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A Risk Assessment of Dietary Ochratoxin A in the United States

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1. Introduction

Ochratoxin A (OTA) is a fungal toxin, or mycotoxin, produced by certain fungal species of the genera *Aspergillus* and *Penicillium* including *P. verrucosum*, *A. carbonarius*, *A. niger*, and *A. ochraceus*; across a large range of climates in multiple foodstuffs (Wu et al. 2014a). OTA can contaminate cereal grains and their finished products, nuts, dried fruits, dried meats, blood sausages, spices, meat, milk, wine, beer, coffee, infant formula, and baby foods (JECFA 2008). OTA is absorbed from the gastrointestinal tract, it binds strongly to plasma proteins and can enter enterohepatic recirculation through biliary secretion and reabsorption from the intestine and the kidney tubules. This causes secondary distribution of OTA in the serum and intestinal contents; it is then slowly eliminated by urinary and faecal excretions, with a half-life in human blood of about 35 days after oral ingestion (Studer-Rohr et al. 2000; Ringot et al. 2006; Wu et al. 2014a). OTA has been shown, in a variety of animal studies, to cause renal cancer and lifetime exposure to OTA induced renal adenomas or carcinomas in male Fisher-344 rats (NTP 1989). OTA can also cause decreased kidney function at just 8 µg/kg bw/day in female swine (Krogh et al. 1974). While the renal system is the main target for OTA toxicity, adverse effects have been observed in other organs; such as cardiac and hepatic histological abnormalities (Hagelberg et al. 1989), gastro-intestinal tract and lymphoid tissue lesions, intestinal fragility and kidney lesions (Elling et al. 1975), and immunotoxic effects (Bondy and Pestka 2000). Maternal OTA can cross the placenta

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Declaration of Interest

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and lead to fetal deformations in mice (Fukui et al. 1987). Based on evidence of carcinogenicity in animals, but no such evidence in humans, the International Agency for Research on Cancer (IARC) has classified OTA as a Group 2B (possible) human carcinogen (IARC 1993).

Indeed, there is no confirmatory epidemiological evidence of OTA exposure causing adverse effects in humans. OTA had been implicated in an endemic kidney disease observed in Eastern Europe (Balkan Endemic Nephropathy and related urinary tract tumors), but convincing epidemiological evidence associating this disease with OTA exposure is lacking (Bui-Klimke and Wu 2014). A systematic review of the epidemiological studies linking OTA with adverse effects in humans showed no evidence linking the two, except for one preliminary study (Wafa et al. 1998) in which, unusually high OTA-exposed individuals also had a higher risk of nephritic syndrome (Bui-Klimke and Wu 2015). However, that study did not control for other potential risk factors, such as bacterial or viral infection, diabetes, lupus, and high blood pressure.

1.1 OTA guidelines worldwide and past risk assessments

Relatively few nations around the world - Brazil, Israel, Switzerland, Uruguay, and the European Union (EU) among them – have set maximum regulatory limits for OTA in food, compared with other mycotoxins such as aflatoxin (FAO 2004). Because OTA can occur in so many different commodities, the nations that regulate it often set different maximum limits for different items. For example, the EU has different maximum allowable OTA concentrations for commodities ranging from cereals to raisins to coffee to licorice; these limits can be found in the European Commission (EC) regulations (2006, 2010). Brazil has set OTA standards of 10 ng/g in rice, barley, legumes, and maize (Saude 2011). Uruguay's OTA standard for these same crops, as well as coffee, is 50 ng/g (Richard and Payne 2003). Likewise, Israel has applied a 50 ng/g OTA standard to all cereals and pulses. Switzerland's OTA standard is considerably stricter than these, at 2 ng/g for all cereal products. Currently, the United States Food and Drug Administration (FDA) has not set regulatory guidelines for OTA in food or feed. Since 2009, Health Canada has considered setting maximum limits (MLs) for OTA in multiple commodities (Health Canada 2009); however, such standards have not yet entered into law.

The Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA) has concluded that there is not sufficient evidence to support a direct genotoxic mode of action for OTA (JECFA 2008). In its earliest evaluation of OTA in 1991, based on a lowest observed effect level (LOEL) causing renal dysfunction in pigs (Krogh et al. 1974) and applying a safety factor of 500, JECFA, set a provisional tolerable weekly intake (PTWI) of 112 ng/kg body weight per week (JECFA 1991). This finding was reconfirmed in its 1995 evaluation, with the PTWI rounded to 100 ng/kg bw/week (JECFA 1995). Again, in the JECFA 2001 and 2008 re-evaluations of OTA, carcinogenicity data from rat bioassays performed by the US National Toxicology Program (NTP 1989) was analyzed, and the previously established PTWI was retained (JECFA 2001, 2008).

Similarly, the European Food Safety Authority (EFSA) has set a PTWI for OTA of 120 ng/kg bw (EFSA 2006). EFSA used the same 90-day pig study used by JECFA (Krogh et al.

1974), and divided by a composite uncertainty factor of 450; accounting for interspecies differences from pig to human, kinetic differences (half-life of OTA), intraspecies variability, and use of a LOEL. From the EFSA assessment, the EC set maximum allowable concentrations of OTA in multiple commodities (EC 2006, 2010).

In 2009, Health Canada proposed maximum concentrations for OTA in various commodities; but as of yet (September 2016), these MLs are still in “proposed” status (Health Canada 2016). Health Canada’s proposed MLs were based on a risk assessment by Kuiper-Goodman et al. (2010) that assumed that OTA could have genotoxic effects; thus, a cancer-based risk assessment approach was used. A negligible cancer risk intake (NCRI) was calculated and defined as ‘the exposure associated with a risk level of 1:100,000 and equivalent in units to a tolerable daily intake (TDI)’ (Kuiper-Goodman et al. 2010). A NCRI was derived from a tumorigenic rat study (NTP 1989), where the OTA dose associated with a 5% increase in tumor incidence above background (TD_{05}) was 27.4 $\mu\text{g/kg bw}$, this was adjusted to 19.6 $\mu\text{g/kg bw}$ because the rats in the NTP study were gavaged for only 5 out of 7 days, then a safety factor of 5000 (considered equivalent to linear extrapolation to zero exposure based on a non-threshold carcinogenicity concept) was applied resulting in a NCRI value of 3.9 ng/kg bw/day which was rounded to 4 ng/kg bw/day . Based on this safety level, Kuiper-Goodman et al. (2010) also conducted a health risk assessment of OTA for all age-sex strata in the Canadian population. In Canadian children’s diets, the major contributors of OTA are wheat-based foods followed by oats, rice, and raisins. The mean adjusted exposures were generally below the NCRI of 4 ng/kg bw/day , except for 1- to 4-year olds as a result of their lower body weight. However, they were all below the JECFA PTWI of 100 ng/kg bw/week . Assessment of the same NTP data set suggests that OTA is the best example of a linear log-dose-renal carcinoma response relationship. This would indicate that hormesis applies to carcinogenesis and that there is in fact a cancer threshold for OTA exposure (Waddell 2006). Therefore, use of a NCRI value based on a non-threshold carcinogenicity theory could be overestimating the risk for human carcinogenesis. For instance, Haighton et al. (2012) revisited this risk assessment as well as the EFSA assessment and concluded that the most plausible toxicological mechanism of OTA did not involve genotoxicity, but rather, a threshold (below which no risk of renal cancer would be expected); and found the risk to the Canadian population of OTA-related cancer negligible.

As of yet, the United States has not set a regulatory limit on allowable OTA in foodstuffs. In this analysis, we present our data on the concentrations of OTA in a variety of foods and drinks bought from grocery stores around the US during 2012 and 2013 (Lee and Ryu 2015; Palumbo et al. 2015; Al-Taher et al. 2017a,b). From these, we imputed the levels of exposure in the US, based on average levels of consumption across all US citizens as well as in a special group for those who were considered ‘regular consumers’. Finally, we conducted a risk assessment to determine, among the different age and consumption groups, whose OTA exposure did or did not exceed the JECFA PTWI or the NCRI utilized in the proposed Health Canada MLs.

2. Materials and Methods

This risk assessment was conducted with OTA contamination data from foodstuffs that have been analysed by the authors in previous reports. Palumbo et al. (2015) described the OTA methodology and contamination observed in dried fruits and nuts; Lee and Ryu (2015) describe the OTA methodology and contamination observed in breakfast cereals; and Al-Taher et al. (2017a,b) describe the OTA methodology and contamination observed in infant cereal, infant formula and milk. For materials and methodology for those foodstuffs, please refer to the cited references. Additional food commodities utilized in this risk assessment include wine, coffee, cocoa, and pork and the analytical methodology for those commodities are discussed below.

2.1 Sampling

A total of 2296 food samples were collected over two years (2012–2013 and 2013–2014) by random selection from different local retail markets across the United States. Sampling locations included Chicago (IL), San Francisco (CA), Dallas (TX), Pittsburgh (PA), Fargo (ND), Moscow (ID), Minneapolis (MN), East Lansing (MI) and Lincoln (NE). Types of foods purchased were those that had the potential to be contaminated with OTA; hence, these included raisins and other dried fruits, nuts, breakfast cereals, oatmeal, infant formula, infant cereal, wine, milk, coffee, cocoa, and pork. Samples included organic, traditional and imported products. Further description of the sampling methods and contamination of OTA in the sampled food commodities can be found in previous work conducted by our group (Lee and Ryu 2015; Palumbo et al. 2015; Al-Taher et al. 2017). Contamination values for wine, coffee, cocoa and pork are being reported for the first time in this risk assessment.

2.2 Materials

OTA standard was purchased from Sigma-Aldrich (St. Louis, MO, USA). Standard solutions were prepared with proper dilutions of 100% methanol and stored in amber vials at -20°C . HPLC grade methanol and acetonitrile were purchased from Fisher Scientific (Pittsburgh, PA, USA) and acetic acid (99.5%) and phosphate-buffered saline (PBS) tablets were purchased from Sigma-Aldrich (St. Louis, MO, USA). OchraTest immunoaffinity columns (IAC) were obtained from VICAM (Watertown, MA, USA).

2.3 Analytical procedures

2.3.1 Wine—Wine samples (3 ml) were filtered through a 17 mm, 0.2 μm Nylon syringe filter (Fisher Scientific, Hanover Park, IL, USA). A dilution of 1 to 5 was made by mixing 20 μL of sample, 20 μL IS and 60 μL of 30:70 acetonitrile/water, v/v. A 10 μL injection of the diluted samples was made into a UHPLC-MS/MS system. An Agilent 1260 Infinity HPLC system equipped with an Agilent Zorbax Poroshell 120 EC-C18 (100 mm $\times$ 2.1 mm, 2.7 μm) column and mobile phases composed of 5 mM ammonium formate and A) 0.1% formic acid in water and B) 0.1% formic acid in methanol were used for chromatographic separation. The mobile phases were applied in a gradient of 30% B (initial); 100% B (8 min) and re-equilibration from 10–12 min at a flow rate of 0.3 ml/min and column temperature of 35°C . Mycotoxins were quantified using an Agilent 6460 Triple Quadrupole LC-MS/MS with Jet Stream Technology. OTA was identified by dynamic multi-reaction monitoring

(DMRM) in positive electrospray ionization mode (ESI+). The OTA ion (m/z 404.1) fragmented to yield daughter ions at m/z 358, 239, and 193. Quantification was determined by a standard calibration curve. The overall recoveries were 80–137% at three spiking levels.

2.3.2 Coffee, cocoa—Cocoa samples were used without further preparation; while roasted coffee samples were ground using a coffee grinder (Burr Mill, Ltd). For both commodities a 15 g sample was mixed with 150 ml of extraction solvent for 30 min. The extraction solution was filtered through a Whatmann #4 filter paper. The filtrate (10 ml) was diluted with 10 ml of extraction solvent and passed through a solid phase extraction (SPE) column (J.T Baker, Europe). The columns were washed with methanol: 3% aqueous sodium bicarbonate (1:3) and 1% aqueous sodium bicarbonate. The toxin was eluted using methanol:water, 7:93, v/v. The eluent was diluted with 30 ml of PBS buffer (pH 7.4). The diluted eluent was passed through OchraTest (Vicom, Ltd) immunoaffinity columns. Procedures suggested by the manufacturer were followed. Diluted eluent from the SPE column was passed through the OchraTest column followed by 10 ml of water and air dried for 10–20 seconds. OTA was eluted with methanol (4 ml) into a vial. The eluent was evaporated to dryness under a stream of air and the residue reconstituted into 1 ml of water:acetonitrile:acetic acid, 51:48:1 by vortexing for 1 min. The solution was then filtered using 0.2 μ m (nylon membrane) filter discs (Pall, Acro Discs). Samples and standards (100 μ l) were injected into the HPLC-fluorescence detector system. A Dionex Ultimate 3000 series with a C18 column (30 $\times$ 2.1 mm, 1.8 μ m, CA, USA) was used for the HPLC analysis. Excitation and emission wavelengths of 333 nm and 460 nm, respectively was used for detection of OTA. Recovery rates for coffee varied from 80.6–85.8%, with a limit of detection of 0.47 μ g/kg and analysis of the cocoa samples had recovery rates from 74.8–90.5% with a limit of detection of 0.47 μ g/kg.

2.3.3 Pork—Analysis of OTA in meat samples was conducted as suggested by Jorgenson and Petersen (2002). Extraction solvent (dichloromethane:ethyl acetate, 1:3) (100 ml) was added to a 25 g sample and blended for 1 min. The mixture was filtered using Whatmann #4 filter paper and 10 ml aliquot of the filtrate was evaporated to dryness and the residue re-dissolved in 2 ml methanol and 30 ml PBS buffer (pH 7.4) then further filtered to remove any suspended fat. The filtered solution was then passed through an OchraTest immunoaffinity column (Vicom, Ltd) and the column washed using 20 ml of water. The OTA was eluted from the column using 4 ml of methanol. The extract was evaporated under a stream of air and the residue was reconstituted in 1 ml of water:acetonitrile:acetic acid, 51:48:1 and filtered using 0.2 μ m (Nylon membrane) filter discs (Pall, Acro Discs). Samples (100 μ l) were injected into a HPLC-fluorescence system for analysis. The parameters used for the HPLC analysis were the same as the ones used for coffee and cocoa analysis. Samples were extracted and analysed in 5 replicates and recoveries calculated. Recovery rates varied from 82.8–111.0% with a limit of detection of 0.22 μ g/kg.

2.4 Food consumption data

For OTA exposure assessment in the American population, we used the database ‘What we eat in America’ to obtain consumption information by age group of the multiple foodstuffs that could contain OTA (EPA 2012). This database is an integrated federal food survey that

was conducted as a partnership between the US Department of Agriculture and the US Department of Health and Human Services. The database includes the dietary intake interview component of the National Health and Nutrition Examination Survey (NHANES). For our exposure assessment, the US population was divided into four different age groups;

12 months, >12 months-5years, >5 years-18 years, and >18 years. The 'What we eat in America' database provides consumption information in grams of foodstuff per kilogram body weight by age. Our dried fruits and nuts foodstuffs analyzed included raisins, dates, figs, prunes, almonds, pistachios, and walnuts. The breakfast cereal foodstuffs were classified by primary grain ingredient; corn, oat, wheat, or rice. Similarly, the primary grain ingredient classified infant cereal; barley, rice, oat, or wheat. Infant formula was divided into animal milk and soy based formulas. Other foodstuffs included wine, beer, milk, pork, coffee, and cocoa. Consumption data that represented the mean and 95th percentile (p95) of consumption for both the total population and the consumer population (those who responded "yes" to consuming a certain product) within each age group were exported to MS Excel.

2.5 Exposure assessment

Exposure assessment of OTA was based on the analytical results of the food samples described above. Samples with non-detectable concentrations of OTA were given a value of the square root of the analytical limit of detection (LOD) divided by 2 for exposure assessment purposes. Dietary exposures of OTA for each commodity were calculated by multiplying daily consumption (ng/kg bw) with corresponding median OTA contamination level. Exposure was divided into 'regular eaters' (mean consumption) and 'heavy eaters' (p95 consumption) among the total population and the consumers population. Therefore, we calculated four values: 1) 'regular eater' exposure for the total population, 2) 'heavy eater' exposure for the total population, 3) 'regular eater' exposure for the consumers population, and 4) 'heavy eater' exposure for the consumers population. These classes of individuals within the specified age groups are defined as follows: For regular eaters:

$$Exposure = \frac{OTA \text{ concentration} \times \text{Mean consumption}}{BW} \quad (1)$$

For heavy eaters:

$$Exposure = \frac{OTA \text{ concentration} \times p95 \text{ consumption}}{BW} \quad (2)$$

In the total population, consumption values are based on the total population surveyed in the NHANES database in a given age range; including those people who did not report eating a specific commodity. In the consumer population, consumption values are based only on the subpopulation in each specified age range that reported consumption of the specific foodstuff (e.g., pistachios). Median OTA contamination values were used in exposure calculations due to the non-normal distribution of values. Aggregate daily exposure was calculated by summing these exposures across all commodities.

3. Results

3.1 Occurrence and concentrations of OTA in food commodities

Occurrence and concentrations of OTA in food commodities are listed in Table 1. Frequency distributions of OTA occurrence in some food commodities are illustrated in Figure 1.

3.2 Total population exposures to OTA

Across the US population as a whole, average OTA exposures are much lower than the previously estimated maximum tolerable intakes on either a daily or weekly basis (Health Canada NCRI: 4 ng/kg bw/day; JECFA: 100 ng/kg bw/wk, or about 14 ng/kg bw/day). For 12 month, >12 month-5 year, >5-18 year and >18 year old subpopulations, the overall mean exposures were 0.37, 0.39, 0.14, and 0.12 ng/kg bw/day, respectively; while the 95th percentile exposure was estimated to be 2.26, 1.63, 0.66, and 0.69 ng/kg bw/day for these age groups, respectively (Table 2). Generally, OTA exposures decreased with age. The greater exposure levels observed in children can be attributed to higher food consumption rates relative to their body weight. OTA exposure proportions of individual food commodities for different age groups in the total population are shown in Figure 2.

For the 12 month (infant) age group, the commodities contributing most to OTA exposure were oat-based infant cereal and oat-based breakfast cereal, with the exposure from these two commodities making up 56% and 19% of the US infants' total exposure, respectively. For all other age groups, oat-based breakfast cereals were the highest contributor to exposure; typically followed by pork, milk, cocoa, and coffee. For example, the >18 (adult) group had contributing proportions of OTA from oat (breakfast cereal): 25%, pork: 25%, milk: 17%, and coffee: 17%.

3.3 Consumer population exposures to OTA

The exposures for individual commodities used in the total population calculations included many non-consumers; e.g., individuals who stated that they never consumed pork or never drank coffee. Thus, exposures of regular consumers of these commodities, or the 'consumer population,' are underestimated in the 'total population' exposure assessment. Specific exposures from those commodities that were main contributors to real consumers are elaborated below.

3.3.1 Oat-based infant cereal—In the food consumption survey, approximately 26% and 3% of 12 month-old infants and >12 month-5 year-old young children, respectively, consume oat-based infant cereal. The mean and 95th percentile of OTA exposure for the 12 month group were 0.81 and 2.75 ng/kg bw/day; and for the 1-5 year group, were 0.56 and 1.73 ng/kg bw/day. These values for the 12 month age group were nearly four (mean) and two (p95) times higher than the 'total population' exposure levels, which were estimated to be 0.21 and 1.32 ng/kg bw/day, respectively.

3.3.2 Oat-based breakfast cereals—The consumption of oat-based breakfast cereal peaks in the age group of 6-18 years old: 39% of this subpopulation reported consuming oat-based cereals frequently. The consumers of this age group had a mean daily OTA

exposure of 0.18 ng/kg bw/day, when compared with 0.05 ng/kg bw/day for the general population of this age. For heavy consumers of this food item (95th percentile of average daily consumption), their OTA exposure was calculated as 0.68 ng/kg bw/day.

3.3.3 Milk—Almost all persons older than 1 year old in the US are milk drinkers. For the adult consumer population (>18 years) group, the milk-based OTA exposures of average and heavy (p95) milk drinkers were 0.02 and 0.04 ng/kg bw/day, respectively, which is almost the same as that of the general population (Table 2).

3.3.4 Coffee—According to the consumption survey, approximately 60% of adults were coffee drinkers. The mean and p95 OTA exposure levels from coffee consumed by the >18-year-old subpopulation were 0.05 and 0.12 ng/kg bw/day, respectively.

3.3.5 Cocoa—Cocoa was a contributor of OTA exposure for children and adolescents, with the mean and p95 exposure levels of 0.05 and 0.18 (>12 months-5years); and 0.03 and 0.08 ng/kg bw/day (>5–18 years), respectively. Cocoa is consumed by 41% and 45% of these two subpopulations. The estimations for the total population were approximately two times lower than that of consumers exposure levels.

3.3.6 Pork—The consumption of pork increases with age, and approximately half of adults are consumers. OTA exposure from pork in the consumer population was highest for >12 month-5 year-old children, which was 0.16 (mean) and 0.6 (p95) ng/kg bw/day.

3.4 Risk assessment

The JECFA PTWI of 100 ng/kg bw/wk and the Health Canada NCRI of 4 ng/kg bw/day were used to compare with the exposure levels as an example of OTA as a threshold non-genotoxic carcinogen and the more conservative non-threshold approach. The result of dividing the adopted reference values by the population's imputed exposures is referred to as the *margin of safety* (MOS). The MOS provides an estimate of how many times smaller the predicted OTA exposure is than the toxicity-based benchmarks. When the MOS > 1, the actual exposure is lower than the reference value; thus, risk is considered negligible. When the MOS < 1, the population's exposure is equivalent to or higher than the reference value; thus, risk mitigation measures may be appropriate. The MOS values for each commodity by age group and the totals, based on the JECFA PTWI (divided by 7 for daily exposure) can be found in Table 3. The MOS values based on the NCRI of Health Canada are represented in Table 4.

In the total population group, the cumulative MOS for mean and p95 OTA exposure for 12 month infants was 38.6 and 6.32 for the JECFA PTWI and 10.71 and 1.77 for the NCRI, respectively. For adults (>18 years), the cumulative MOS based on JECFA was 119 and 20.7 for mean and p95 OTA exposure, respectively. The cumulative NCRI-based MOS for the same age group was 33.47 and 5.8, for mean and p95 OTA exposures, respectively. As expected, the MOS for OTA exposure of consumers, based on all commodities, was lower than MOS for total population exposures. However, the only MOS values < 1, indicating risk of OTA exposure over the NCRI reference, occurred in the 95th percentile groups of consumer population in the 12 month and 1–5 year age groups. No age groups had a MOS

1 for the JECFA-based values. For all other age groups in the US, because the MOS is greater than 1, there is no expected health risk from OTA exposure in the diet.

The use of a reference dose from a cancer endpoint of a non-genotoxic carcinogen that is considered a threshold carcinogen, like OTA, requires the assumption that risk associated with an acute dose is equivalent to low dose spread over time (Waddell, 2006; Haighton et al. 2012). Due to uncertainty in intermittent or varying levels of exposure experienced by humans over a lifetime, the US EPA has recommended calculating lifetime average daily dose (EPA 2005). For this US population we calculated lifetime cancer risk for the cumulative MOS values based on the most conservative metric, the NCRI, across all food commodities. The lifetime MOS was calculated by multiplying the number of years across each age group by the age-specific cumulative MOS, then summing these values across all age groups and dividing by 78 years (considered average US lifespan). Based on this lifetime risk calculation even those individuals within the p95 of those in the consumers population (highest exposure group) had negligible risk for development of renal cancer from OTA exposure (MOS=2.51).

4. Discussion

Although dietary patterns are likely between different regions of the United States, the consumption data by region were not available during the development of this risk assessment. However, those populations at highest risk for exposure are represented in the p95 of the consumer population in this analysis. The overall risk associated with OTA consumption was negligible for all age groups except the 12 months and the >12 months-5 years upper 95th percentile (p95) of the consumer population. The largest contributors of OTA exposure in the US population, and particularly for these two age groups, were consumption of oat-based breakfast cereals and oat-based infant cereals. However, even with the excursions over the Health Canada-derived NCRI in these age groups, the lifetime cancer risk is negligible. It is not clear that health risks are significantly increased by the OTA exposures; as the OTA NCRI was based on an assumption of genotoxicity that is not supported by JECFA (2008). Additionally, when considering the metrics of the JECFA PTWI (14.3 ng/kg bw/day), the associated nephrotoxic risk is negligible to all segments of the US population. The p95 OTA exposure estimates for the most vulnerable subpopulation of consumers (6.19 ng/kg bw/day) were less than 50% of JECFA's guidance value. The calculation of the lifetime MOS risk was calculated for the cumulative MOS values across all food commodities within the heaviest eaters for all foods (p95 of consumer population). The actual lifetime risk for the average US citizen would be even lower, considering that it is highly unlikely that any one person would consume every considered food commodity within the upper 95% of the population across their lifetime.

It is important to note, that in the current analysis of the US population a deterministic method of exposure and risk assessment was undertaken due to the availability of actual OTA concentrations and food consumption data. Other reports, such as those conducted for the Canadian population, utilized a probabilistic model to account for a lack of appropriate contamination data. Although the risk for the Canadian population and the US population

were calculated with different methodologies, both indicate a negligible risk from OTA exposure.

The extreme excursions in OTA occurrence and exposure are, however, worth noting. There was one unusually high occurrence of OTA in a pistachio sample: in 2012, the only pistachio sample that tested above the limit of detection for OTA had an OTA concentration of 821 ng/g. However, the proportion of the population that reported consuming pistachios was less than 1% for all the age groups. Therefore, based on the infrequency of high OTA excursions in pistachios, and relatively low pistachio consumption in the US, it is unlikely that OTA exposure would become dangerously high based on pistachio intake.

The European Commission (EC 2002) estimated OTA exposure in European Union member states to range from 0.13 to 3.55 ng/kg bw/day, which is comparable to that of the US population calculated here. The EC Scientific Committee for Food suggested a TDI of 5 ng/kg bw/day for OTA, which indicates that the calculated exposures and OTA associated health risks are minimal in both the EU and US populations.

One limitation of our analysis, and others like it, is the uncertainty and variability in OTA sampling. OTA can be heterogeneously distributed in food samples, which affects variability in sampling (Wu et al. 2014b). Moreover, the analytical results presented here are based on OTA concentrations in samples taken from grocery markets across the United States during 2012–2013. It is likely that in a different year, OTA concentrations in these same foodstuffs would be slightly different. Furthermore, we assessed OTA concentrations in foods purchased in grocery markets only. It is possible that foods obtained in places other than grocery markets (e.g., farmers' markets and directly consumed from the garden or the farm) could have different OTA concentrations than those same foodstuffs purchased in grocery stores. Another set of limitations concerns the variability in consumption of particular foodstuffs. Such uncertainty was captured in the NHANES food frequency questionnaire, and there is also variability over time in consumption of certain foods, even within a particular age range.

Finally, the lack of agreement among different risk assessment and regulatory policy bodies worldwide on a safe human OTA exposure means that there are still significant knowledge gaps about the nature of OTA's toxicity and its implications for human health. To err on the safe side, we compared our US population exposures to the most precautionary of the derived tolerable daily intakes: the Health Canada NCRI of 4 ng/kg bw/day. Even then, the vast majority of Americans were exposed to lower dietary OTA levels than this NCRI. Additionally, when lifetime exposure risk is considered the MOS for those people in the p95 of consumers had negligible risk. Had the JECFA or EFSA limits been used, the estimated American OTA exposures for all age groups in this study would have fallen well within the safe range.

5. Conclusions

The current work is the first human exposure and risk assessment done for dietary OTA exposure in the US population. In summary, based on the current risk calculations from

foodstuffs in American marketplaces, there is negligible risk to the US population from OTA exposure. Current OTA concentrations are not high enough to elicit toxic effects, even at the mean consumption levels of the consumers who eat high amounts of the foods that may contain OTA. In general, exposure to OTA in the United States is highest among individuals less than 5 years of age, because of lower body weight and relatively higher consumption of oat-based cereals, however their lifetime cancer risk is negligible. With the exception of one pistachio sample that had extremely high OTA, other foodstuffs had sufficiently low OTA concentrations that the associated risks from current food consumptions do not exceed levels of concern.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

1. OTA, a mycotoxin found in many foods and drinks, is linked to kidney disease.
2. OTA levels in food and drinks gathered from grocery stores across the US were low.
3. Worst-case scenarios for OTA exposure were assessed by age group and diet.
4. OTA exposure is highest for infants, due to oat-based cereals and low bodyweight.
5. US lifetime disease risk estimates for worst cases of OTA exposure are negligible.

Figure 1.
Frequency distributions of OTA occurrence in food commodities which are main contributors to the total exposure of OTA.

Figure 2.
OTA exposure proportions of individual food commodities for subpopulations of different age groups of US total population.

Occurrence of Ochratoxin A (OTA) in food commodities collected from the United States

Table 1

Food type	Commodity	N	Number of positives	Range (ng/g)	No. over EU limit	EU limit (ng/g)	LOD (ng/g)
Dried fruits & nuts [*]	Raisins	109	48	0.3–15.3	2		
	Dates	95	1	0.4	0		
	Figs	88	4	0.5–3.3	0	10	0.08
	Prunes	92	0	^a	-		
	Almonds	102	0	-	-		
	Pistachios	85	4	0.7–890	-	-	0.08
	Walnuts	94	0	-	-		
Breakfast cereal [*]	Corn	103	15	0.1–0.5	0		
	Oat	203	142	0.1–9.3	16	3	0.032
	Rice	66	10	0.1–1.5	0		
	Wheat	117	38	0.1–0.5	0		
Infant formula [*]	Milk	53	0	-	-	0.5	0.1
	Soy	45	0	-	-		
Infant cereal [*]	Barley	9	1	14.4	1		
	Oat	51	30	0.6–22.1	30		
	Rice	54	2	1.4	2	0.5	0.1
	Wheat	6	2	1.2	2		
Milk [*]		76	0	-	-	-	0.1
Wine		343	6	0.1–0.4	0	2	0.1
Coffee		376	5	1.7–4.8	0	5	0.47
Cocoa		47	6	1.6–18.0	-	-	0.47
Pork		94	3	0.9–1.8	-	-	0.22

^{*} Source of data: Lee and Ryu, 2015; Palumbo et al., 2015; Al-Taher et al. 2017/a,b.

^a , not applicable

Table 2

Estimation of the exposures mean and (p95) for US 'total population', and 'consumers', to OTA (ng/kg bw/day).

Food type	Commodity	12 month-old			>12 months-5 year-old			>6-18 year-old			>18 year-old		
		Total population	Consumers	Consumers	Total population	Consumers	Consumers	Total population	Consumers	Consumers	Total population	Consumers	Consumers
Dried fruits & nuts	Raisins	0.0004 (0)	0.01 (0.1)	0.02 (0.11)	0.003 (0.01)	0.01 (0.06)	0.006 (0.03)	0.0008 (0.003)	0.006 (0.03)	0.0008 (0.005)	0.004 (0.02)	0.008 (0.04)	
	Dates	^a	0.01 (0.02)	0.01 (0.06)	-	0.02 (0.1)	0.009 (0.03)	-	0.01 (0.04)	-	0.007 (0.02)	0.008 (0.04)	
	Figs	-	0.02 (0.02)	0.02 (0.1)	-	0.02 (0.05)	0.005 (0.02)	-	0.02 (0.08)	-	0.02 (0.06)	0.007 (0.03)	
	Prunes	-	0.03 (0.13)	0.007 (0.03)	-	0.05 (0.13)	0.003 (0.009)	-	0.006 (0.001)	-	0.004 (0.02)	0.005 (0.02)	
	Almonds	0 (0)	0.002 (0.005)	0.006 (0.03)	0.001 (0.003)	0.006 (0.03)	0.003 (0.009)	0.0006 (0.002)	0.003 (0.009)	0.0006 (0.001)	0.004 (0.02)	0.005 (0.02)	
	Pistachios	-	N/A ^b	0.006 (0.03)	-	0.006 (0.03)	0.003 (0.009)	0.0006 (0.002)	0.003 (0.009)	0.0006 (0.001)	0.004 (0.02)	0.005 (0.02)	
	Walnuts	0 (0)	0.001 (0.006)	0.006 (0.03)	0.0006 (0.002)	0.006 (0.03)	0.003 (0.009)	0.0006 (0.002)	0.003 (0.009)	0.0006 (0.001)	0.004 (0.02)	0.005 (0.02)	
Breakfast cereal	Corn	0.0005 (0.001)	0.007 (0.03)	0.01 (0.04)	0.004 (0.02)	0.01 (0.04)	0.007 (0.02)	0.002 (0.01)	0.007 (0.02)	0.001 (0.008)	0.005 (0.02)	0.013 (0.41)	
	Oat	0.07 (0.45)	0.46 (1.69)	0.43 (1.46)	0.17 (0.84)	0.43 (1.46)	0.18 (0.68)	0.05 (0.28)	0.18 (0.68)	0.03 (0.22)	0.13 (0.41)	0.008 (0.03)	
	Wheat	0.002 (0.01)	0.02 (0.05)	0.02 (0.07)	0.008 (0.04)	0.02 (0.07)	0.01 (0.04)	0.004 (0.02)	0.01 (0.04)	0.003 (0.02)	0.008 (0.03)	0.0004 (0.002)	
	Rice	0.0002 (0)	0.0008 (0.003)	0.002 (0.02)	0.001 (0.008)	0.002 (0.02)	0.001 (0.006)	0.0006 (0.003)	0.001 (0.006)	0.0002 (0.0004)	0.0004 (0.002)	0.0004 (0.002)	
Infant formula	Milk	0.0007 (0.001)	0.007 (0.03)	0.008 (0.03)	0 (0)	0.008 (0.03)	N/A	N/A	N/A	N/A	N/A	N/A	
	Barley	0.0006 (0)	0.02 (0.12)	0.0006 (0.008)	0 (0)	0.0006 (0.008)	N/A	N/A	N/A	N/A	N/A	N/A	
	Rice	0.04 (0.19)	0.09 (0.33)	0.03 (0.09)	0.0006 (0)	0.03 (0.09)	N/A	N/A	N/A	N/A	N/A	N/A	
	Oat	0.21 (1.32)	0.81 (2.75)	0.56 (1.73)	0.02 (0)	0.56 (1.73)	N/A	N/A	N/A	N/A	N/A	N/A	
	Wheat	0.009 (0.06)	0.042 (0.14)	0.05 (0.12)	0.001 (0)	0.05 (0.12)	N/A	N/A	N/A	N/A	N/A	N/A	
Wine	Milk	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.01 (0.1)	0.08 (0.36)	0.02 (0.04)	
	Milk	0.03 (0.19)	0.08 (0.27)	0.09 (0.22)	0.09 (0.22)	0.09 (0.22)	0.03 (0.09)	0.03 (0.09)	0.03 (0.09)	0.02 (0.04)	0.07 (0.24)	0.05 (0.12)	
	Pork	0.01 (0.04)	0.14 (0.44)	0.16 (0.6)	0.07 (0.37)	0.16 (0.6)	0.09 (0.34)	0.04 (0.23)	0.09 (0.34)	0.03 (0.18)	0.009 (0.03)	0.42 (1.5)	
	Coffee	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.02 (0.09)	0.05 (0.12)	0.009 (0.03)	
	Cocoa	0 (0)	0.02 (0.06)	0.05 (0.18)	0.02 (0.112)	0.05 (0.18)	0.03 (0.08)	0.01 (0.02)	0.03 (0.08)	0.003 (0.02)	0.12 (0.69)	0.009 (0.03)	
	Cumulative	0.37 (2.26)	1.77 (6.19)	1.54 (5.08)	0.39 (1.63)	1.54 (5.08)	0.42 (1.5)	0.14 (0.66)	0.42 (1.5)	0.12 (0.69)	0.42 (1.5)	0.42 (1.5)	

^a commodities with no positive OTA concentrations.

^b N/A, commodities with positive OTA contamination, but not applicable consumption patterns for a specific age group.

Table 3

MOS for mean and (p95) OTA exposures for US 'total population', and 'consumers' based on JECFA PTWL.

Food type	Commodity	12 month-old			>12 months-5 year-old			>6-18 year-old			>18 year-old		
		Total population	Consumers	Consumers	Total population	Consumers	Consumers	Total population	Consumers	Consumers	Total population	Consumers	Consumers
Dried fruits & nuts	Raisins	35725 (- ^a)	1429 (143)	1429 (143)	4763 (1429)	715 (130)	715 (130)	17863 (4763)	2382 (476)	2382 (476)	17863 (2858)	3573 (715)	3573 (715)
	Dates		1429 (715)		-	1429 (238)	1429 (238)	-	1588 (476)	1588 (476)	-	1786(357)	1786(357)
	Figs		715 (715)		-	715 (143)	715 (143)	-	1429 (357)	1429 (357)	-	2041 (715)	2041 (715)
	Prunes		476 (110)		-	715 (286)	715 (286)	-	715 (357)	715 (357)	-	715 (238)	715 (238)
	Almonds		7145 (2858)		14290 (4763)	2382 (476)	2382 (476)	23817 (7145)	2858 (715)	2858 (715)	14290 (2858)	2041 (476)	2041 (476)
	Pistachios		-		-	286 (110)	286 (110)	-	715 (179)	715 (179)	-	715(238)	715(238)
Breakfast cereal	Walnuts		14290 (2382)		23817 (7145)	2381 (476)	2381 (476)	- (14290)	4763 (1588)	4763 (1588)	23817 (14290)	3573 (715)	3573 (715)
	Corn	28580 (14290)	2041 (476)	2041 (476)	3573 (715)	1429 (357)	1429 (357)	7145 (1429)	2041 (715)	2041 (715)	14290 (1786)	2858 (715)	2858 (715)
	Oat	204 (32)	31 (8.5)	31 (8.5)	84 (17)	33 (10)	33 (10)	286 (51)	79 (21)	79 (21)	476 (65)	110 (35)	110 (35)
	Wheat	7145 (1429)	715 (286)	715 (286)	1786 (357)	715 (204)	715 (204)	3573 (715)	1429 (357)	1429 (357)	4763 (715)	1786 (1476)	1786 (1476)
Infant formula	Rice	71450 (-)	17863 (4673)	14290 (1786)	14290 (1786)	7145 (715)	7145 (715)	23817 (4763)	14290 (2382)	14290 (2382)	71450 (35725)	35725 (7145)	35725 (7145)
	Milk	20414 (14290)	2041 (476)	2041 (476)	-	1786 (476)	1786 (476)	-	-	-	-	-	-
	Barley	23817 (-)	715 (119)	715 (119)	-	23816 (1786)	23816 (1786)	-	-	-	-	-	-
	Rice	357 (75)	159 (43)	159 (43)	23817 (-)	476 (159)	476 (159)	-	-	-	-	-	-
	Oat	68 (11)	18 (5.2)	18 (5.2)	715 (-)	26 (8.26)	26 (8.26)	-	-	-	-	-	-
Wine	Wheat	1588 (238)	340 (102)	340 (102)	14290 (-)	286 (119)	286 (119)	-	-	-	-	-	-
Infant cereal	Milk	476 (75)	179 (53)	179 (53)	159 (65)	159 (65)	159 (65)	476 (159)	476 (159)	476 (159)	1429 (143)	179 (40)	179 (40)
Pork		1429 (357)	102 (32)	102 (32)	204 (39)	89 (23.8)	89 (23.8)	357 (62)	158 (42)	158 (42)	476 (79)	204 (60)	204 (60)
Coffee													
Cocoa													
Cumulative		38.6 (6.32)	8.07 (2.31)	8.07 (2.31)	36.6 (8.77)	9.28 (2.81)	9.28 (2.81)	102 (21.7)	34.0 (9.53)	34.0 (9.53)	119 (20.7)	34.0 (9.52)	34.0 (9.52)

^aNot applicable due to zero exposure levels. MOS values are calculated with the JECFA PTWL, divided by 7 for daily exposure, as the reference metric

Table 4

MOS for mean and (p95) OTA exposures for US 'total population', and 'consumers' based on NCRI.

Food type	Commodity	12 month-old			>12 moths-5 year-old			>6-18 year-old			>18 year-old		
		Total population	Consumers	Total population	Consumers	Total population	Consumers	Total population	Consumers	Total population	Consumers		
Dried fruits & nuts	Raisins	10000 (- ^a)	400 (40)	1333 (400)	200 (36)	5000 (1333)	667 (133)	5000 (800)	667 (133)	5000 (800)	1000 (200)	1000 (200)	
	Dates	-	400 (200)	-	400 (67)	-	444 (133)	-	444 (133)	-	500 (100)	500 (100)	
	Figs	-	200 (200)	-	200 (40)	-	400 (100)	-	400 (100)	-	572 (200)	572 (200)	
	Prunes	-	133 (31)	-	200 (80)	-	200 (100)	-	200 (100)	-	200 (67)	200 (67)	
	Almonds	-	2000 (800)	4000 (1333)	572 (133)	6667 (2000)	800 (200)	4000 (800)	800 (200)	4000 (800)	572 (133)	572 (133)	
	Pistachios	-	-	-	80 (31)	-	200 (50)	-	200 (50)	-	200 (67)	200 (67)	
	Walnuts	-	4000 (667)	6667 (2000)	667 (133)	- (4000)	1333 (444)	6667 (4000)	1333 (444)	6667 (4000)	1000 (200)	1000 (200)	
Breakfast cereal	Corn	8000 (4000)	572 (133)	1000 (200)	400 (100)	2000 (400)	571 (200)	4000 (500)	571 (200)	4000 (500)	800 (200)	800 (200)	
	Oat	57 (9)	9 (2)	23 (5)	9 (3)	80 (14)	22 (6)	133 (18)	22 (6)	133 (18)	31 (10)	31 (10)	
	Wheat	2000 (400)	200 (80)	500 (100)	200 (57)	1000 (200)	400 (100)	1333 (200)	400 (100)	1333 (200)	500 (133)	500 (133)	
	Rice	20000 (-)	5000 (1333)	4000 (500)	2000 (200)	6667 (1333)	4000 (667)	20000 (10000)	4000 (667)	20000 (10000)	10000 (2000)	10000 (2000)	
Infant formula Infant cereal	Milk	5715 (4000)	572 (133)	-	500 (133)	-	-	-	-	-	-	-	
	Barley	6667 (-)	200 (33)	-	6667 (500)	-	-	-	-	-	-	-	
	Rice	100 (21)	44 (12)	6667 (-)	133 (44)	-	-	-	-	-	-	-	
	Oat	19 (3)	5 (1)	200 (-)	7 (2)	-	-	-	-	-	-	-	
	Wheat	444 (67)	95 (29)	4000 (-)	80 (33)	-	-	-	-	-	-	-	
Wine Milk Pork Coffee Cocoa Cumulative	-	-	-	-	-	-	-	400 (40)	-	400 (40)	50 (11)	50 (11)	
	133 (21)	50 (15)	44 (18)	44 (18)	133 (44)	133 (44)	200 (100)	200 (100)	133 (44)	200 (100)	200 (100)	200 (100)	
	400 (100)	29 (9)	57 (11)	25 (7)	100 (17)	44 (12)	133 (22)	133 (22)	44 (12)	133 (22)	57 (17)	57 (17)	
	-	-	-	-	-	-	200 (44)	200 (44)	-	200 (44)	80 (33)	80 (33)	
	-	200 (67)	200 (36)	80 (22)	400 (200)	133 (50)	1333 (200)	1333 (200)	133 (50)	1333 (200)	444 (133)	444 (133)	
	10.71 (1.77)	2.27 (0.64)	10.28 (2.47)	2.59 (0.79)	28.93 (6.07)	9.51 (2.65)	33.47 (5.8)	33.47 (5.8)	9.51 (2.65)	33.47 (5.8)	9.04 (2.67)	9.04 (2.67)	

^aNot applicable due to zero exposure levels. MOS values are calculated as the Health Canada NCRI value (4 ng/kg bw/day) as the reference metric.