ASIA PACIFIC JOURNAL of MEDICAL TOXICOLOGY
APJMT 6;3 http://apjmt.mums.ac.ir September 2017

REVIEW ARTICLE

Comparative Cancer Risk Assessment to Estimate Risk of Hepatocellular Carcinoma Attributable to Dietary Exposure of Aflatoxin through a Surrogate (Maize) in Eastern Mediterranean Region (Iran) as Compared to East (Canada) and West Pacific (China) Regions

SNEHAL VAGHELA[1], REZA AFSHARI[2,*]

[1]Master of Public Health candidate, Faculty of Health Sciences, Simon Fraser University, Burnaby, BC, Canada
[2]Senior Toxicologist, Environmental Health Services, British Columbia Centre for Disease Control, Vancouver, BC, Canada

Abstract

Background: Hepatocellular Carcinoma (HCC) is the most common primary liver malignancy and the second leading cause of cancer related deaths worldwide. Chronic infection with Hepatitis B (HBV) and Hepatitis C (HCV) virus are significant risk factors of HCC. Aflatoxins, type of mycotoxin, produced by fungi Aspergillus *flavus* and Aspergillus *parasiticus* are potent liver carcinogen. This cancer risk assessment was conducted with aim to compare risk of aflatoxin attributable HCC in the countries of Eastern Mediterranean region with countries of region of Americas (East) and Western Pacific region (West).
Methods: Cancer risk assessment was conducted using data on maize consumption for select countries from food balance sheets (FBS) database of the Food and Agriculture Organization of the United Nations (FAO), aflatoxin contamination level of the maize and chronic HBV infection prevalence from 37 publications retrieved from literature review.
Results: Risk of HCC attributable to aflatoxin exposure in Iran is 0.02 (0.0001 – 0.095) HCC cases per 100,000 chronic HBV negative population which reflects in 15-75 HCC cases per year. Among the select WHO regions, most cases occur in China and Philippines from Western Pacific region and Mexico from region of Americas.
Conclusion: Risk of aflatoxin related HCC in Iran is comparable to high income countries from region of Americas and Western Pacific region.

How to cite this article: Vaghela S, Afshari R. Comparative Cancer Risk Assessment to Estimate Risk of Hepatocellular Carcinoma Attributable to Dietary Exposure of Aflatoxin through a Surrogate (Maize) in Eastern Mediterranean Region (Iran) as Compared to East (Canada) and West Pacific (China) Regions. *Asia Pac J Med Toxicol* 2017;6(3):67-73.

INTRODUCTION

Hepatocellular Carcinoma (HCC) is the most common primary liver malignancy across the world. Each year more than 700,000 new cases of HCC are diagnosed worldwide (1). With average survival of 6-20 months and more than 600,000 HCC attributable deaths per year, HCC has become the second leading cause of cancer related deaths worldwide (1–3).

As compared to other cancers, the most distinct feature of HCC epidemiology is that major risk factors and predisposing factors have been clearly identified based on animal bioassays and human epidemiological studies (1). However, there is differential distribution of these risk factors in different regions of the world. Chronic infection with either Hepatitis B virus (HBV) or Hepatitis C virus (HCV) has been associated with almost 80% of HCC cases (4). Chronic HBV infection is the significant contributor towards HCC cases in low or middle-income countries and chronic HCV infection is the important risk factor in high income countries (5). Chronic dietary exposure to aflatoxin-B_1 through ingestion of aflatoxin contaminated food products is another major risk factor for HCC in low or middle-income countries. Other contributing risk factors include excessive consumption of alcohol, obesity, diabetes, non-alcoholic fatty liver disease and certain rare metabolic disorders, such as hemochromatosis, α – 1 antitrypsin deficiency and few types of porphyria (4). A synergistic action has been established between chronic HBV infection and dietary exposure to aflatoxin B_1 for development of HCC (6). The risk of developing HCC in individuals with exposure of both chronic HBV infection and dietary aflatoxin B_1 is 30 times greater than individuals exposed to aflatoxin B_1 alone (7).

Aflatoxins are difuranocoumarin derivatives, a type of mycotoxin, produced by fungi Aspergillus *flavus* and Aspergillus *parasiticus* (8). These mycotoxins exert high hepatotoxic, hepatocarcinogenic and mutagenic potential and can contaminate number of agricultural commodities

*Correspondence to: Reza Afshari;MD, PhD, MPH. Environmental Health Services, BC Centre for Disease Control, 655 West 12th Avenue, Vancouver, BC, V5Z 4R4
Tel: +1 604-707-2462, Email: Reza.Afshari@bccdc.ca
Received 12 July 2017; Accepted 25 August 2017

including staple food like corn, groundnuts and rice in tropical and subtropical climate (9). Among the family of 20 related fungal metabolites, four major aflatoxins which have predominant adverse effects on human health are aflatoxin B_1, B_2, G_1 and G_2. Unique feature of aflatoxin M_1 is the transmission through milk (including breastmilk), hence if dairy cattle are fed with aflatoxin contaminated feeds then aflatoxin M_1 is excreted in milk (9).

Among all aflatoxins, aflatoxin B_1 is known to be a potent human carcinogen (10). International Agency for Research on Cancer (IARC) and National Toxicology Program (NTP) of the United States have classified aflatoxins as “Group-1, carcinogen to human” and “known to be human carcinogen” respectively based on evidence from laboratory animal studies, human epidemiological studies and mechanistic data (10,11). Liu and Wu estimated that out of 555,000-600,000 incident cases of HCC globally every year, about 25,000-155,000 HCC cases may be attributable to dietary exposure to aflatoxin (12).

Although HCC is more prevalent in low or middle income countries from World Health Organization (WHO) regions of Africa, Southeast Asia and Western Pacific region, there is evidence that incidence of HCC is increasing in high income countries of Eastern Mediterranean, European region and North America (1). In the countries of Eastern Mediterranean region, HCC is a major concern, specially among men, in certain countries such as Egypt and Saudi Arabia and to a lesser extent in other countries of this region (5). This quantitative cancer risk assessment was conducted to compare risk of HCC attributable to dietary exposure to aflatoxin in Eastern Mediterranean region with risk in countries of Western Pacific region and region of America.

This risk assessment was conducted with an aim to compare dietary aflatoxin exposure and risk of HCC attributable to dietary exposure of aflatoxin through maize in select countries of Eastern Mediterranean region, Western Pacific region and region of Americas.

METHODS

Risk assessment is the process of quantifying the magnitude and exposure, or probability, of a harmful effect to individuals or populations from certain agents or activities. Four steps involved in the process of risk assessment are: hazard identification, dose-response assessment, exposure assessment and risk characterization (13). This risk assessment involved comprehensive literature review to obtain and compile information about level of aflatoxin contamination in maize, food consumption pattern (for maize), chronic HBV infection prevalence and population size in select countries from Eastern Mediterranean region, Western Pacific region and region of Americas.

Hazard identification: Hazard Identification is the process of determining whether exposure to a stressor can cause an increase in the incidence of specific adverse health effects (e.g., cancer, birth defects) (13). Aflatoxins are most extensively researched group of mycotoxins due to manifestations of carcinogenic and toxic health effects in livestock, laboratory animals and human beings. Based on weight of evidence from animal and human studies supporting increased risk of HCC from dietary exposure to aflatoxin, International Agency for Research on Cancer (IARC) and US National Toxicology Program (NTP) have classified naturally occurring mixture of aflatoxins as “Group-1 human carcinogen” and “Known to be human carcinogen” respectively (10,11).

Dose-response assessment: A dose-response relationship describes how the likelihood and severity of adverse health effects (the responses) are related to the amount and condition of exposure to an agent (the dose provided) (13). Aflatoxin exerts its carcinogenic potential by mutagenic mode of action through interaction of its reactive metabolite with DNA and it is assumed that there is no threshold of exposure to aflatoxin below which cancer would never occur, supporting a linear dose response assessment (6,11). Dose response assessment for carcinogenic compounds is based on calculating the slope of linear dose response curve which is known as slope factor or cancer potency factor (13). Aflatoxin is a potent liver carcinogen and due to it’s synergistic action with chronic HBV infection, risk of developing HCC in individual exposed to chronic HBV infection and aflatoxin is up to 30 times greater then risk in individuals exposed to aflatoxin alone (7,14–16). The forty-ninth meeting of Joint FAO/WHO Expert Committee on Food Additives (JECFA) provided differential slope factors for aflatoxin; 0.3 HCC cases per year per 100,000 population per ng AFB_1 exposure per kg bodyweight per day for HBsAg+ population and 0.01 HCC cases per year per 100,000 population per ng AFB_1 exposure per kg bodyweight per day for HBsAg- population, based on multifactor risk model by Bowers *et al*, 1993 which used data from a prospective cohort study in China (16–18). This risk assessment we have considered these cancer potency factor values in assessing risk of HCC due to dietary exposure to aflatoxin.

Exposure Assessment: Exposure assessment is the process of measuring or estimating the magnitude, frequency, and duration of human exposure to an agent in the environment, or estimating future exposures for an agent that has not yet been released (13). Three critical steps involved in exposure assessment include; i) characterizing exposure setting i.e. physical environment and description of the human populations exposed to the agent, ii) identifying exposure pathway for the population and iii) quantifying exposure (6).

Aflatoxins contaminate staple foods like maize, peanuts and cereal grains in tropical and subtropical climate (12,19). Biological markers such as aflatoxin-albumin adducts in serum or aflatoxin-N7-guanine in urine provides more precise estimates of aflatoxin exposure in the population, but it is relatively recent technology and exposure estimates based on their use are geographically restricted to a small fraction of low or middle income countries (9,12,20). In the absence of availability of these biomarker data, more conventional approach to quantify exposure is by estimating average consumption of food products (maize, peanuts or rice) and level of aflatoxin contamination in these food products. Due to lack of nationally representative data about aflatoxin biomarkers, exposure assessment in this risk assessment was

Table 1. Maize consumption in select countries

WHO Region/ Country	Maize Consumption[a] (g/person/day)
Region of the Americas	
Canada	52.0
Argentina	29.0
Brazil	73.0
Mexico	319.0
Eastern Mediterranean Region	
Egypt	173.0
Iran	7.0
Pakistan	40.0
Western Pacific Region	
China	18.0
Malaysia	36.0
Philippines	51.0
Republic of Korea	34.0

[a] Based on data from the Food and Agriculture Organization of the United Nations (FAO) food balance sheets (21)

Table 2. Chronic Hepatitis B virus infection prevalence in select countries

WHO Region/ Country	Chronic HBV Prevalence (%)[a]	95 % CI
Region of the Americas		
Canada	0.76	0.74-0.79
Argentina	0.77	0.77-0.78
Brazil	0.65	0.65-0.66
Mexico	0.2	0.19-0.21
Eastern Mediterranean Region		
Egypt	1.71	1.67-1.76
Iran	0.96	0.95-0.96
Pakistan	2.76	2.73-2.79
Western Pacific Region		
China	5.49	5.47-5.50
Malaysia	0.74	0.70-0.77
Philippines	4.63	4.53-4.73
Republic of Korea	4.36	4.36-4.37

[a] based on HBsAg seroprevalence (25)

carried out by estimating average consumption of maize and maize products and average aflatoxin contamination levels in these food products (Table-3).

$D_{Exp} = (Maize_{Cons} \text{ x } Maize_{Cont}) / Rf_{wt}$

Where D_{Exp} is estimated dietary exposure of aflatoxin through maize in nanogram(ng)/kg body weight/day; $Maize_{Cons}$ is per capita average daily consumption of maize in grams/day; $Maize_{Cont}$ is average level aflatoxin contamination in maize in ng/gram; Rf_{wt} is reference body weight in kg.

Average per capita daily maize consumption was estimated based on data of maize and maize products consumption from supply utilization accounts (SUA) and food balance sheets (FBS) database of the Food and Agriculture Organization of the United Nations (FAO) for the year 2011,2012 and 2013 (21). WHO's Global Environment Monitoring System (GEMS)/Food Cluster Diets database uses the FAO food balance sheets (FBS) and supply utilization account (SUA) data to determine food consumption pattern in clusters of different countries which are commonly used in dietary risk assessments conducted at international level (22–24). Average aflatoxin contamination level in maize and maize food products is estimated from multiple resources through literature review. Total 36 publications with data on aflatoxin contamination in maize or maize products published between 1999-2017 were retrieved (Table-3).

Risk characterization: Risk characterization, the final step in risk assessment, combines the information on exposure assessment and dose–response assessment to describe overall nature and magnitude of risk based on exposure to a hazardous agent (6). In this risk assessment, risk of aflatoxin exposure was described by estimating annual incidence (cancer risk) of hepatocellular carcinoma (HCC) in chronic HBV infection positive and negative population. Incidence of HCC was calculated by multiplying the cancer potency factors with estimated aflatoxin exposure for select countries (Table-4).

$HCC_{risk} = D_{Exp} \text{ x } SF$

Where HCC_{risk} is estimated annual incidence of HCC per 100,000 population; D_{Exp} is estimated dietary exposure of aflatoxin through maize consumption in ng/kg body weight/day; SF is slope factor (cancer potency factor) which is 0.3 HCC cases/year/100,000 population/ng AFB_1 exposure/kg bodyweight/day for chronic HBV infection positive population and 0.01 HCC cases/year/100,000 population/ng AFB_1 exposure/kg bodyweight/day for chronic HBV infection negative population.

Estimated number of annual HCC cases attributable to dietary aflatoxin exposure through maize in select countries were calculated by multiplying incidence of HCC with chronic HBV infection positive and negative population, estimated based on chronic HBV prevalence and total country population (Table-5). The worldwide estimated prevalence of chronic HBV infection published by Schweitzer *et al*, 2015 was used to estimate the prevalence of chronic HBV infection in select countries (25).

RESULTS

For comparison of risk of HCC attributable to dietary aflatoxin exposure through maize in population of Iran with countries of Western and Eastern part of world, countries were selected from and grouped together based on WHO designated regions (WHO, 2016). Table-1 lists average per capita maize consumption in gram/day in select countries from Eastern Mediterranean, Western Pacific region and

Table 3. Estimated dietary aflatoxin exposure through consumption of maize

WHO Region/ country	Aflatoxin Exposure Mean (Min. – Max.) ng/kg body weight/day[a]	Reference
Region of the Americas		
Canada	0.014 (0.003 – 2.3)	(29) (Food Safety Action Plan Report – 2010-2011, 2011-2012, 2013-2014)
Argentina	4.0 (0.3 – 6.5)	(30–32)
Brazil	9.3 (0.4 –135.5)	(33–36)
Mexico	20.3 (3.0 – 310.0)	(Castillo-Urueta, Carvajal, Méndez, Meza, & Gálvez, 2011; García & Heredia, 2006; Guzmán-de-Peña & Peña-Cabriales, 2005)
Eastern Mediterranean Region		
Egypt	24.0 (0.7 – 263.5)	(40–43)
Iran	10.0 (0.1 – 48.5)	(44–46)
Pakistan	9.1 (0.5 –51.9)	(47–50)
Western Pacific Region		
China	25.7 (0.1 – 280.0)	(51–55)
Malaysia	3.6 (0.6 – 93.3)	(56–58)
Philippines	43.4 (1.0 – 127.8)	(57,59)
Republic of Korea	2.3 (0.0197 – 19.7)	(60–62)

[a] Assuming 62 kg body weight as reference body weight (63)

Table 4. Estimated incidence of hepatocellular carcinoma (HCC) attributable to aflatoxin exposure through maize

WHO Region/ country	Estimated annual HCC (per 100,000)	
	HBsAg – negative Mean (Min. - Max.)	HBsAg – positive Mean (Min.- Max.)
Region of the Americas		
Canada	0.00008 (0.00002 - 0.013)	0.0025 (0.0005 –0.4)
Argentina	0.0013 (0.001 – 0.021)	0.39 (0.03 – 0.62)
Brazil	0.104 (0.005 – 1.519)	3.13 (0.14 – 45.57)
Mexico	1.043 (0.154 – 15.93)	31.30 (4.63 – 478.05)
Eastern Mediterranean Region		
Egypt	0.295 (0.008 – 3.244)	8.85 (0.25 – 97.31)
Iran	0.02 (0.0001 – 0.095)	0.59 (0.003 – 2.86)
Pakistan	0.1 (0.006 –0.571)	3.0 (0.17 – 17.14)
Western Pacific Region		
China	0.128 (0.001 – 1.394)	3.84 (0.02 – 41.81)
Malaysia	0.035 (0.006 – 0.929)	1.06 (0.17 – 27.87)
Philippines	0.362 (0.008 – 1.069)	10.86 (0.25 – 32.08)
Republic of Korea	0.013 (0.0001-0.11)	0.38 (0.003 – 3.30)

region of Americas based on food balance sheets (FBS) database of the Food and Agriculture Organization of the United Nations (FAO) for the year 2011,2012 and 2013 (21). Maize consumption is lowest in Iran (7 grams/day) and highest in Mexico (319 grams/day) among select countries from three WHO regions. Average maize consumption in the Western Pacific region is in the range of 18-51 grams/day.

Schweitzer *et al*, condcted systematic review and pooled analysis of the data published between 19965 to 2013 to estimate worldwide prevalence of chronic HBV infection (25). Burden of chronic Hepatitis B virus (HBV) infection is highest in countries from Western Pacific region (Table-2). Prevalence of chronic HBV infection in Iran (0.96%) is

Table 5. Estimated number of hepatocellular carcinoma (HCC) cases per year attributable to aflatoxin exposure through maize

WHO Region/ country	Population[a] (millions)	Estimated numbers of annual HCC Cases	
		Chronic HBV negative Mean (Min. - Max.)	Chronic HBV positive Mean (Min. - Max.)
Region of the Americas			
Canada	35.8	1 (1 – 5)	1 (1 – 2)
Argentina	43.4	6 (1 – 9)	2 (1 – 2)
Brazil	207.8	215 (10 – 3136)	42 (2 – 615)
Mexico	127.0	1323 (195 – 20197)	80 (12 – 1214)
Eastern Mediterranean Region			
Egypt	91.5	265 (8 – 2917)	138 (4 – 1523)
Iran	79.1	15 (1 – 75)	4 (1 – 22)
Pakistan	188.9	184 (11 – 1049)	156 (9 – 893)
Western Pacific Region			
China	1371.2	1657 (8 – 18059)	2888 (13 – 31471)
Malaysia	30.3	11 (2 – 279)	2 (1 – 62)
Philippines	100.7	348 (8 – 1027)	506 (12 – 1496)
Republic of Korea	50.6	6 (1 – 53)	8 (1 – 73)
Total estimated cases in select countries		4031 (246 – 46,806)	3827 (57 – 37,373)

[a] World Bank database (27)

comparable to that of countries from the region of Americas.

Dietary aflatoxin exposure through maize are estimated using data of estimated per capita maize consumption and average aflatoxin contamination level in maize and maize products in these countries (Table-3). Aflatoxin exposure is high in Philippines, China, Egypt and Mexico where as it is moderate in Brazil and Iran and lowest in Canada. Risk of developing HCC attributable to dietary aflatoxin exposure in countries of Eastern Mediterranean region is compared with countries from regions of Americas and Western Pacific region by estimating incidence of HCC attributable to aflatoxin exposure in chronic HBV infection negative and positive population in select countries (Table-4). Table-5 lists total population in these countries based on world bank database and annual estimated HCC cases attributable to aflatoxin exposure in chronic HBV infection negative and positive population (27).

Incidence of HCC in the Eastern Mediterranean region is 0.295 and 0.1 per 100,000 chronic HBV infection negative population in Egypt and Pakistan respectively. Risk of developing HCC in Iran is 0.02 per 100,000 chronic HBV infection negative population which is comparable to risk of aflatoxin related HCC in countries from region of Americas (Canada and Argentina) and Western Pacific region (Malaysia and Republic of Korea). Lowest risk of HCC was found in Canada (0.00008 HCC cases per 100,000 chronic HBV infection negative population) and highest HCC risk was found in Mexico (1.043 HCC cases per 100,000 chronic HBV infection negative population) followed by Philippines (0.362 HCC cases per 100,000 chronic HBV infection negative population).

DISCUSSION

In this risk assessment, we have compared dietary aflatoxin exposure through maize and risk of aflatoxin related HCC in select countries from the Eastern Mediterranean region with countries from region of Americas(East) and Western Pacific region (West) based on data from the published literature about aflatoxin contamination of maize, chronic HBV infection prevalence and maize consumption pattern from FAO's food balance sheets.

It is interesting to note that risk of HCC attributable to aflatoxin in maize is highest in Mexico where chronic HBV infection prevalence is low (0.2%). This high risk of HCC is mainly due to high per capita maize consumption and high level of aflatoxin contamination in maize in Mexico. Liu and Wu noted similar findings in their study (12). Burden of hepatocellular carcinoma is highest in the countries of Western Pacific region, specially China and Philippines (28). In this risk assessment, risk of HCC in these two countries is high due to high chronic HBV infection prevalence and high dietary exposure to aflatoxin. We have estimated 4545 (21-49,530) and 854 (20-2453) annual HCC cases in China and Philippines respectively in this risk assessment. Risk of HCC in both chronic HBV infection positive and negative population in Iran is comparable to high income countries from region of Americas and Western Pacific region due to low aflatoxin contamination in maize and lowest per capita maize consumption (7 gram/day) among select countries.

Scientific research focussing on contamination of agricultural commodities may not follow strict sampling methodology and generally include samples from a certain geographical area of the country or from an outbreak of contamination of the food crops only and not from monitoring or surveillance program which is more representative for their country. Higher incidence and aflatoxin exposure in this risk assessment may be due to higher aflatoxin levels in maize in published literature. Large range in the HCC risk and annual HCC cases estimates are because of uncertainty and variability in the data of chronic HBV infection prevalence, aflatoxin contamination in maize, and geographic as well as cultural and seasonal variability in dietary consumption of maize within the country.

ACKNOWLEDGEMENT

We extend sincere gratitude to the Environmental Health Services, BC Centre for Disease Control and Faculty of Health Sciences, Simon Fraser University for providing the opportunity to conduct this study as a part of Master of Public Health practicum.

Conflict of Interest: None to be declared.
Funding and support: None.

REFERENCES

1. Dhanasekaran R, Limaye A, Cabrera R. Hepatocellular carcinoma: current trends in worldwide epidemiology, risk factors, diagnosis, and therapeutics. *Hepat Med* 2012;4:19–37.
2. Waller LP, Deshpande V, Pyrsopoulos N. Hepatocellular carcinoma: A comprehensive review. *World J Hepatol* 2015;7:2648–63.
3. WHO. Cancer. 2017 [cited 2017 Aug 8]; Available from: http://www.who.int/mediacentre/factsheets/fs297/en/
4. McGlynn K, London W. The Global Epidemiology of Hepatocellular Carcinoma, Present and Future. *Clin Liver Dis* 2011;15:223–43.
5. Poustchi H, Sepanlou S, Esmaili S, Mehrabi N, Ansarymoghadam a. Hepatocellular carcinoma in the world and the middle East. *Middle East J Dig Dis* 2010;2:31–41.
6. Kuiper-Goodman T. Risk assessment and risk management of mycotoxins in food. *Mycotoxins Food* 2004;3–31.
7. Groopman JD, Kensler TW, Wild CP. Protective interventions to prevent aflatoxin-induced carcinogenesis in developing countries. *Annu Rev Public Health* 2008;29:187–203.
8. Abrar M, Anjum FM, Butt MS, Pasha I, Randhawa MA, Saeed F, et al. Aflatoxins: Biosynthesis, Occurrence, Toxicity, and Remedies. *Crit Rev Food Sci Nutr* 2013;53:862–74.
9. Wild CP, Gong YY. Mycotoxins and human disease: A largely ignored global health issue. *Carcinogenesis* 2009;31:71–82.
10. National Toxicology Program. Fourteenth Report on Carcinogens. 2016. Available from: http://ntp.niehs.nih.gov/go/roc14
11. IARC monographs on the evaluation of carcinogenic risks to humans. Some traditional herbal medicines, some mycotoxins, naphthalene and styrene. IARC Press. 2002:1–556.
12. Liu Y, Wu F. Global burden of Aflatoxin-induced hepatocellular carcinoma: A risk assessment. *Environ Health Perspect* 2010;118:818–24.
13. Guidelines for Carcinogen Risk Assessment. Washington, DC: US EPA; 2005.
14. Wu F, Stacy SL, Kensler TW. Global risk assessment of aflatoxins in maize and peanuts: Are regulatory standards adequately protective? *Toxicol Sci* 2013;135:251–9.
15. Magnussen A, Parsi MA. Aflatoxins, hepatocellular carcinoma and public health. *World J Gastroenterol* 2013;19:1508–12.
16. Yeh FS, Yu MC, Mo CC, Luo S, Tong MJ, Henderson BE. Hepatitis B virus, aflatoxins, and hepatocellular carcinoma in southern Guangxi, China. *Cancer Res* 1989;49:2506–9.
17. Bowers J, Brown B, Springer J, Tollefson L, Lorentzen R, Henry S. Risk Assessment for Aflatoxin: An Evaluation Based on the Multistage Model. *Risk Anal* 1993;13:637–42.
18. WHO. Aflatoxins (WHO Food Additives Series 40). Switzerland; World Health Organization: 1998.
19. Mycotoxin Control in Low- and Middle- Income Countries. IARC Working Group Reports; 2015. 66 p.
20. Williams JH, Phillips TD, Jolly PE, Stiles JK, Jolly CM, Aggarwal D. Human aflatoxicosis in developing countries: a review of toxicology, exposure, potential health consequences, and interventions. *Am J Clin Nutr* 2004; 80:1106–22.
21. FAO. FAOSTAT - Food Balance Sheets. Food and Agriculture Organization; United Nations: 2013.
22. Andrade PD, Caldas ED. Aflatoxins in cereals: worldwide occurrence and dietary risk assessment. *World Mycotoxin J* 2015;8:415–31.
23. Moy GG, Vannoort RW. Total diet studies. Switzerland: Food safety consultant international; 2013.
24. WHO/FAO. GEMS_cluster_diets_2012. Available from: https://extranet.who.int/sree/Reports?op=vs&path=/WHO_HQ_Reports/G7/PROD/EXT/GEMS_cluster_diets_2012&userid=G7_ro&password=inetsoft123
25. Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: A systematic review of data published between 1965 and 2013. *Lancet* 2015;386:1546–55.
26. WHO. WHO regional offices. 2016 [cited 2017 Aug 30]; Available from: http://www.who.int/about/regions/en/
27. World Bank. Population. 2016 [cited 2017 Aug 31]. Available from: https://data.worldbank.org/indicator/SP.POP.TOTL
28. Zhu RX, Seto WK, Lai CL, Yuen MF. Epidemiology of hepatocellular carcinoma in the Asia-Pacific region. *Gut Liver* 2016;10:332–9.
29. Tam J, Mankotia M, Mably M, Pantazopoulos P, Neil RJ, Calway P, et al. Survey of breakfast and infant cereals for aflatoxins B1, B2, G1 and G2. *Food Addit Contam* 2006;23:693–9.
30. Solovey MMS, Somoza C, Cano G, Pacin A, Resnik S. A survey of fumonisins, deoxynivalenol, zearalenone and aflatoxins contamination in corn-based food products in Argentina. *Food Addit*

Contam 1999; 16:325–9.

31. Broggi LE, Pacin AM, Gasparovic A, Sacchi C, Rothermel A, Gallay A, et al. Natural occurrence of aflatoxins, deoxynivalenol, fumonisins and zearalenone in maize from Entre Ríos Province, Argentina. *Mycotoxin Res* 2007;23:59–64.
32. Garrido CE, Hernández Pezzani C, Pacin A. Mycotoxins occurrence in Argentina's maize (Zea mays L.), from 1999 to 2010. *Food Control* 2012; 25:660–5.
33. Rocha LO, Nakai VK, Braghini R, Reis TA, Kobashigawa E, Corrêa B. Mycoflora and co-occurrence of fumonisins and aflatoxins in freshly harvested corn in different regions of Brazil. *Int J Mol Sci* 2009;10:5090–103.
34. Vargas EA, Preis RA, Castro L, Silva CMG. Co-occurrence of aflatoxins B 1, B 2, G 1, G 2, zearalenone and fumonisin B 1 in Brazilian corn. *Food Addit Contam* 2001;18:981–6.
35. Andrade PD, de Mello MH, França JA, Caldas ED. Aflatoxins in food products consumed in Brazil: a preliminary dietary risk assessment. *Food Addit Contam* 2013;30:127–36.
36. Oliveira MS, Rocha A, Sulyok M, Krska R, Mallmann CA. Natural mycotoxin contamination of maize (Zea mays L.) in the South region of Brazil. *Food Control* 2017;73:127–32.
37. García S, Heredia N. Mycotoxins in Mexico: Epidemiology, management, and control strategies. *Mycopathologia* 2006;162:255–64.
38. Guzmán-de-Peña D, Peña-Cabriales JJ. Regulatory considerations of aflatoxin contamination of food in Mexico. *Rev Latinoam Microbiol* 2005;47:160–4.
39. Castillo-Urueta P, Carvajal M, Méndez I, Meza F, Gálvez A. Survey of aflatoxins in maize tortillas from Mexico City. *Food Addit Contam* 2011;4:42–51.
40. El-Sayed AMAA, Soher EA, Sahab AF. Occurrence of certain mycotoxins in corn and corn-based products and thermostability of fumonisin B1 during processing. *Nahrung/Food* 2003;47:222–5.
41. El-Tahan FH, El-Tahan MH, Shebl MA. Occurrence of aflatoxins in cereal grains from four Egyptian governorates. *Nahrung/Food* 2000;44:279–80.
42. Madbouly AK, Ibrahim MIM, Sehab AF, Abdel-Wahhab MA. Co-occurrence of mycoflora, aflatoxins and fumonisins in maize and rice seeds from markets of different districts in Cairo, Egypt. *Food Addit Contam* 2012;5:112–20.
43. Abdallah MF, Girgin G, Baydar T, Krska R, Sulyok M. Occurrence of multiple mycotoxins and other fungal metabolites in animal feed and maize samples from Egypt using LC-MS/MS. *J Sci Food Agric* 2017;97:4419-28.
44. Yazdanpanah H, Miraglia M, Calfapietra F, Brera C. Natural occurrence of aflatoxins and ochratoxin a in corn and barley from mazandaran and golestan in north provinces of I. R. Iran. *Mycotoxin Res* 2001;17:21–30.
45. Ghiasian SA, Shephard GS, Yazdanpanah H. Natural Occurrence of Aflatoxins from Maize in Iran. *Mycopathologia* 2011;172:153–60.
46. Hadiani MR, Yazdanpanah H, Amirahmadi M, Soleimani H, Shoeibi Sh, Khosrokhavar R. Evaluation of Aflatoxin Contamination in Maize from Mazandaran Province in Iran. *J Med Plant* 2009;1:109-14.
47. Shah HU, Simpson TJ, Alam S, Khattak KF, Perveen S. Mould incidence and mycotoxin contamination in maize kernels from Swat Valley, North West Frontier Province of Pakistan. *Food Chem Toxicol* 2010;48:1111–6.
48. Iram W, Anjum T, Abbas M, Khan AM. Aflatoxins and ochratoxin A in maize of Punjab, Pakistan. *Food Addit Contam* 2014;7:57–62.
49. Lutfullah G, Hussain A. Studies on contamination level of aflatoxins in some cereals and beans of Pakistan. *Food Control* 2012;23:32–6.
50. Firdous S, Ashfaq A, Khan SJ, Khan N. Aflatoxins in corn and rice sold in Lahore, Pakistan. *Food Addit Contam* 2014;7:95–8.
51. Gao X, Yin S, Zhang H, Han C, Zhao X, Ji R. Aflatoxin contamination of corn samples collected from six regions of China. *Wei Sheng Yan Jiu* 2011;40:46–9.
52. Li FQ, Yoshizawa T, Kawamura O, Luo XY, Li YW. Aflatoxins and fumonisins in corn from the high-incidence area for human hepatocellular carcinoma in Guangxi, China. *J Agric Food Chem* 2001;49:4122–6.
53. Wang J, Liu X. Surveillance on contamination of total aflatoxins in corn, peanut, rice, walnut and pine nut in several areas in China. *Zhonghua Yu Fang Yi Xue Za Zhi* 2006;40:33–7.
54. Sun G, Wang S, Hu X, Su J, Zhang Y, Xie Y, et al. Co-contamination of aflatoxin B 1 and fumonisin B 1 in food and human dietary exposure in three areas of China. *Food Addit Contam* 2011;28:461–70.
55. Wang J, Liu X-M. Contamination of aflatoxins in different kinds of foods in China. *Biomed Environ Sci* 2007;20:483–7.
56. Loh SH, Iryani Mohd Yusof N, Mun Ling H. Determination of Aflatoxins B1 and B2 in Peanuts and Corn Based Products. *Sains Malaysiana* 2010;39:731–5.
57. Ali N, Hashim NH, Yoshizawa T. Evaluation and application of a simple and rapid method for the analysis of aflatoxins in commercial foods from Malaysia and the Philippines. *Food Addit Contam* 1999;16:273–80.
58. Reddy KRN, Farhana NI, Salleh B. Occurrence of Aspergillus spp. and Aflatoxin B1 in Malaysian Foods Used for Human Consumption. *J Food Sci* 2011;76:T99–104.
59. Sales AC, Yoshizawa T. Updated profile of aflatoxin and Aspergillus section Flavi contamination in rice and its byproducts from the Philippines. *Food Addit Contam* 2005;22:429–36.
60. Ok HE, Kim HJ, Shim WB, Lee H, Bae D-H, Chung D-H, et al. Natural occurrence of aflatoxin B1 in marketed foods and risk estimates of dietary exposure in Koreans. *J Food Prot* 2007;70:2824–8.
61. Kim DM, Lee N, Kim SM, Chung SH, Kim M, Han SB, et al. Occurrence of aflatoxin and aflatoxigenic Aspergillus species in corn harvested in Korea. *J Korean Soc Appl Biol Chem* 2013;56:221–5.
62. Park JW, Kim EK, Kim YB. Estimation of the daily exposure of Koreans to aflatoxin B 1 through food consumption. *Food Addit Contam* 2004;21:70–5.
63. Walpole SC, Prieto-Merino D, Edwards P, Cleland J, Stevens G, Roberts I. The weight of nations: an estimation of adult human biomass. *BMC Public Health* 2012;12:439.