime, heating, activated carbon, ozone, microwave, and UV were tested. The chlorinated lime was selected as the most effective method for detoxification of MON in water. Furthermore, spray treatment with solution of 5% H₂O₂ was the best method for detoxification of MON in grains.

Biological methods – Wu (1997) established an approach in the control of mycotoxins in animals by supplementing drinking water with the Poultry Aid Plus (PAP) formulation. PAP is a *Lactobacillus acidophilus* fermentation liquid formula intended for water application to reduce digestive stress in poultry. The application of PAP

also reduces mortality and improves weight gain when poultry is fed with food contaminated with *F. proliferatum*. However, there is a different approach to the control of mycotoxins in plants. Duvick and Rood (1999) found that *Ochrobactrum anthropi*, isolated from moldy maize, capable of using MON as the only source of carbon and thus partially or completely degrades it in the process. The treatment can be done in field, pre-harvest, locally applying a suspension of bacteria on a plant or applying it post-harvest, on harvested grain.

LEGISLATION

Currently, there are no Regulations related to the maximum levels of MON in food and feed all over the world (EFSA, 2018).

CONCLUSIONS

Taking into account the lack of data on toxicity, occurrence and methods of reduction of MON, and therefore of food safety and protection of human and animal health, it is necessary to further collect data on the presence of this mycotoxin in food and feed. Further research should focus on maize and maize-based products, as well as other cereals and cereal-based products in which the presence of MON in high concentrations has been established so far. Studies on the ecology of the main fungi involved in the production of MON are also necessary.

ACKNOWLEDGEMENTS

This paper is a result of the research within the project TR31029 “Functional products based on cereals designed for people with metabolic disorders”, financed by the Ministry of Education, Science and Technological Development, Republic of Serbia.

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ПОЈАВА МОНИЛИФОРМИНА У ЖИТАРИЦАМА

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Сажетак: Плесни из рода *Fusarium* често се јављају као контаминенти житарица (кукуруз, пшеница, јечам, раж и овас) широм света. Монилиформин (МОН) је микотоксин кога производе плесни рода *Fusarium*, најчешће *F. proliferatum*, *F. subglutinans* и *F. avenaceum*. Појава МОН је забележена широм света, при чему је највећа детектована вредност (530 мг/кг) забележена у кукурузу намењеном за људску потрошњу. Ограничене информације о токсичности МОН-а код експерименталних и домаћих животиња указују на његов потенцијални хематотоксични и кардиотоксични ефекат на здравље људи. Надаље, његова стабилност и понашање током прераде хране је такође слабо истражена, тако да се још увек не може са сигурношћу изразити степен ризика изложености потрошача.

Овај преглед сумира доступне информације о хемији МОН-а, токсичности, његовој појави у житарицама, методама детекције и потенцијалним методама за његову деконтаминацију у храни и храни за животиње.

Кључне речи: монилиформин, токсичност, храна, храна за животиње, деконтаминација

Received: 26 July 2019

Received in revised form: 10. September 2019

Accepted: 1 October 2019