Food and Chemical Toxicology 103 (2017) 79–85

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

The need to revisit ochratoxin A risk in light of diabetes, obesity, and chronic kidney disease prevalence

Chen Chen, Felicia Wu*

Department of Food Science and Human Nutrition, Michigan State University, East Lansing, MI USA

ARTICLE INFO

Article history:
Received 19 December 2016
Received in revised form
21 February 2017
Accepted 1 March 2017
Available online 2 March 2017

Keywords:
Ochratoxin A
Type 2 diabetes
Obesity
Kidney disease

ABSTRACT

Ochratoxin A (OTA) is a mycotoxin, or fungal toxin, that contaminates multiple foodstuffs worldwide. Affected commodities include oats, wheat, maize, barley, raisins and other dried vine fruits, wine, beer, coffee, and cocoa. Although OTA has been shown to cause kidney disease, including kidney cancer, in multiple animal species, the impact of dietary OTA on human health from a global perspective has been less clear. Several epidemiological studies suggest an association between OTA exposure and human kidney disease, but evidence of causality has been limited. Nonetheless, because OTA is common in so many foodstuffs and may play a role in kidney disease, we consider it important to improve the body of evidence surrounding OTA's adverse effects to humans, as well as human dietary exposures in different parts of the world. This is especially true in the light of increasing type 2 diabetes and obesity prevalence worldwide; both conditions frequently lead to chronic kidney disease (CKD), and may synergize with dietary OTA exposure to increase CKD risk.

1. Introduction

One of the most commonly occurring mycotoxins (fungal toxins) in the world, ochratoxin A (OTA) is present in a wide variety of foodstuffs. It has been shown to cause kidney toxicity in multiple animal species, and there is limited evidence of OTA-associated chronic kidney disease in humans (Bui-Klimke and Wu, 2015). Chronic kidney disease (CKD) is a common comorbidity in patients with type 2 diabetes (T2D). Indeed, diabetes is the leading cause of chronic kidney disease and kidney failure in humans. Although OTA has been detected worldwide in multiple foodstuffs, and causes kidney toxicity in many species, it is possible that few epidemiological studies have demonstrated a relationship between human kidney disease and OTA exposure because other risk factors for CKD – most notably diabetes were relatively less prevalent in the past. However, with the dramatic increase of T2D prevalence worldwide, especially in low- and mid-income countries during the past two decades, there is a need for a better understanding of the potential interactive role of diabetes and OTA in human kidney disease.

The main fungi involved in the production of OTA are *Aspergillus ochraceus*, *A. carbonarius*, *A. niger*, and *Penicillium verrucosum*; which cover a broad range of climates worldwide (JECFA, 2008). Hence, OTA has been found in multiple agricultural commodities from most parts of the world. The foodstuffs in which OTA has been found include cereals and their products (wheat, maize, barley, and oats), fresh and dried vine fruits, wine, nuts, spices, pork and dried meats, milk, fruit juices, beer, cocoa, coffee, and infant formula (EC, 2002; Pfohl-Leszkowicz et al., 2007; Polisenska et al., 2010; Lee and Ryu, 2015). OTA contamination may increase from poor storage practices during food drying, under certain conditions of moisture and temperature (Milićević et al., 2010). OTA can also bio-accumulate in the blood and milk of animals exposed to OTA in feed, which can then be incorporated into human foods (Bullerman and Bianchini, 2007; Wu et al., 2014a). OTA is not easily removed or destroyed in food processing. The milling process for wheat was found to have only a very limited effect on reducing OTA levels (Scudamore et al., 2003; Alldrick, 1996).

Many countries have established regulatory maximum limits of OTA in foods, including Brazil, Israel, Switzerland, Uruguay, and the European Union (Wu et al., 2014b). Currently, the United States Food and Drug Administration (FDA) has not set regulatory guidelines for OTA in food. Health Canada has considered setting maximum limits (MLs) for OTA in multiple commodities; but until now (November 2016), these MLs have not entered into force (Health Canada, 2009).

Summary data on the incidence OTA in various foods across the

* Corresponding author.
E-mail address: fwu@msu.edu (F. Wu).

http://dx.doi.org/10.1016/j.fct.2017.03.001
0278-6915/

Table 1
Commodities affected by OTA contamination by country of origin and year.

Commodity	Country (Year)	Incidence Rate	Range (mean) ng/g	Reference
Maize	US (2015)	15/103 (15%)	n.d.-0.52 (0.22)	Lee and Ryu, 2015
	Canada (2008)	6/34 (18%)	n.d.-0.15 (0.12)	Lee and Ryu, 2015
	Croatia (2001)	15/51 (33%)	0.02–40.0	Lee and Ryu, 2015
	Italy (1999–2000)	19/70 (27.1%)	n.d.-5.2 (1.7)	Wu et al., 2014b
	Ivory Coast (1998)	16/16 (100%)	27-64 (44)	Wu et al., 2014b
Wheat	US (2015)	38/117 (32%)	n.d.-1.49 (0.25)	Lee and Ryu, 2015
	Czech Republic (2010)	4/22 (18%)	n.d.-4.71	Polisenska et al., 2010
	Canada (2008)	11/29 (38%)	n.d.-0.64 (0.3)	Lee and Ryu, 2015
	France (2007)	39/83 (47%)	n.d.-11.6	Pfohl-Leszkowicz et al., 2007
	Croatia (2001)	74/93 (80%)	0.02–160	Lee and Ryu, 2015
	UK (2000)	32/201 (15.9%)	0.3–231	Wu et al., 2014b
	Poland (1997)	n.d.	n.d.	Wu et al., 2014b
	Poland (1998)	18/37 (48.6%)	0.60–1024 (267)	Wu et al., 2014b
	Italy (1999–2000)	6/70 (8.6%)	n.d.-1.4 (1.47)	Wu et al., 2014b
	Ethiopia (1999)	25/107 (23.4%)	n.d.-66 (19.6)	Wu et al., 2014b
	Tunisia	42/110 (38%)	n.d.-250 (55)	Wu et al., 2014b
Barley	UK (2000)	20/106 (18.9%)	0.3–117	Wu et al., 2014b
	Czech Republic (2010)	6/10 (60%)	n.d.- 48.63	Polisenska et al., 2010
	Poland (1997)	1/26 (3.9%)	0.3	Wu et al., 2014b
	Poland (1998)	2/36 (5.5%)	1.20–9.70 (5.45)	Wu et al., 2014b
	Korea (2003)	5/22 (22.7%)	n.d.-0.9 (0.8)	Wu et al., 2014b
	Ethiopia (1999)	27/103 (26.2%)	n.d.-164 (17.2)	Wu et al., 2014b
Oats	US (2015)	142/203 (70%)	n.d.-9.3 (1.09)	Lee and Ryu, 2015
	Canada (2008)	17/27 (63%)	n.d.-1.40 (0.61)	Lee and Ryu, 2015
	Bulgary (2000)	7/9 (78%)	0.89–85	Lee and Ryu, 2015
	Poland (2009)	42/71 (60%)	1.0–5.8	Lee and Ryu, 2015
	UK (2000)	0/13 (0%)	n.d.	Wu et al., 2014b
Rice	US (2015)	10/66 (%)	0.1, 0.25	Lee and Ryu, 2015
	UK (1997)	3/40 (8%)	1–19	Lee and Ryu, 2015
	Vietnam (2001)	2/25 (8%)	21.3–26.2	Lee and Ryu, 2015
	Vietnam (2007)	35/100 (35%)	n.d.-2.78 (0.75)	Nguyen et al., 2007
	Spain (2006)	5/64 (8%)	4.3–27.3	Lee and Ryu, 2015
		6/20 (30%) (organic)	1.0–7.1 (organic)	
	Portugal (2005)	6/42 (14%)	0.09–3.52	Lee and Ryu, 2015
	Korea (2003)	5/60 (8.3%)	n.d.-6.0 (1.0)	Wu et al., 2014b
	Morocco (2005)	18/20 (90%)	n.d.-32.4 (4.15)	Wu et al., 2014b
	Tunisia (2004–05)	4/16 (25%)	n.d.-2.3 (1.4)	Wu et al., 2014b
	Chile (2006)	13/31 (42%)	n.d.-12.5	Wu et al., 2014b
Breakfast cereals	US (2015)	142/203 (70%)	n.d.-9.3 (0.79–1.88)	Lee and Ryu, 2015
	Spain (2005)	19/31 (61.3%)	0.07–0.98	Lee and Ryu, 2015
	France (2005)	31/45 (69%)	0.02–0.87	Lee and Ryu, 2015
	Morocco (2005)	4/48 (8.3%)	n.d.-224.6	Lee and Ryu, 2015
	Greece 2006–2007	33/55 (60%)	n.d.-0.87 (0.11)	Wu et al., 2014b
	Canada (1999–2001)	53/156 (35%)	n.d.-1.4 (0.752)	Wu et al., 2014b
	Turkey (2007)	9/24 (37.5%)	n.d.-1.84 (0.752)	Wu et al., 2014b
Infant cereals	Turkey (2007)	4/24 (16.7%)	n.d.-0.374 (0.221)	Wu et al., 2014b
	Canada (1997–99)	42/161 (26.1%)	n.d.-6.9	Wu et al., 2014b
Red grape juice	Canada (1999–2000)	3/24 (12.5%)	NA	Wu et al., 2014b
	Canada (2001–02)	0/13 (0%)	NA	Wu et al., 2014b
	USA (2001–2002)	0/7 (0%)	NA	Wu et al., 2014b
White grape juice	Canada (1999–2000)	1/12 (8%)	NA	Wu et al., 2014b
	Canada (2001–02)	0/7 (0%)	NA	Wu et al., 2014b
	USA (2001–2002)	0/4 (0%)	NA	Wu et al., 2014b
Grape juice	Brazilian retail market	24/48 (70.8%)	21.2–100	Wu et al., 2014b
Dried vine fruit	Canadian retail market (1998–2000) (raisins)	67/85 (79%)	2.29	Wu et al., 2014b
	Canadian retail market (1998–2000) (sultanas)	39/66 (59%)	3.11	Wu et al., 2014b
	Argentina (raisins)	9/15 (60%)	0.26–20.28	Wu et al., 2014b
	UK retail market	53/60 (88%)	n.d.-53.6	Wu et al., 2014b
	Argentina markets (dried black fruits)	21/31 (68%)	1.5–14	Wu et al., 2014b
	Argentina markets (dried white fruits)	16/19 (84%)	1.4–7.5	Wu et al., 2014b
Meat	European Union (2002)	328/1860 (18%)	n.d.-9.33 (0.198)	EC, 2002
Wine	European Union (2002)	872/1470 (59%)	n.d.-15.6 (0.357)	EC, 2002
Coffee (processed)	European Union (2002)	549/1184 (46%)	11.5 (0.724)	EC, 2002
	France (2010)	29/30 (97%)	n.d.-11.9	Tozlovanu and Pfohl-Leszkowicz, 2010
	Czech Republic (2014)	31/48 (65%)	n.d.-1.37 (0.51)	Malir et al., 2014
Cocoa	European Union (2002)	445/547 (81%)	n.d.-3.6 (0.236)	EC, 2002

world are listed in Table 1. These OTA concentrations in foods demonstrate a wide variability across different commodities, as well as within the same commodity. Additionally, there is substantial geographical variation in OTA concentrations for these foodstuffs. For example, maize sampled in the United States and Canada has low OTA levels (typically below 1 μg/kg), but OTA levels in maize from Croatia and Ivory Coast have levels that reach as high as 40 and 60 μg/kg, respectively.

2. OTA and kidney disease

OTA causes nephrotoxic, teratogenic, and immunosuppressive effects in multiple animal species (O'Brien and Dietrich, 2005; Pfohl-Leszkowicz and Manderville, 2007; Malir et al., 2014). Because of some evidence of carcinogenicity in animal studies but no available evidence in humans, OTA has been classified by the International Agency for Research on Cancer (IARC) as a Group 2B possible human carcinogen (IARC, 1993). OTA was found to cause DNA adduct formation in animal kidneys, relating its toxicity to its genotoxicity and carcinogenicity in study animals (Malir et al., 2014).

A systematic review of epidemiological studies on OTA examined the evidence linking OTA exposure to human disease (Bui-Klimke and Wu, 2015). Of the over 2000 epidemiological studies on OTA, only a few showed a statistically significant difference in disease rates in those highly exposed to OTA vs. those who were unexposed; most of the other studies did not have study populations that represented exposed vs. unexposed groups. In a case-control study, it was found that patients with end-stage renal disease (ESRD) or nephritic syndrome in Egypt had significantly higher levels of urinary OTA than reference groups (Wafa et al., 1998). The authors speculated that OTA might be involved in the genesis of renal disease leading to nephritic syndrome and ESRD. Similar results were found in a clinical study conducted in Taiwan (Hsieh et al., 2004). The same study also found that OTA may play a role in diabetes patients with nephropathy and the mean excretion of OTA in patients with diabetes mellitus was significantly higher than other groups (Hsieh et al., 2004).

When two risk factors for a disease co-occur in a population, or a subset of the population, they may potentiate each other, or act synergistically in increasing disease risk. This has proven true in multiple populations worldwide of another mycotoxin, aflatoxin, and chronic hepatitis infection in causing liver cancer (JECFA, 1998). That is why it is so important to elucidate the co-occurrence of aflatoxin and chronic hepatitis B and C infection (Palliyaguru and Wu, 2013), to determine which populations worldwide are at greatest risk. Because type 2 diabetes rates are increasing worldwide, in high-income, middle-income, and low-income nations alike, it is critical to revisit the question of human health risks posed by dietary OTA; and to assess the extent to which OTA exposure and type 2 diabetes overlap worldwide.

3. OTA exposure in human diets worldwide

Based on a lowest observed effect level found in a study of renal damage in pigs (Krogh et al., 1974) and applying a combined uncertainty factor of 500, the Joint Expert Committee on Food Additives of the Food and Agriculture Organization and World Health Organization has set a provisional tolerable weekly intake (PTWI) of 100 ng OTA per kilogram bodyweight per week, or about 14 ng/kg bw/day (JECFA, 2008).

Because no human biomarkers of OTA exposure have been validated, the best means to estimate OTA exposure is to determine concentrations of OTA in vulnerable foodstuffs and the average intake rates of these different foodstuffs in different populations worldwide, then divide by average bodyweight. In 2008, JECFA had estimated that globally, human dietary exposure levels to OTA ranged from 8 to 17 ng/kg bw/wk. Cereals and cereal products are the most significant contributors to dietary OTA exposure.

Separately, the European Commission estimated OTA exposure in European Union member states to range from 0.13 to 3.55 ng/kg bw/day on a total diet basis (EC, 2002). In Europe, aside from cereals, wine and coffee were major contributors of OTA to the human diet, at 13% and 10% of total OTA exposure, respectively. The EC Scientific Committee for Food (SCF) conducted its own risk assessment of OTA and established a tolerable daily intake (TDI) of 5 ng/kg bw/day: more precautionary than the JECFA maximum tolerable level and more similar to the Negligible Cancer Risk Intake (NCRI) estimated by Kuiper-Goodman et al. (2010).

OTA exposure assessments were also reported from some individual European countries (Ostry et al., 2015). Average dietary exposures of OTA for adults in Czech Republic were estimated at 1.2–1.8 ng/kg bw/day. Grain-based products and drinks (beer) were identified to be the main contributors. The dietary intake of OTA in the French population was 2.2 ng/kg bw/day for adults based on a Total Diet Study (TDS), with cereals and cereal products contributing most to the total intakes. Similar results were obtained from duplicate diet studies in UK and the Netherlands, where the mean OTA intake estimate was 0.9 and 1.2 ng/kg bw/day, respectively. In Portugal, dietary intake of OTA was calculated at 0.81 ng/kg bw/day for the total population, with wheat being the most important source (Ostry et al., 2015). As indicated by the estimates described above, OTA exposures in these European nations are well below the EC SCF TDI of 5 ng/kg bw/day, suggesting low risk of adverse effects from OTA consumption.

There have been several investigations on OTA exposure from Middle-Eastern and Asian countries. In Egypt, the exposure assessment to OTA was achieved by using a duplicate diet and a biomarker method (Ostry et al., 2015). The daily intakes ranged from 1.07 to 8.43 ng/kg bw/day. Raad et al. (2014) reported that cereal-based products sold in Lebanon represented the highest concentrations of OTA particularly in “Biscuits and croissants” (2.84 μg/kg) and “Alcoholic beverages” (1.47 μg/kg). OTA exposures for “average” and frequent cereal consumers were estimated to be 0.31 and 0.99 ng/day, representing 29.9% and 95.1% of the JECFA maximum limit, respectively. Yau et al. (2016) estimated dietary exposure of Hong Kong adults to OTA in a TDS and assessed the associated health risk to the population. The highest mean level, calculated from the upper bound, was 0.22 μg/kg bw/day. The estimated 95th percentile dietary exposure to OTA was about 9.2% of the JECFA maximum limit, indicating that the Hong Kong population generally has very low OTA exposure; likely because of low consumption of wheat and oats. In another study from Shanghai city of China (Han et al., 2013), mean and high percentile (97.5th) dietary intake of OTA for the adult inhabitants was 1.15 and 8.57 ng/kg bw/day. The food groups contributing most were cereals and derived products; again, lower than the JECFA maximum limit but close to the EC SCF TDI at the higher exposures. However, Chinese population exposures could be substantially higher in particular regions; particularly where wheat consumption is high.

4. Risk assessment of OTA

To conduct a population-wide risk assessment of OTA, it is necessary to compare actual human dietary exposures to a recommended “safe” level of exposure to OTA: a tolerable daily or weekly intake, or a reference dose. Different agencies have, however, set different tolerable limits of dietary OTA exposure. For example, JECFA set the provisional tolerable weekly intake (PTWI) of OTA at 100 ng/kg bw/week (about 14 ng/kg bw/day); while

Health Canada set a negligible cancer risk intake (NCRI) at only 4 ng/kg bw/day. The difference in these limits reflects differences in the assumption of whether OTA is a genotoxic carcinogen. Although JECFA finds no evidence of OTA's genotoxicity, the Health Canada NCRI assumes that OTA could be genotoxic. Haighton et al. (2012) proposed that the most critical toxicological mechanism of OTA did not involve genotoxicity, therefore a threshold value would be more plausible. However, Malir et al. (2014) review several studies that described potential genotoxic mechanisms in study animals.

Population-wide risk assessments of OTA in the diet were performed for both Canada (Haighton et al., 2012; Kuiper-Goodman et al., 2010) and the United States (Mitchell et al., 2017). Kuiper-Goodman et al. (2010) imputed average daily exposure levels for OTA in the Canadian population, based on American consumptions of the different foodstuffs (assuming Canadian consumption patterns were similar to American). Among all age groups, OTA exposures from all foodstuffs were lower than the JECFA PTWI, except for the upper bound exposure (14.98 ng OTA/kg bw/day) from hot oatmeal consumption for 1-year-old "regular commodity eaters" (if they consume this foodstuff at least once per week on average). If the Health Canada NCRI (4 ng/kg bw/day) were taken as the safe dietary OTA limit instead of the JECFA value, then all adults would have OTA exposures that are of no concern, but 1-year-olds who are "regular commodity eaters" of oatmeal and oat-based cereals would have OTA exposures that exceed the NCRI. In a follow-up exposure assessment study for Canadians, the mean adjusted exposures for all age groups were found below the NCRI value of 4 ng/kg bw/day; and upon adjustment for lifetime exposure found a negligible risk in the Canadian population (Haighton et al., 2012).

Mitchell et al. (2017) imputed the overall mean exposure for the "total population" and "regular eaters" on the basis of the occurrence of OTA in a variety of food commodity samples collected from grocery shelves throughout the US in 2012 and 2013. Similar to the Canadian population, most age groups in the US are not at risk of excessive OTA exposures and potential resulting health effects, even when the more precautionary NCRI of 4 ng/kg bw/day was used as the threshold. The only age groups whose exposure exceeded the NCRI were those in the 0–12 month and 1-5-year-old age groups who were at the 95th percentile of "regular consumers" of oatmeal and oat-based products. In the food samples gathered from the grocery shelves, there was a single pistachio sample that contained exceedingly high concentrations of OTA (>800 ng/g). However, even if this were taken as a "norm" for pistachio OTA levels, US OTA exposures would not exceed the NCRI or JECFA PTWI, because of low pistachio consumption rate across all age groups.

5. Increasing diabetes, overweight, and obesity

Overweight and obesity are major risk factors for multiple chronic diseases, including T2D, cardiovascular disease, kidney disease, and cancer. Their prevalence has risen dramatically in low- and middle-income countries over the last decade, particularly in urban settings. A person with a body mass index (BMI) of 30 or more is generally considered obese, while a BMI of 25–30 is considered overweight (WHO, 2016).

Closely associated with the epidemic of obesity and overweight, T2D is an expanding global health problem. Individuals with T2D are at high risk for both microvascular complications, including nephropathy, retinopathy, and neuropathy; and macrovascular complications such as cardiovascular diseases (DeFronzo et al., 2015). Diabetes prevalence among the global adult population is 8.5%. In 2014, 422 million people in the world had T2D; this number is expected to rise to 592 million by 2035 (Guariguata et al., 2014), with the fastest growing rate in low- and middle-income countries. Importantly, diabetes is among the leading causes of chronic kidney disease, in many cases progressing to kidney failure that needs to be treated by dialysis or a kidney transplant (WHO, 2016).

6. The need to conduct new epidemiological studies on OTA and kidney disease

As the kidney is the main target organ for OTA, it is important to re-evaluate the risk of OTA in the presence of T2D and chronic kidney disease. Chronic kidney disease (CKD) is long-term, progressive deterioration of renal function, which occurs in approximately 50% of individuals with a diagnosis of T2D. CKD was ranked 18th among causes of human deaths worldwide in 2010, with an annual mortality rate of 16.3 per 100,000 (Jha et al., 2013). The prevalence of obesity (Ng et al., 2014), type 2 diabetes (Vos et al., 2015), and CKD (Jha et al., 2013) in different countries are listed in Table 2. Unfortunately, patients from lower-income countries often do not have easy access to health care infrastructures such as dialysis, kidney transplants, and basic care for diabetes and CKD. In addition, the increasing prevalence of youth-onset T2D is considered to enhance the risks for long-term metabolic, cardiovascular, and renal failures, which consequently adds to the global burden of CKD. As a result, the epidemiology of T2D in the last few decades is believed to be associated with spiking risks of CKD across different populations and clinical settings (Thomas et al., 2016). It is also reported that more than half of nephrotic syndrome cases in adults have secondary causes, in which diabetes is the most common (NIDDK, 2014). Other risk factors for such kidney diseases must also be considered in light of potential synergisms in risks, and to inform potential interventions.

7. Statistical correlations between prevalence of CKD, T2D, and obesity

We investigated the association between the prevalence of CKD and the prevalence of obesity, as well as that of CKD and T2D, in different countries. Studies conducted within certain nations have found that obesity and T2D are associated with an increased risk of CKD (Bailey et al., 2014; Ishizaka et al., 2007; MacLaughlin et al., 2015; Satirapoj et al., 2013). However, there has not been significant research on determining the associations from a global perspective. The Pearson's correlation coefficient was used to analyze data and level of statistical significance was set at $\alpha \leq 0.05$ ($p \leq 0.05$). Associations were also conducted based on the prevalence values after excluding Asian countries or regions.

When including all nations, we found that there were weak positive correlations between the prevalence rate of CKD and obesity ($r = 0.079$, $p = 0.58$), and between that of CKD and T2D ($r = 0.39$, $p = 0.004$) for adult populations (Fig. 1a and b). When excluding Asian nations from the analyses, statistically significant associations between CKD prevalence and both obesity and type 2 diabetes were observed: 0.50 ($p = 0.001$) and 0.38 ($p = 0.012$), respectively (Fig. 1c and d). This may be because Asian populations experience increased risk of overweight/obesity-related illnesses at correspondingly lower BMIs than other populations. They are at an increased risk for developing kidney disease and have a higher risk of T2D at BMIs lower than the current WHO cut-off point for overweight of a BMI exceeding 25 (WHO Expert Consultation, 2004).

8. Discussion and conclusion

OTA contaminates multiple foodstuffs worldwide; thus, most people are exposed to OTA through their diet on a daily basis. From a global dietary perspective, although average estimated OTA exposures in several populations worldwide were found not to exceed

Table 2
The annual incidence and prevalence rate of CKD (Jha et al., 2013), obesity (Ng et al., 2014) and type 2 diabetes (Vos et al., 2015) in the adult population between 1990 and 2013 in different countries of the world.

Country	Prevalence of CKD		Prevalence of obesity (BMI ≥ 30)		Prevalence of diabetes	
	Per million population (2013)	% change, 1990–2013	Prevalence % (2013)	% change, 1990–2013	Prevalence % (2013)	% change, 1990–2013
Argentina	800	39.6	20.8	−1.9	10.2	76.2
Australia	855	59.5	28.7	82.5	7.3	216.8
Austria	998	30.9	17.9	34.6	6	77.2
Bangladesh	17	83.2	3.6	71.4	8	158.4
Belgium	1210	28.6	20.9	23.7	6.4	54.1
Benin	18	103.8	9.7	86.5	5.1	375.4
Bolivia	145	76.6	17.4	38.8	6.6	163.3
Brazil	494	42.5	16.2	52.4	8.1	191.2
Cameroon	10	79.4	14.3	49.0	4.7	207.3
Canada	1150	64.6	21.2	26.9	7.2	133.3
Chile	907	64.0	26.2	18.9	11.4	132.3
China	90	52.9	4.4	109.5	9.4	151.8
Croatia	910	7.6	19.8	31.7	9.9	21.6
Cuba	285	32.9	22.9	20.3	10.2	98.9
Czech Republic	550	22.5	19.3	7.8	9.6	40.9
Ecuador	275	86.3	13.4	11.7	7.3	166.8
Estonia	468	−3.6	22.3	25.3	9.3	30.2
Finland	796	30.9	21.6	28.6	7.7	112.9
France	1056	33.3	19.5	24.2	8	94.5
Ghana	5	84.8	11.1	132.6	4.8	305.7
India	54	57.1	4.0	19.7	7.8	119.6
Israel	1010	89.6	23.1	19.1	7.2	163.9
Italy	1061	28.4	18.0	17.3	8.5	44.2
Japan	2245	40.7	3.9	85.7	10.1	133.0
Kenya	25	110.3	10.8	20.1	4	174.1
Latvia	405	−13.2	21.6	0.7	9.4	2.9
Macedonia	708	32.0	19.2	22.3	8.4	47.7
Malaysia	953	113.7	14.1	30.1	9.8	201.7
Mauritania	45	98.8	17.0	21.4	6.7	236.4
Mexico	510	74.8	26.7	51.4	10.4	183.2
Montenegro	342	19.5	21.8	18.2	8.7	40.0
Netherlands	918	34.7	14.3	8.7	6.1	91.0
New Zealand	578	56.7	29.1	81.6	8.5	142.6
Nigeria	12	71.0	11.1	77.6	4.3	274.4
Panama	342	79.4	15.2	29.5	9	196.0
Paraguay	100	61.8	25.9	10.9	6.9	163.1
Portugal	1410	32.0	22.2	20.1	9.2	68.8
Russia	210	0.4	21.9	34.8	9.3	40.8
Senegal	7	88.9	15.7	60.2	5.1	260.1
Serbia	708	18.0	17.8	19.1	8.6	31.9
South Africa	90	64.6	27.8	27.9	9.8	95.3
South Korea	1150	58.6	6.3	13.5	9.5	112.7
Spain	1000	36.5	20.6	12.0	9.4	75.8
Taiwan	2579	69.2	5.4	32.1	9.8	125.4
Thailand	651	56.0	8.9	108.2	9.6	229.8
Turkey	855	66.1	27.1	6.5	13.2	111.6
Ukraine	99	−6.4	19.9	10.6	9.1	19.9
United Kingdom of Great Britain and Northern Ireland	815	20.7	25.0	68.0	7.7	124.1
United States of America	1882	64.0	32.8	50.8	9.1	154.2
Uruguay	1042	24.8	24.4	9.4	11.1	44.8
Venezuela	468	66.0	18.2	31.4	8.8	189.3

reference values set by regulatory bodies to protect human health, attention should be paid to potentially sensitive populations. These might include subpopulations based on diet as well as on health status. In the United States, for example, the main contributors to OTA exposure are oat products, which account for about 70% of OTA exposure in infants (oat-based infant cereal) and 30% of OTA exposure in adults (Mitchell et al., 2017). Cereal products were consistently the major source of human OTA exposure from a global point of view. Increased dietary diversity may help reduce the dietary risk for chronic OTA exposure, especially for sensitive populations who are diabetics and obese (Wu et al., 2014c).

Likewise, those whose health conditions predispose them to chronic kidney disease could also be at relatively greater risk of OTA-related adverse effects than the general population. These include individuals with diabetes and/or overweight and obesity. During the past two decades, the prevalence of obesity and T2D have been dramatically increasing worldwide. The highest increases in global prevalence between 1990 and 2013 were observed in Ghana (132.6%) and Benin (375.4%), for the condition of obesity and T2D, respectively (Table 2). T2D is also among the leading causes of kidney failure (WHO, 2016). While during the 1990s when the prevalence of these two conditions were relatively low, they were not considered as main risk factors in inducing chronic kidney disease. In the present study, positive correlations were found between the prevalence rate of CKD and obesity, as well as that of CKD and T2D in different countries of the world. Meanwhile, OTA is

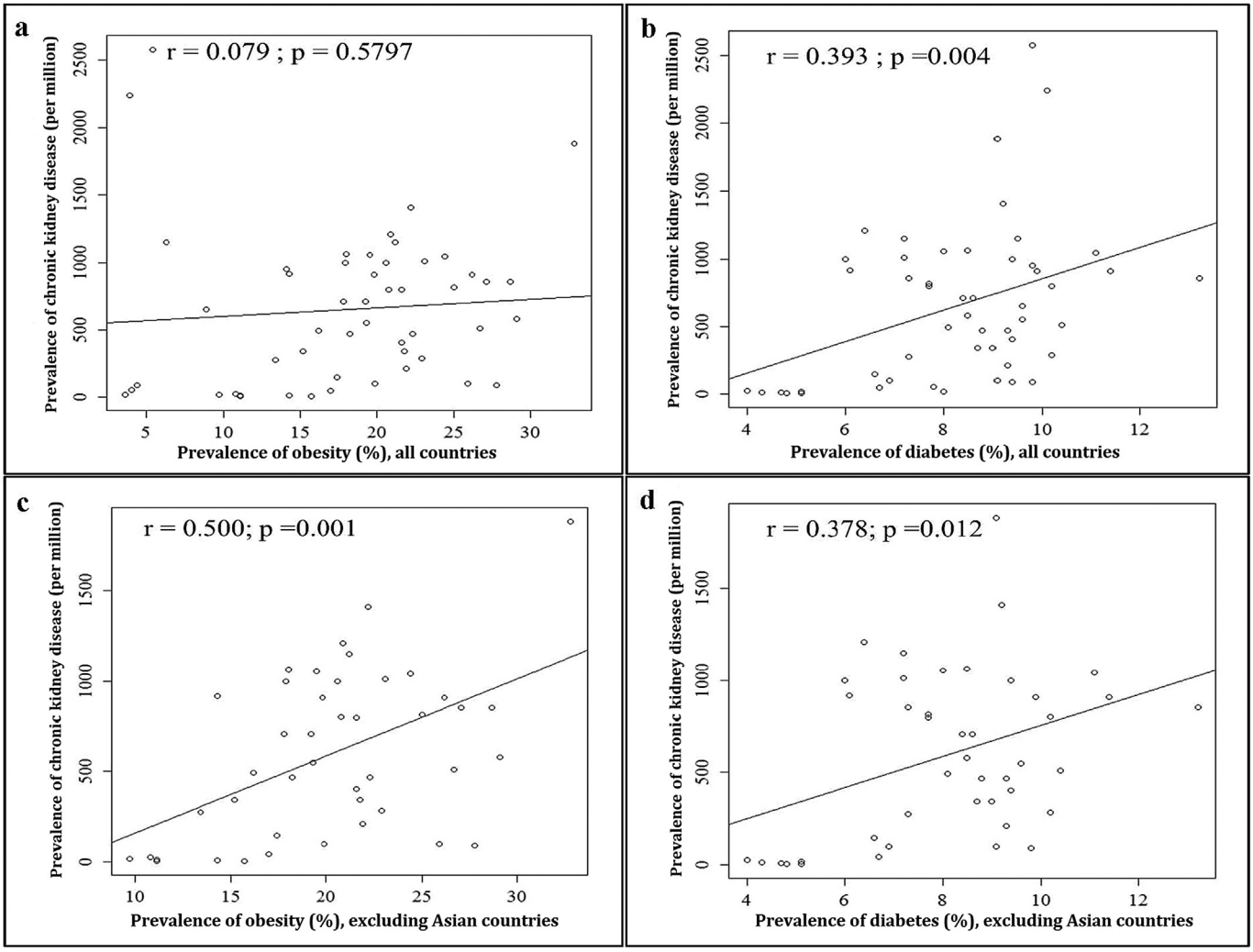

Fig. 1. a: Correlation between the prevalence of CKD and obesity, all countries. b: Correlation between the prevalence of CKD and T2D, all countries. c: Correlation between the prevalence of CKD and obesity, excluding Asian countries. d: Correlation between the prevalence of CKD and T2D, excluding Asian countries.

considered to be correlated to the renal disease leading to kidney failure (Wafa et al., 1998; Hsieh et al., 2004). Therefore, the risk of OTA from dietary sources in the presence of T2D may have a synergistic effect on inducing chronic renal disease.

It is important to improve the body of evidence surrounding OTA's adverse effects to humans as well as human dietary exposures, in the light of increasing T2D prevalence worldwide. Greater toxicological knowledge is needed to establish the potential interactions of OTA with other risk factors for kidney disease, to determine whether there are synergisms in increasing CKD risk. Moreover, research on finding validated human biomarkers for OTA exposure and effect would improve the reliability of OTA exposure and risk assessment efforts.

Acknowledgements

This work was supported by the United States Department of Agriculture National Institute of Food and Agriculture (2011-67005-20676).

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.03.001.

References

Alldrick, A.J., 1996. The effects of processing on the occurrence of ochratoxin A in cereals. Food Addit. Contam. 13 (Suppl. 1), 27–28.
Bailey, R.A., Wang, Y., Zhu, V., Rupnow, M.F., 2014. Chronic kidney disease in US adults with type 2 diabetes: an updated national estimate of prevalence based on Kidney Disease: improving Global Outcomes (KDIGO) staging. BMC Res. Notes 7, 415.
Bui-Klimke, T.R., Wu, F., 2015. Ochratoxin A and human health risk: a review of the evidence. Crit. Rev. Food Sci. Nutr. 55 (13), 1860–1869.
Bullerman, L.B., Bianchini, A., 2007. Stability of mycotoxins during food processing. Int. J. Food Microbiol. 119 (1–2), 140–146.
DeFronzo, R.A., Ferrannini, E., Groop, L., Henry, R.R., Herman, W.H., Holst, J.J., et al., 2015. Type 2 diabetes mellitus. Nat. Rev. Dis. Prim. 1, 15019.
European Commission, 2002. SCOOP Task 3.2.7. Assessment of Dietary Intake by the Population in EU Member States. Available from:. European Commission https://ec.europa.eu/food/sites/food/files/safety/docs/cs_contaminants_catalogue_ochratoxin_task_3-2-7_en.pdf [cited 2016 Nov 10].
Guariguata, L., Whiting, D.R., Hambleton, I., Beagley, J., Linnenkamp, U., Shaw, J.E., 2014. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res. Clin. Pract. 103 (2), 137–149.
Haighton, L.A., Lynch, B.S., Magnuson, B.A., Nestmann, E.R., 2012. A reassessment of risk associated with dietary intake of ochratoxin A based on a lifetime exposure model. Crit. Rev. Toxicol. 42 (2), 147–168.
Han, Z., Nie, D., Yang, X., Wang, J., Peng, S., Wu, A., 2013. Quantitative assessment of risk associated with dietary intake of mycotoxin ochratoxin A on the adult inhabitants in Shanghai city of P.R. China. Food control. 32 (2), 490–495.

Hsieh, M.F., Chiu, H.Y., Lin-Tan, D.T., Lin, J.L., 2004. Does human ochratoxin A aggravate proteinuria in patients with chronic renal disease? Ren. Fail. 26 (3), 311–316.

Health Canada, 2009. Information Document on Health Canada's Proposed Maximum Limits (Standards) for the Presence of the Mycotoxin Ochratoxin a in Foods. Available from: http://www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/consultation/myco_consult_ochra-eng.pdf [cited 2016 Nov 17].

IARC (International Agency for Research on Cancer), 1993. Some naturally occurring substances: food items and constituents, heterocyclic aromatic amines and mycotoxins. Available from:. In: Monographs on the Evaluation of Carcinogenic Risks to Humans IARC Monograph, vol. 56. IARC, Lyon, France, pp. 489–521 https://monographs.iarc.fr/ENG/Monographs/vol56/mono56.pdf [cited 2016 Nov 10].

Ishizaka, N., Ishizaka, Y., Toda, E., Koike, K., Seki, G., Nagai, R., Yamakado, M., 2007. Association between obesity and chronic kidney disease in Japanese: differences in gender and hypertensive status? Hypertens. Res. 30 (11), 1059–1064.

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 1998. Safety evaluation of certain food additives and contaminants, WHO Food Additives Series 40, Aflatoxins. Available from:. In: The Forty-ninth Meeting of the Joint FAO/WHO Expert Committee on Food Additives. World Health Organization, Geneva http://apps.who.int/iris/bitstream/10665/42142/1/WHO_TRS_884.pdf [cited 2016 Dec 6].

JECFA (Joint FAO/WHO Expert Committee on Food Additives), 2008 (WHO Food Additives Series, No. 59) Available from:. In: Ochratoxin, A. (Ed.), Safety Evaluation of Certain Mycotoxins in Food: Prepared by the 68th Meeting of the JECFA. World Health Organization, Geneva, Switzerland, pp. 357–429 http://www.inchem.org/documents/jecfa/jecmono/v59je01.pdf [cited 2016 Nov 17].

Jha, V., Garcia-Garcia, G., Iseki, K., Li, Z., Naicker, S., Plattner, B., et al., 2013. Chronic kidney disease: global dimension and perspectives. Lancet 382 (9888), 260–272.

Krogh, P., Axelsen, N.H., Elling, F., Gyrd-Hansen, N., Hald, B., Hyldgaard-Jensen, J., et al., 1974. Experimental porcine nephropathy. Changes of renal function and structure induced by ochratoxin A-contaminated feed. Acta Pathol. Microbiol. Scand. Suppl. 0 (Suppl. 246), 1–21.

Kuiper-Goodman, T., Hilts, C., Billiard, S.M., Kiparissis, Y., Richard, I.D., Hayward, S., 2010. Health risk assessment of ochratoxin A for all age-sex strata in a market economy. Food Addit. Contam. 27 (2), 212–240.

Lee, H.J., Ryu, D., 2015. Significance of ochratoxin A in breakfast cereals from the United States. J. Agric. Food Chem. 63 (43), 9404–9409.

MacLaughlin, H.L., Hall, W.L., Sanders, T.A., Macdougall, I.C., 2015. Risk for chronic kidney disease increases with obesity: health Survey for England 2010. Public Health Nutr. 18 (18), 3349–3354.

Malir, F., Ostry, V., Pfohl-Leszkowicz, A., Toman, J., Bazin, I., Roubal, T., 2014. Transfer of ochratoxin A into tea and coffee beverages. Toxins (Basel) 6 (12), 3438–3453.

Milićević, D.R., Škrinjar, M., Baltić, T., 2010. Real and perceived risks for mycotoxin contamination in foods and feeds: challenges for food safety control. Toxins (Basel) 2 (4), 572–592.

Mitchell, N.J., Chen, C., Jeffrey, D., Palumbo, J.D., Bianchini, A., Stratton, J., et al., 2017. A risk assessment of dietary ochratoxin A in the United States. Food Chem. Toxicol. 100, 265–273.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 2014. Nephrotic Syndrome in Adults. Available from: https://www.niddk.nih.gov/health-information/health-topics/kidney-disease/nephrotic-syndrome-in-adults/Pages/facts.aspx [cited 2016 Nov 19].

Ng, M., Fleming, T., Robinson, M., Thomson, B., Graetz, N., Margono, C., et al., 2014. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 384 (9945), 766–781.

Nguyen, M.T., Tozlovanu, M., Tran, T.L., Pfohl-Leszkowicz, A., 2007. Occurrence of aflatoxin B1, citrinin and ochratoxin A in rice in five provinces of the central region of Vietnam. Food Chem. 105, 42–47.

O'Brien, E., Dietrich, D.R., 2005 Jan. Ochratoxin A: the continuing enigma. Crit. Rev. Toxicol. 35 (1), 33–60.

Ostry, V., Malir, F., Dofkova, M., Skarkova, J., Pfohl-Leszkowicz, A., Ruprich, J., 2015. Ochratoxin a dietary exposure of ten population groups in the Czech Republic: comparison with data over the world. Toxins (Basel) 7 (9), 3608–3635.

Palliyaguru, D., Wu, F., 2013. Global geographical overlap of aflatoxin and hepatitis C: controlling risk factors for liver cancer worldwide. Food Addit. Contam. 30 (3), 534–540.

Pfohl-Leszkowicz, A., Manderville, R.A., 2007. Ochratoxin A: an overview on toxicity and carcinogenicity in animals and humans. Mol. Nutr. Food Res. 51 (1), 61–99.

Pfohl-Leszkowicz, A., Tozlovanu, M., Manderville, R., Peraica, M., Castegnaro, M., Stefanovic, V., 2007. New molecular and field evidences for the implication of mycotoxins but not aristolochic acid in human nephropathy and urinary tract tumor. Mol. Nutr. Food Res. 51 (9), 1131–1146.

Polisenska, I., Pfohl-Leszkowicz, A., Hadjeba, K., Dohnal, V., Jirsa, O., Denesova, O., et al., 2010. Occurrence of ochratoxin A and citrinin in Czech cereals and comparison of two HPLC methods for ochratoxin A detection. Food Addit. Contam. Part A Chem. Anal. Control Expo. Risk Assess. 27 (11), 1545–1557.

Raad, F., Nasreddine, L., Hilan, C., Bartosik, M., Parent-Massin, D., 2014. Dietary exposure to aflatoxins, ochratoxin A and deoxynivalenol from a total diet study in an adult urban Lebanese population. Food Chem. Toxicol. 73, 35–43.

Satirapoj, B., Supasyndh, O., Mayteedol, N., Punpanich, D., Chaiprasert, A., Nata, N., et al., 2013. Obesity and its relation to chronic kidney disease: a population-based, cross-sectional study of a Thai army population and relatives. Nephrol. Carlt. 18 (3), 229–234.

Scudamore, K.A., Banks, J., MacDonald, S.J., 2003. Fate of ochratoxin A in the processing of whole wheat grains during milling and bread production. Food Addit. Contam. 20 (12), 1153–1163.

Thomas, M.C., Cooper, M.E., Zimmet, P., 2016. Changing epidemiology of type 2 diabetes mellitus and associated chronic kidney disease. Nat. Rev. Nephrol. 12 (2), 73–81.

Tozlovanu, M., Pfohl-Leszkowicz, A., 2010. Ochratoxin A in roasted coffee from French supermarkets and transfer in coffee beverages: comparison of analysis methods. Toxins (Basel) 2 (8), 1928–1942.

Vos, T., Barber, R.M., Bell, B., Bertozzi-Villa, A., Biryukov, S., Bolliger, I., et al., 2015. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 386 (9995), 743–800.

Wafa, E.W., Yahya, R.S., Sobh, M.A., Eraky, I., El-Baz, M., El-Gayar, H.A., et al., 1998. Human ochratoxicosis and nephropathy in Egypt: a preliminary study. Hum. Exp. Toxicol. 17 (2), 124–129.

WHO Expert Consultation, 2004. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 363 (9403), 157–163.

WHO (World Health Organization), 2016. Global Report on Diabetes. Available from:. World Health Organization, Geneva http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf?ua=1 [cited 2016 Nov 17].

Wu, F., Groopman, J.D., Pestka, J.J., 2014a. Public health impacts of foodborne mycotoxins. Annu. Rev. Food Sci. Technol. 5, 351–372.

Wu, F., Bui-Klimke, T., Shields, K.N., 2014b. Potential economic and health impacts of ochratoxin A regulatory standards. World Mycotoxin J. 7 (3), 387–398.

Wu, F., Mitchell, N.J., Male, D., Kensler, T.W., 2014c. Reduced foodborne toxin exposure is a benefit of improving dietary diversity. Toxicol. Sci. 141 (2), 329–334.

Yau, A.T., Chen, M.Y., Lam, C.H., Ho, Y.Y., Xiao, Y., Chung, S.W., 2016. Dietary exposure to mycotoxins of the Hong Kong adult population from a Total Diet Study. Food Addit. Contam. 33 (6), 1026–1035.