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## Occurrence of mycotoxins in rice consumed by Iranians: a probabilistic assessment of risk to health

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### ABSTRACT

Risks based on cancer and non-cancer endpoints, to Iranians from exposure to several mycotoxins (aflatoxin B1, ochratoxin, deoxynivalenol and T-2 toxin) following consumption of rice were evaluated. Point estimates of hazard were made for each mycotoxin and a hazard index (HI) and probabilistic estimates were based on results of Monte Carlo Simulations (MCS). All known 17 peer-reviewed studies, published in databases included in Science Direct, PubMed, Scopus and Web of Science, as well as grey literature published in Google Scholar from 2008 to 2017 were considered. The 95<sup>th</sup> and 50<sup>th</sup> centiles of Hazard Index (HI) in Iranians due to ingestion of rice were estimated to be 2.5 and 0.5, respectively. The 95<sup>th</sup> and 50<sup>th</sup> centiles of people with positive surface antigens for hepatitis B (HBsAg+) risk characterisation for AFB<sub>1</sub> in Iranian consumers of rice were 81 and 79.1, respectively. The 95<sup>th</sup> and 50<sup>th</sup> centiles for risks of Iranians negative for the surface antigen of hepatitis B HBsAg (HBsAg-) were 4.4 and 2.6, respectively. Based on results of the MCS for risks to cancer effects, the 95<sup>th</sup> and 50<sup>th</sup> centiles of margins of exposure (MOE) were 233 and 231, respectively. Therefore, it is recommended to update agricultural approaches and storage methods and implement monitoring and regulations based on risks to health posed by consumption of rice by the Iranian population.

### ARTICLE HISTORY

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### KEYWORDS

Carcinogenicity; Monte Carlo simulation; Mycotoxin; rice; risk assessment

## Introduction

Mycotoxins (MTs), which are contaminants in agricultural products, include aflatoxins (AFs), ochratoxins (OTs), fumonisins (FBs), deoxynivalenol (DON), zearalenone (ZEN), citrinin (CIT), sterigmatocystin (STE), cyclopiazonic acid (CPA), patulin (PAT), gliotoxin (GLI) and T-2 toxin. They are produced by four eco-physiological groups of toxicogenic fungi. These include: (I) the Hydrophilic group which includes *Fusarium* spp., *Epicoccum* spp., *Alternaria* spp., *Rhizopus* spp. and *Mucor* spp.; (II) the Psychrophilic group, which includes *Penicillium verrucosum*, *Paecilomyces* spp. and other *penicillia*; (III) the Thermotolerant group, which includes *Aspergillus flavus*, *A. candidus* and *A. nidulans*; and (IV) the Xerotolerant group,

which includes *Eurotium* spp. and *Aspergillus* spp. (Ferre 2016; Fleurat-Lessard 2017; Khaneghah et al. 2018).

More than 300 MTs associated with agricultural products have been negatively associated with health of humans and thus considered issues for safety of food. MTs that can cause significant economic losses to food industries are found in both primary MT-contaminated agricultural products such as cereals and fruits, and secondary MT-contaminated materials such as milk and eggs (Flores-Flores et al. 2015; Ji et al. 2016).

Food processes such as extrusion, roasting, cooking, sorting, cleaning and frying may have effects on mycotoxins level. Most food processes have variable effects on mycotoxins, with those

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that apply the highest temperatures having maximum effects. Food processing methods result in reduction of mycotoxin concentrations but do not remove them completely. Obvious reduction of ZEN, moderate decrease of AFs, variable to low reduction of DON and good reduction of FBs were observed by extrusion processing at temperatures greater than 150°C. It was shown that ordinary cooking of rice leads to 34% reduction of AFB1 level. Additionally, a remarkable reduction (78–88%) was achieved by pressure-cooking. Sorting and trimming may reduce mycotoxin levels by removal of polluted materials. However, these processes do not destroy mycotoxins (Bullerman and Bianchini 2007).

Liver cytochrome P450 monooxygenase (CYP1A2 and CYP3A4) is responsible for conversion of AFB1 into AFB1-8,9-exo-epoxide which can bind to DNA, RNA, and proteins. CYP1A2 and CYP3A4 monooxygenases are active when AFB1 is present at low and high concentrations, respectively. The main site of AFB1 biotransformation and toxicity is the liver. Kidneys play a role in detoxification of AFs and their residues. It was shown that the combination of AFB1 and OTA in cultured monkey kidney Vero cells results in additive interactions with respect to reduced cell viability, elevated DNA fragmentation and p53 activation and reduced expression of the antiapoptotic factor bcl-2. It was suggested that AFB1 might induce oxidative stress due to the formation of deoxyguanosine, increase of lipid peroxidation and induction of heat shock protein-70 expression. Employing a comet assay modified using formamidopyrimidine-DNA glycosylase in hepatocellular carcinoma epithelial cells, the potential role of oxidative stress in AFB1 and OTA combined genotoxicity was studied. Remarkably, the mixture provoked a significant decrease in DNA damage, as compared to treatment with AFB1 alone. As shown by the dichlorofluorescein assay, ROS levels were elevated. The possible mechanism is competition of AFB1 and OTA for the same CYP enzymes, which in turn leads to higher levels of ROS, and less AFB1-DNA adducts. In rats, co-administration of single doses of OTA (0.5 mg/kg bw) and AFB1 (0.25 mg/kg bw) induced acute liver toxicity but no

significant toxicity in the kidneys or immunological organs. Herein, OTA accelerates the metabolism and excretion of AFB1 within 24 h (Klarić et al. 2013).

The Food and Agriculture Organisation of the United Nations (FAO) established four criteria, including availability, access, utilisation, and stability of food that should be met to have access to affordable and safe food required for having a healthy life. These factors not only contribute to enhancement of health of individuals, but also ameliorate social, economic, and political status of society (Udomkun et al. 2017).

The European Union set AF maximum concentrations (MLs) in Regulation 165/2010. These MLs in all cereals and products derived from cereals, with the exception of maize, are 2 µg/kg for aflatoxin B<sub>1</sub> (AFB<sub>1</sub>), 4 µg/kg for the sum of AFB<sub>1</sub>, AFB<sub>2</sub>, AFG<sub>1</sub> and AFG<sub>2</sub> and 5 µg/kg for OTA (Commission E 2010). Depending on food type, ML values vary among governmental regulations (Sarma et al. 2017). Nevertheless, there is global acceptance that maximum concentrations of toxins should be decreased based on provisional maximum tolerable daily intakes of various MTs (Anukul et al. 2013). The Institute of Standard and Industrial Research of I.R. Iran (ISIRI) set MLs of 30 and 5 µg/kg for AFs and AFB<sub>1</sub>, respectively, in cereals (Mazaheri 2009; Sani et al. 2014) (Table 1).

In traditional risk assessment methodologies, just single contaminants are considered. In cumulative risk assessment, methodologies utilise aggregate exposures, which refer to exposure to multiple compounds or mixtures causing similar toxicological effects, and use different risk characterisation approaches. Mathematical methodologies are commonly used as the main component-based approaches for assessing mixture risks. Such methods can include different or similar modes of action. Recently, probabilistic modelling was proposed as an approach for cumulative risk assessment (Rotter et al. 2018).

In the present study, reports of concentrations of MTs in rice, collected from various regions of Iran, were evaluated and the cumulative risk of oral exposure to rice for Iranian consumers was calculated. Some MTs are carcinogenic, while

**Table 1.** Mycotoxin maximum levels in eight (8) countries.

Country	Mycotoxin MLs ( $\mu\text{g}/\text{kg}$ )					Reference
	AFs	AFB <sub>1</sub>	OTA	DON	T-2	
Australia	5	nc	nc	nc	nc	(FAO/WHO 2017)
China	5–50	10	5	1000	nc	(PROGRAMME and FOODS 2017, USDA 2018)
European Union (EFSA)	4	2	5	1250	nc	(EFSA 2010, EFSA 2017)
India	30	Ne	nc	nc	nc	(PROGRAMME and FOODS 2017)
Iran (ISIRI)	30	5	5	1000	nc	(ISIRI 2002)
Japan	10	Nc	nc	nc	nc	(PROGRAMME and FOODS 2017)
Korea	10	nc	nc	nc	nc	(PROGRAMME and FOODS 2017)
United States (USDA and FDA)	0.5–20	10	5	1000	nc	(FAO/WHO 2017)

EFSA: European Union Food Safety Authority; ISIRI: Institute of Standard and Industrial Research of I.R. Iran; USDA: United States Department of Agriculture; FDA: Food and Drug Administration.

AFs: Aflatoxins; AFB<sub>1</sub>: Aflatoxin B<sub>1</sub>; OTA: Ochratoxin A; DON: Deoxynivalenol; T-2: T-2 toxin.

MLs: Maximum Levels.

nc: not controlled.

others are not. Thus, the margins of exposure (MOE) and Hazard Quotients (HQs) were calculated based on carcinogenic and non-carcinogenic effects. Monte Carlo Simulations (MCS) were used to predict risks.

### Mycotoxigenic fungi in rice

Numerous agricultural crops, especially those with high carbohydrate and/or fat contents, such as cereals like maize (*Zea mays*), rice (*Oryza sativa*), barley (*Hordeum vulgare*), sorghum (*Sorghum bicolor* L.), soybean (*Glycine max*), wheat (*Triticum aestivum*), millet (*Pennisetum glaucum*) and cereal-derived food products, such as cereal-based food for infants and children, dietetic food for diabetics, snack foods, bread, pasta, and rice-based meals, are likely to become contaminated with AFs (Authority 2013; Achaglinkame et al. 2017).

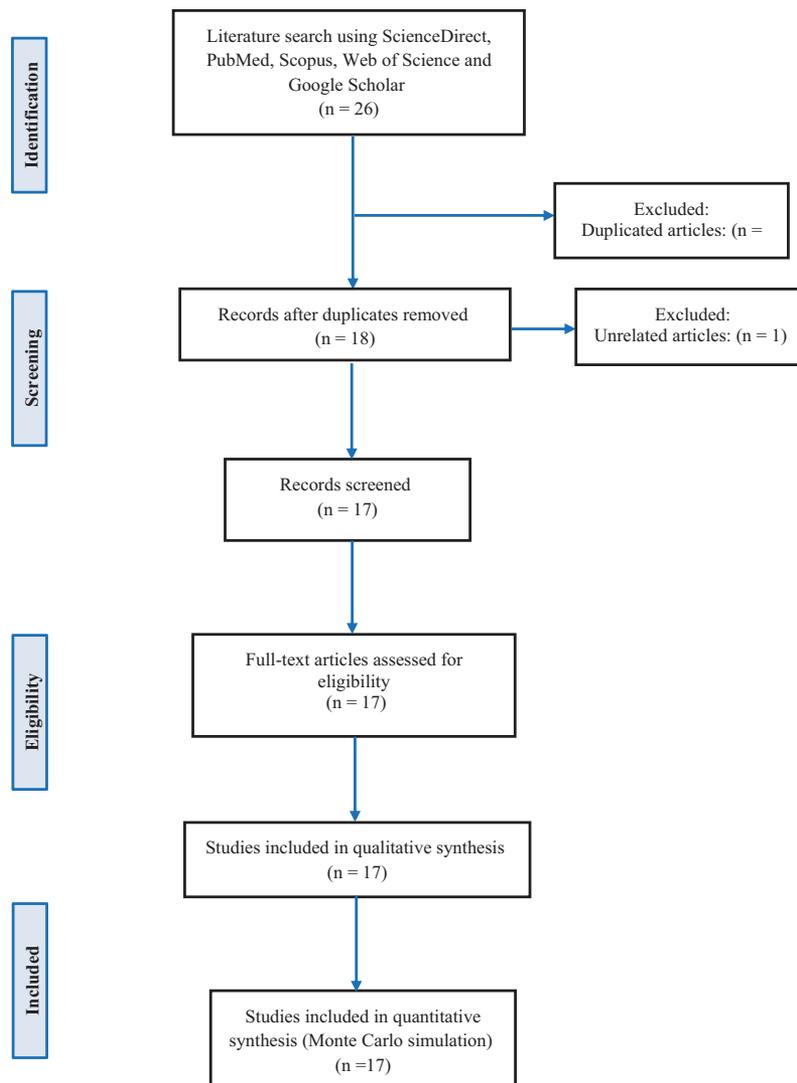
Rice is globally the second most-important cereal after wheat. It is the main nutritional source to supply calories for a third of the world's population; worldwide, in 2010, 603 million tons of rice were produced, sufficient to meet the needs of 50% of the world's population (Ferre 2016; Sharafati Chaleshtori et al. 2017; Shirani et al. 2017; Temba et al. 2017). For Iranians, rice is the main source of dietary energy and comprises the main part of daily food. Therefore, the rate of ingestion of rice is approximately 110 g/day in Iran, and almost 4.9 tons per hectare is produced annually making Iran the 11<sup>th</sup> largest producer of rice in the world. Since this production does not suffice for the domestic consumption, Iran imports rice from other countries (Mazaheri 2009; Eslami et al. 2015; Sharafi

et al. 2019). MTs in rice do not exceed those of wheat and maize, but considering its daily intake even small amounts of contamination can produce serious health problems (Elzupir et al. 2015; Prietto et al. 2015).

Approximately 143 species of fungi have been found in rice, but the predominant genera were *Aspergillus*, *Penicillium* and *Fusarium* (Reddy et al. 2010). Rice may contain AFs and other MTs including AFB<sub>1</sub>, AFB<sub>2</sub>, AFG<sub>1</sub>, AFG<sub>2</sub>, CIT, STE, FB<sub>1</sub>, FB<sub>2</sub>, FB<sub>3</sub>, ZEN, CPA, PAT and GLL, which have frequently been isolated from this cereal (Suárez-Bonnet et al. 2013; Ferre 2016). Most regions of Iran, where rice is cultivated, have heavy rains and high humidity, which predispose growth of fungi and production of MTs. Thus, considering the deleterious effects of MTs on human health, the present work presents an assessment of risks based on concentrations of MTs, reported previously for samples collected from Iranian markets.

### Search strategy used for the survey of literature

In this review article, scientific databases, including Science Direct, PubMed, Scopus, and Web of Science, as well as unpublished "gray" literature published in Google Scholar, were searched for articles published between 2008 and 2017, by use of the following combination of terms: [Iran] AND [Rice] AND [AFB<sub>1</sub> OR OTA OR DON OR T-2 OR Aflatoxin B1 OR Ochratoxin OR Deoxynivalenol OR T-2 Toxin OR Mycotoxins]. First, some articles were excluded following evaluation of their title. After excluding irrelevant articles, full texts of



**Figure 1.** Flow diagram of search process and inclusion.

remaining articles were downloaded and carefully evaluated. The search of the literature yielded 17 manuscripts published in English (Figure 1).

### Occurrences of MTs in samples of rice collected from Iranian market

Concentrations of MTs in rice collected from various regions of Iran have been reported (Table 2). In the following four sections, the studies retrieved using the above-noted strategy, are discussed and finally, their reported data were used to perform a probabilistic assessment of adverse effects (risks).

### Aflatoxins

Of the 18 known AFs, AFB<sub>1</sub>, AFB<sub>2</sub>, AFG<sub>1</sub> and AFG<sub>2</sub> exert more potent carcinogenic, mutagenic, oestrogenic, tumorigenic, teratogenic and immunosuppressive effects (Heshmati et al. 2017; Taghizadeh et al. 2018). The “G” and “B” letters at the end of their acronyms indicate green and blue, respectively, which represent the fluorescence colour produced by each MT after exposure to ultraviolet light (Campagnollo et al. 2016). These four forms of AFs are found in plant-based food, while AFB<sub>1</sub> and AFB<sub>2</sub>, that produce hydroxy metabolites M<sub>1</sub> and M<sub>2</sub>, are found in foods of animal origin (Godwin 2012).

**Table 2.** Summary of results of studies that measured MTs in rice consumed in Iran.

No. of sample analysed	Detection Method	Mycotoxin	Incidence (%)	Range ( $\mu\text{g}/\text{kg}$ )	Mean ( $\mu\text{g}/\text{kg}$ )	Reference
100	HPLC	AFB1	47	ne	0.5	(Karajibani et al. 2013)
60	HPLC	AFB1	8.3	ne	2.5	(Faraji et al. 2010)
152	HPLC	AFB1	75	0.09–3.3	0.4	(Mohammadi et al. 2012)
71	HPLC	AFB1	83	ne	1.8	(Mazaheri 2009)
40	ELISA	AFB1	100	0.2–2.9	2.0	(Eslami et al. 2015)
256	HPLC	AFB1	98	0–5.8	1.4	(Rahmani et al. 2011)
261	HPLC	AFB1	68.9	ne	0.7	(Feizy et al. 2010)
18	HPLC	AFB1	50	ne	4.1	(Yazdanpanah et al. 2013)
140 (imported)	ELISA	T-2	ne	ne	13.0	(Riazipour et al. 2009)
60 (domestic)		T-2	ne	ne	11.2	
275	HPLC	AFB1	73.8	ne	2.9	(Safara et al. 2010)
24	HPLC	AFB1	37.5	ne	0.3	(Ebrahimi et al. 2010)
308	ELISA	OTA	9.4	0.8–11.3	3.6	(Rahimi 2016)
ne	HPLC	AFB1	105.5	ne	12.3	(Sabet et al. 2017)
ne	HPLC	AFB1	47.4	ne	0.01	(Es'haghi et al. 2011)
ne	HPLC	AFB1	93.5	ne	1.2	(Hashemi et al. 2014)
ne	TLC	AFB1	ne	0.03–0.08	1.3	(Zare et al. 2008)
65	LC-MS/MS	AFB1	21.5	ne	3.9	(Nazari et al. 2014)
		OTA	4.6	ne	5.0	
		DON	0	ne	0	

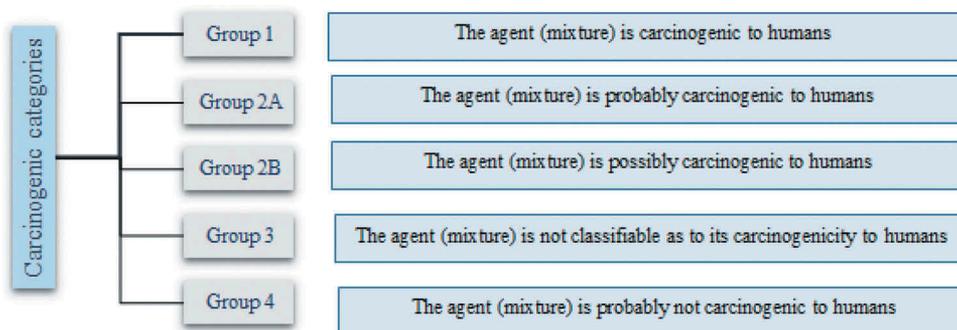
HPLC: High-Performance Liquid Chromatography; ELISA: Enzyme-Linked Ammunosorbant Assay; TLC: Thin-Layer Chromatography; LC- MS/MS: Liquid Chromatography-mass spectrometry; AFB1: Aflatoxin B1; OTA: Ochratoxin; DON: Deoxynivalenol; T-2: T-2 Toxin; ne: Not specified.

Among AFs, which contaminate several agricultural crops, are in the following order or decreasing toxic potencies:  $\text{AFB}_1 > \text{AFG}_1 > \text{AFB}_2 > \text{AFG}_2$ . In this regard, the International Agency for Research on Cancer (IARC) considers  $\text{AFB}_1$  to a chemical that could seriously affect human health and thus, it is classified as Group 1, while  $\text{AFM}_1$  is classified as Group 2B (Es'haghi et al. 2011; Li et al. 2015; Sabet et al. 2017; Udomkun et al. 2017). The IARC and USA Governments Annual Report on Carcinogens made a similar classification with respect to carcinogenic properties of AFs (Figure 2) (Michaels and Monforton 2005; Humans et al. 2007).

The sixth most common cancer worldwide is hepatocellular carcinoma (HCC). Chronic exposure to hepatitis C virus (HCV) or hepatitis B virus (HBV) is associated with 70% and 75%

HCC in the United States and Asia, respectively. Also,  $\text{AFB}_1$  exposure, iron overload and alcohol consumption are the major risk factors correlated with liver carcinogenesis. Importantly, synergistic effects of  $\text{AFB}_1$  and chronic HBV infection on the risk of HCC were reported. It is believed that the  $\text{AFB}_1$ -induced R249S mutant protein binds the transactivation domain of the HBX protein and increases hepatocarcinogenesis via a pathway which bypasses cirrhosis.  $\text{AFB}_1$  was observed to prevent HBV DNA replication, although  $\text{AFB}_1$ -induced DNA damage is not affected by the presence of HBV. It was stated that HBV infection and  $\text{AFB}_1$  exposure increase the risk for HCC by synergistic induction of oxidative stress (Qi et al. 2015).

Both acute and chronic exposures to MTs can cause adverse effects in animals and humans.



**Figure 2.** Carcinogenic categories of aflatoxins as defined by International Agency for Research on Cancer (IARC) and USA Governments Annual Report on Carcinogens (available at [http://monographs.iarc.fr/ENG/Classification/List\\_of\\_Classifications.pdf](http://monographs.iarc.fr/ENG/Classification/List_of_Classifications.pdf)).

AFB1 initiates mutagenic effects and damages DNA, which can initiate carcinogenicity (Sarma et al. 2017). AFs are lipophilic molecules, which can be accumulated in liver and concentrated in hepatocytes, where they can initiate carcinogenesis in liver (Rastegar et al. 2017).

Concentrations of various MTs have been measured in rice from various regions of Iran. During a study in which 100 samples of rice selected randomly from Zahedan, in south-east Iran, from 1 March 2010 to 1 February 2011, samples were kept in zip-locked plastic bag at 4°C until aflatoxin analysis. Forty-seven per cent of samples contained at least 0.5 µg AFB1/kg. However, none of the samples contained MTs at concentrations greater than the MLs (Karajibani et al. 2013). In another study, concentrations of AFB1 were measured in 60 samples of rice and the mean concentration of AFB1 was 2.6 µg/kg, with 8.3% of samples containing concentrations of AFB1 greater than MLs set by ISIRI Iran (Faraji et al. 2010). In another study concentrations of AFs were measured in 152 samples of rice collected from Bushehr, in south-west Iran. In that study, samples were stored in polyethylene bags at 20°C before extraction and subsequent quantification. Seventy-five per cent of samples contained measurable quantities of AFB1 and 77% of samples contained measurable quantities of AFs, but not all of the detected concentrations exceeded the ML set by ISIRI (Mohammadi et al. 2012). In another study, AFs were quantitated by High-Performance Liquid Chromatography (HPLC). Among 71 samples of rice, 59 samples (83% of total) contained a mean concentration of 1.9 µg AFB1/kg and all samples had detectable (>LOD) concentrations of AFB1. Two samples (2.8% of total) contained concentrations of AFB1 that exceeded the ML set by ISIRI. Overall, mean concentrations of the sum of AFs in these samples were 2.1 µg/kg, which was less than MLs set by ISIRI (5 µg/kg) and EU (4 µg/kg) (Table 1). In only nine samples, did concentrations of AFs exceed the ML recommended by EU. Of the samples analysed 12 (17%) contained concentrations of AFs that exceeded the LOD (Mazaheri 2009). Concentrations of AFB1 were measured in 40 samples of “*Tarom*” rice (one of the Iranian rice varieties), collected from Qaemshahr, Mazandaran, Iran. Concentrations of

AFB1 in samples ranged from 0.2 to 2.9 µg/kg. However, concentrations of AFB1 in none of the samples exceeded the ML of 2 µg/kg set by the EU (Eslami et al. 2015). In another study, 256 samples of rice were collected from 30 provinces of Iran and concentrations of MT measured. Ranges of concentrations of AFB1 and total AFs were 0–5.8 and 0.1–6.3 µg/kg, respectively. Concentrations of AFB1 in 21.5% of samples were greater than 2 µg/kg, and 2.7% contained greater than 4 µg total AFs/kg (Rahmani et al. 2011).

Due to differences in climate, such as temperature and humidity, concentrations of MTs vary among regions (Liu 2007; Sun et al. 2017). Concentrations of MTs in rice from Mashhad, Khorasan Razavi, Iran were detectable in 68.9% of the samples with a mean of 0.7 µg AFB1/kg. In general, concentrations of AFs observed were less than ISIRI MLs (Feizy et al. 2010). Of 18 samples of rice marketed in Tehran, Iran, 50% contained detectable concentrations of AFB1 with maximum and mean concentrations of 30.6 and 4.1 µg/kg, respectively (Yazdanpanah et al. 2013).

Alternative methods for quantifying MTs have been applied. The standard method for quantifying MTs is by use of liquid chromatography (LC) coupled with mass spectrometry, specifically MS-MS, but other methods including Enzyme-Linked Immunosorbent Analyses (ELISA) have been applied. Using an aptamer biosensor for detection of AFB1, the mean concentration in rice from a local market was 12.3 µg AFB1/kg (Sabet et al. 2017). AFB1 in rice from local markets of Iran have also been analysed by use of a new method based on hollow fibre solid phase micro extraction combined with HPLC-diode array detection. Using that method, the mean concentration of AFB1 in rice was 0.01 µg/kg (Es’haghi et al. 2011). Solid phase extraction, followed by detection by use of ELISA with magnetic spheres, was used to quantify for detection of AFB<sub>1</sub> and AFB<sub>2</sub> in extracts of rice (Hashemi et al. 2014). In that study, the mean concentration of AFB<sub>1</sub> in rice was 1.2 µg/kg (Hashemi et al. 2014). Concentrations of AFB<sub>1</sub>, as measured by thin-layer chromatography (TLC), in 14 cultivars of cereals including rice in Karaj, Iran, were between 0.03 and 0.08 µg/kg (Zare et al. 2008). AFs were found in 211 of 275 samples of rice (76.7%) in Iran. Among those

samples in which AFs were detected, AFB<sub>1</sub> was detected in 73.8%, with a mean of 3.0 µg/kg. Also, no AFs were detected in 64 samples (Safara et al. 2010). In another study where HPLC was used to quantify AFs in three samples of imported rice collected from the market of Ahvaz, Khuzestan province, Iran, AFB<sub>1</sub> was detected in 37.5% of samples with a mean 0.36 and range of 0.011–2.4 µg/kg. All concentrations of AFB<sub>1</sub> were less than the ML set for rice in Iran (Ebrahimi et al. 2010). During a mycological study of 65 samples of rice from Iran identified co-occurrence of MTs by use of a highly sensitive and selective Liquid Chromatography–Mass Spectrometry (LC-MS/MS) method. In that study, 21.5% of samples contained measurable concentrations of AFB<sub>1</sub> with a mean of 3.9 µg/kg (Nazari et al. 2014).

### Ochratoxins

There are several types of ochratoxins (OTs) including ochratoxin A (OTA), ochratoxin B (OTB) and ochratoxin C (OTC), methylochratoxin A (MeOTA), methylochratoxin B (MeOTB), ethylochratoxin A (EtOTA) and ethylochratoxin B (EtOTB). They are frequently found in cereals, cereal products, oats, coffee, cocoa, chocolate, milk, beer, olive, nuts, raisins and dried fruits (Vecchio et al. 2012; Remiro et al. 2013; Benites et al. 2017). Several reports have suggested that the possibility of co-occurrences of OTs might result in greater exposure and associated risks to health than predicted from individual OTs. OTs can be inter-converted among the various individual OTs as well as to OTB (Mally et al. 2005; Zhang et al. 2018). Since they can cause oxidative damage to DNA, IARC has classified OTs as Group 2B, since they can cause effects that have the potential to result in carcinogenesis in humans. The most potent of the OTs is OTA, which contaminates various foods. It is usually produced by *Aspergillus ochraceus* and *Penicillium verrucosum* (Mashhadizadeh et al. 2013).

Toxic effects of OTA include liver necrosis, liver tumours, reduced body growth, depressed immune responses, carcinogenesis, genotoxicity in humans, and nephropathy in porcine, and various diseases in poultry, as well as modulation of immune systems in mammals (Ferre 2016; Fleurat-Lessard 2017). Chronic exposure to OTA can cause diseases including ochratoxicosis of the

liver via degenerative damage to epithelial cells in type-2 diabetes (T2D) (Afshar et al. 2013; Chen and Wu 2017).

When monitored by use of ELISA, occurrences of OTA in 308 samples of rice collected from six provinces of Iran, 9.4% of which contained OTA with concentrations ranging from 0.8 to 11.4 µg/kg, dm, with 17.3% samples exceeding the ML in cereals (5 µg OTA/kg, dm), set by the ISIRI (Rahimi 2016). In a separate study of 65 samples of rice from Iran, OTA was detected in 4.6% of samples, with a mean concentration of 5.0 µg OTA/kg (Nazari et al. 2014).

### Deoxynivalenol

Deoxynivalenol (DON), one of the trichothecene MTs, and produced primarily by *Fusarium* spp., is found in cereal-based food and can produce toxicity in humans and animals (Del Favero et al. 2018). A major effect of DON is anorexia, which results in loss of weight at greater doses and emesis at lesser doses. Chronic exposure to greater doses caused oxidative damage in rodents (Peng et al. 2017). DON is classified as a Group 3 carcinogen by IARC (Cancer 2016). DON was not detected in the 65 samples collected in Iran by Nazari et al. (Nazari et al. 2014).

### T-2 toxin

The most notorious trichothecene, which is T-2 toxin is produced by *Fusarium sporotrichioides*, *F. poae* and *F. graminearum*, and is found in extremely contaminated cereals. Acute exposure to T-2 toxin and its major metabolite (HT-2) includes the following symptoms: nausea, vomiting, diarrhoea, weight loss, decrease red blood cell and leucocyte counts, necrosis, epidermal sloughing, dermal pain, weakness, ataxia, collapse, DNA damage, apoptosis reduced cardiac output, shock and even death (Kassim et al. 2011; Li et al. 2017). IARC categorised T-2 toxin in Group 3 (<https://monographs.iarc.fr/list-of-classifications-volumes/>). Concentrations of T-2 toxin in 140 imported and 60 domestic rice, grown in Northern Iran had mean concentrations of 13 and 11.2 µg T-2/kg, dm, respectively (Riazipour et al. 2009). These two concentrations

were not significantly different from each other ( $p = .2, 0.2$ ), respectively.

Although concentrations of most MTs in rice that is consumed in Iran were relatively small, considering the large amounts of rice consumed in Iran, even small concentrations of MTs are of concern and might be expected to cause chronic, population-level effects on humans.

**Assessment of exposure characterisation of risks posed by MTs in rice consumed in Iran**

Assessment of risks posed to health of Iranians by consumption of rice was done in four stages (Figure 3) as follows: (1) To assess risks posed by exposure to all MTs, an estimated daily intake (EDI, mg/kg bw/day) was calculated (Equation (1)) (Cunha et al. 2018; Badibostan et al. 2019).

$$\begin{aligned}
 \text{EDI} &= \text{Rice intake (g/kgbw/day)} \\
 &\times \text{Average mycotoxin concentration}(\mu\text{g/kg})
 \end{aligned}
 \tag{1}$$

where rice intake was considered to be 110 g/day and the average concentration of each MT ( $\mu\text{g/kg}$ )

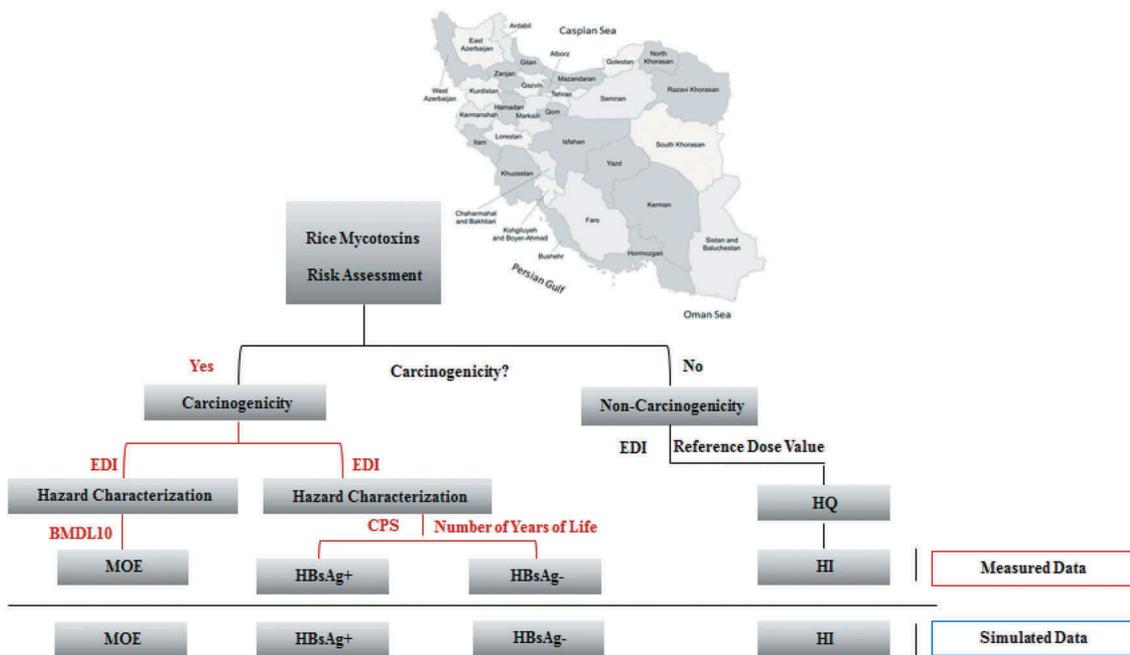
was acquired from Ministry of Agriculture, Iran. (2) For non-carcinogenic MTs including, OTA, DON, and T-2, HQs are given by Equation (2) (Ortiz et al. 2018).

$$\text{HQ} = (\text{EDI/Reference dose value})
 \tag{2}$$

Reference doses, used were Provisional Maximum Tolerable Daily Intake (PMTDI) values: 17 ng/kg bw/day for OTA, 1000 ng/kg bw/day for DON and 100 ng/kg bw/day for T-2 (EFSA 2017). Since rice can contain multiple MTs, there was also a need to perform cumulative health risk assessments. Thus, Hazard Indices (HI) were calculated (Equation (3)) (Taghizadeh et al. 2019).

$$\text{HI} = \sum_{i=1}^{n=3} \text{HQ}
 \tag{3}$$

In order to estimate risks posed by exposure to AFB1, which is a Group-1 compound that can increase the risk of hepatocellular carcinoma (HCC) in humans, cancer risk was calculated (Equation (4)) (IARC and Chemicals to Humans. Aflatoxins, World Health Organisation, Luzardo et al. 2016).



**Figure 3.** Schematic diagram for applications of procedures to assess risks to health due to consumption of rice containing mycotoxins (MT) EDI: Estimated Daily intake; HQ: Hazard Quotient; HI: Hazard Index; BMDL10: Benchmark Dose Lower Limit; CPS: Carcinogenic Potency Slope; MOE: Margin of Exposure; HBsAg+: People with positive surface antigen of hepatitis B; HBsAg-: People with negative surface antigen of hepatitis B.

$$\text{Cancer Risk} = \text{EDI} \times \text{CPS} \times (\text{number of years of life}) \quad (4)$$

As defined by the Joint FAO/WHO Expert Committee on Food Additives, CPS is the carcinogenic potency slope for ingestion (0.3 and 0.01 cancers per year per  $10^5$  individuals per nanogram of total aflatoxins per kg body mass (bm) per day for people with positive and negative surface antigen of hepatitis B (HBsAg+) and (HBsAg-), respectively) (Joint FAO 2007). The EDI value obtained from Equation (1) was used. The Margin of Exposure (MOE) was calculated based on recommendations published by the EFSA and WHO, and expressed as the ratio between the Benchmark Dose Lower Limit ( $\text{BMDL}_{10}$ ) and the average estimated daily exposure (Equations (5) and (6)).

$$\text{BMDL}_{10}(\text{Human}) \text{ for AFB1} = 870 \text{ ng/ kg bm/day} \quad (5)$$

(Available at <https://www.efsa.europa.eu/en/microstrategy/openfoodtox>)

$$\text{MOE} = (\text{BMDL}_{10} / \text{EDI}) \quad (6)$$

Risks posed by exposure to AFB1 and other MTs through consumption of rice were expressed as HQs, HI, risk characterisation for HBsAg+ and HBsAg- people and MOE (Table 3). HIs were calculated as sums of respective HQs for occurrences of MTs, excluding AFB1. An  $\text{HI} < 1$  indicates no significant health risk, an  $\text{HI} = 1.1\text{--}10$  presents moderate risk and an  $\text{HI} > 10$  reflects "high" risk (Taghizadeh et al. 2017). Considering HBsAg+ and HBsAg-, it was shown that the annual cancer risks via consuming rice were 78.96 and 2.63 per 100000 persons, respectively

(Table 3). Use of the MOE is recommended by EFSA Scientific Committee to estimate risk level of carcinogenic and genotoxic PAH. The MOE of  $1 \times 10^4$  or higher signifies low public health concern. The MOE due to ingesting rice was measured to be 231.3 which being  $< 10^4$ , represents a risk for Iranians (Yousefi et al. 2018).

### Monte Carlo simulation

Deterministic methods revealed a single point estimate of individual risk. These methods employed worst-case estimates of exposure factors to derive a worst-case risk estimate. Probabilistic methods estimate the distribution of potential risk for an individual, or the range of probable risk across a population, from least to most at risk. The most common arguments in support of probabilistic methods including that the deterministic methods are too conservative and probabilistic methods are more realistic. The Monte Carlo simulation (MCS) is able to generate probability distribution and probabilities, such as 50<sup>th</sup>, 90<sup>th</sup> or 95<sup>th</sup> centiles of exceeding particular thresholds for specific adverse outcomes. MCS ( $n = 10,000$ ) was used to evaluate the uncertainties and their impact on the risk estimation. This probabilistic modelling employs the entire range of input variable to develop a probability distribution of exposure or risk rather than a single point data. The model input parameters applied in the simulation included Exposure Frequency (EF), Exposure Duration (ED), Ingestion rate (IR), Body Weight (BW), Average Life Span ( $\text{AT} = 25550$  days), Benchmark Dose Lower Limit ( $\text{BMDL}_{10}$ ) and Carcinogenic Potency Slope (CPS). In this study,

**Table 3.** HQ, HI, MOE, HBsAg+ and HBsAg- risk characterisation of measured and simulated data from consumption of selected rice.

Toxin	Measured data						Simulated data*							
	EDI	HQ	HI	RC (HBsAg+)	RC (HBsAg-)	MOE	HI		RC (HBsAg+)		RC (HBsAg-)		MOE	
							50th	95th	50th	95th	50th	95th	50th	95th
AFB1	288.2	-		78.96	2.63	231.3			79.1	81	2.6	4.4	231	233
OTA	287.1	0.3		-	-	-	-	-	-	-	-	-	-	-
DON	0	0		-	-	-	-	-	-	-	-	-	-	-
T-2	1400.3	0.1		-	-	-	-	-	-	-	-	-	-	-
			0.5				0.5	2.5						

EDI: estimated daily intake (EDI, mg/kg bw/day); HQ: Hazard Quotient; HI: Hazard Index; HBsAg+: People with positive surface antigen of hepatitis B; HBsAg-: People with negative surface antigen of hepatitis B; MOE: Margin of Exposure.

RC: Risk Characterisation.

\*As analysed by Monte Carlo Simulation.

MCSs were carried out by use of JMP 8 software (SAS Campus Drive, Cary, NC 27513). Simulated assessments of risks posed by exposure to non-carcinogenic MTs (OTA, DON, and T-2) indicated that the probability of exposure through ingestion of rice were 95% and 50% HIs of 2.5 and 0.5, respectively. The 95<sup>th</sup> and 50<sup>th</sup> centiles for HBsAg+ were 81 and 79.1, respectively. The 95<sup>th</sup> and 50<sup>th</sup> centiles for risks of Iranians having HBsAg+ were 4.4 and 2.6, respectively. Also, the MOE associated with a probability of exposure of 95% and 50% to AFB1 through consumption of rice in Iran were 233 and 231, respectively (Table 3).

Concentrations of MTs in rice eaten in Iran along with uncertainty associated with application of the model used to predict risks to humans in Iran from consumption of rice, indicated risks to health, especially for AFB1. Also, the mean HI in measured data, which was <1 showed that non-carcinogenic toxins (OTA, DON and T-2) in rice posed no risk to health of Iranians.

Concentrations of MTs in rice varied among different locations in Iran. Frequencies of detection of secondary metabolites of MTs in rice indicated that they were the primary source of exposure of the Iranian population to MTs. Probabilities of exposure of Iranians to MTs might be reduced in several ways. First, rice products should be protected against fungal contamination from field to consumer. Second, legislation should be established to specify safe concentrations and apply preventative strategies. To achieve this goal, use of fungicides to reduce infection with fungi that produce MTs, could be considered. However, this carries the risk of exposing the population to residual fungicides. Another way to minimise MTs in rice is to keep the cereal dry during harvest, transport and storage. Depending on the type or mode of application, several innovative strategies have been created to control mycotoxins damage, including novel practical approaches using biological control and sorting technology. Other innovative management tools such as ozone fumigation, chemical control and packaging materials can also enhance the level of food safety and security and improve economic conditions. The present analysis indicated that even with very conservative estimates of

parameters, the risks posed by MTs to the general Iranian population are *de minimis*, even though Iranians eat rice more than many other countries.

## Conclusions

In the current study, the levels of mycotoxins (aflatoxin B1, ochratoxin, deoxynivalenol and T-2 toxin) in rice samples were evaluated. Measured data and cumulative risk assessment were calculated to evaluate the effect of chronic consumption of rice on consumers' health based on a newly proposed methodology for adversity groups based on critical effects. According to the results for both measured and cumulative risk assessment scenarios, the HI was calculated as sums of respective HQ's for occurrences of MTs, excluding AFB1. Our results showed that the HI in measured data was below 1, indicating no health risk through chronic consumption. HI >1 in simulated data (in 95<sup>th</sup> centile) indicates moderate risk. Comparison of the results of measured and probabilistic risk analysis revealed that in cases where input variables used in deterministic method are comparable to those of the probabilistic method, the final results will not differ significantly. However, values obtained from the probabilistic method at P95% are apparently higher than those of the deterministic method. Further research on MTs content in Iran in dietary products is needed to continuously control the exposure of Iranians to hazardous compounds.

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## Disclosure statement

No potential conflict of interest was reported by the authors.

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