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Increase in Aflatoxin Exposure in Two Populations Residing in East and West Texas, United States.

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Abstract

Although aflatoxin (AF) exposure has not been recognized as a major problem in the United States and other developed nations, recent global climate change may have a profound impact on distribution of toxigenic fungi growth and production of AFs in grain and groundnuts. Alterations in the contamination pattern can increase human dietary exposure, and further invoke public health concerns and associated disease risks. In this study, two populations from East and West Texas, known for their high risk of liver cancer, were examined for their AF exposure at three different time periods from 2004 to 2014. Serum samples (n = 1124) were collected from participants recruited for various studies from Bexar County and Lubbock County, TX, over the span of 2004 through 2014. The exposure biomarker, serum AFB_1-lysine adduct, was analyzed by HPLC-FLD and confirmed by LC-MS. Both populations showed a significant increase in detection rate, as well as median levels of serum AFB_1-lysine adduct over time, from 2.35 to 4.34 pg/mg albumin in East Texas (2007–2014), and 0.63 to 3.98 pg/mg albumin in West Texas (2004–2010). This observed shift in exposure likely represents a shift in the AF contamination pattern in the State of Texas, and may warrant further studies on risk assessment for the potential etiological effects of such increased exposures.

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Conflict of Interest

None

Keywords

aflatoxin B_1; molecular epidemiology

Introduction

Global climate change has profound impact on public health. Changes in air quality, increased extreme weather events, disease vectors and disease-causing microbes would play major roles in altering existing disease patterns (Lopez & Sekaran, 2016; Patz et al., 2005; Samet & Woodward, 2019). Increased occurrences of extreme temperatures and weather conditions, such as drought and heavy storms, could result in an increase of fungal contamination in food, both pre- and post-harvest (Cotty & Jaime-Garcia, 2007; Van der Fels-Klerx et al., 2016). Many mycotoxin-producing species, including *Aspergillus* (*A.*) and *Fusarium* (*F.*), would also have enhanced mycotoxin production rates under extreme climate conditions (Guo et al., 2008; A Medina et al., 2015). Historically, mycotoxins pose a major challenge to food security, economy, and public health (Kumar et al., 2017; Lamb & Sternitzke, 2001; Mitchell et al., 2016; Ráduly et al., 2020; Wu et al., 2011). It would thus be reasonable to expect that, with higher incidences of extreme climate conditions, concerns over these challenges would intensify over time (Angel Medina et al., 2017; Wu et al., 2011).

Aflatoxins (AF), the most well-known of mycotoxins, are a group of naturally occurring compounds produced as secondary metabolites by fungal contaminants, mainly *A. flavus* and *A. parasitics,* commonly found in corn, groundnuts, and cereal-based food. Aflatoxin B_1 (AFB_1), the signature mycotoxin and most toxic of the AF family, is classified as a Class 1 human carcinogen by the International Agency for Research on Cancer (IARC, 2002). The hepatotoxicity and genotoxicity of AFB_1 has been demonstrated in many animal studies, and epidemiological evidence has established a strong link between human exposure and high incidences of hepatocellular carcinoma in many low- and middle- income nations, including parts of Asia and Africa (IARC, 2015; Kensler et al., 2011). Consequently, long-term exposure to AF has been considered a major risk factor for liver cancer, in addition to hepatitis B and C infections (Liu & Wu, 2010).

The American Cancer Society Cancer Facts & Figures (2020) showed that the incidence and mortality of hepatocellular carcinoma (HCC) has been increasing in the United States since the 1980s (Altekruse et al., 2014; American Cancer Society, 2020; H. B. El-Serag & Mason, 1999). The current estimate of new incidences of liver and bile duct cancer for 2020 is approximately 42,810 (American Cancer Society, 2020). Texas has a historically high incidence of liver cancer, with a significant cluster found in Eastern Texas (Zhan, 2002; Zhan & Lin, 2003). The current estimate for new cases is 4,230 with 2,740 for death; both are second only to California (American Cancer Society, 2020). The US-born Latino population, which constitutes a large proportion of the population of both Texas and California, has shown disproportionally high rates of liver cancer (Pinheiro et al., 2017; Ramirez et al., 2014; Ramirez et al., 2012). While the more common causes of liver cancer in the US have been dietary- and lifestyle-based, recently there has been a surge of cases

associated with other risk factors, including Hepatitis C infection (Hashem B. El-Serag & Mason, 2000; Larsson & Wolk, 2007). In the past decade global climate change has significantly extended the growth and distribution of toxigenic fungi, thus enhancing AF exposure from contaminated food and feed and liver cancer rates in developed countries (Cotty & Jaime-Garcia, 2007; Solomon et al., 2007; Van der Fels-Klerx et al., 2016). Despite these observations, there are limited studies evaluating human AF exposure in the United States (Johnson et al., 2010; Pollock et al., 2016; Schleicher et al., 2013), and none of these have examined changes in the trend over time.

In evaluating AFB_1 exposure and potential risk, serum AFB_1-lysine adduct is a reliable long-term biomarker and has been applied for different population studies. This adduct is formed as a part of the metabolic pathway of AFB_1, where the AFB_1-diol byproduct binds to lysine residues in albumin. This is the only serum protein shown to bind AFB_1 significantly, and can be released via enzymatic digestion for quantification purposes (Sabbioni et al., 1987). As the half-life of serum albumin is approximately 20–25 days, serum AFB_1-lysine can reflect an exposure history of up to 3 months, with considerably less variation in concentration when compared to urinary biomarkers (Peters Jr, 1995; Sabbioni et al., 2020; Sabbioni & Turesky, 2017). This biomarker has been validated in both animal and human studies and is considered a reliable biomarker for assessing chronic AFB_1 exposure (Kensler et al., 2011; Sabbioni et al., 1990).

In this study, we assessed AF exposure in archived human serum samples collected from previously conducted studies in West and East Texas, spanning from years 2004 through 2014, and evaluated trends associated with the exposure pattern.

Materials and Methods

Chemicals and Supplies

AFB_1-lysine adduct standard was biosynthesized and purified as described by Sabbioni et al (Sabbioni et al., 1987). Albumin determination reagent (bromocreosol green) and normal human serum used for normalization were purchased from Sigma Aldrich Chemical Co. (St. Louis, MO), while albumin standard was acquired from Pointe Scientific (Canton, MI, USA). Pronase (25 kU, Nuclease-free) was purchased from Calbiochem (La Jolla, CA). Protein assay dye reagent concentrate was obtained from Bio-Rad Laboratories Inc. (Hercules, CA). Total protein standards, ammonium hydroxide, ammonium phosphate monobasic, and formic acid were purchased from Sigma-Aldrich (St. Louis, MO, USA). Mixed mode solid phase extraction (SPE) cartridges were purchased from the Waters Corp. (Milford, MA). All other chemicals and solvents were of highest grade and purity available.

Study Population

Participants from East Texas were enrolled based on three zip codes within San Antonio associated with the metropolitan area of Bexar County. A High incidence of liver cancer in this area has been reported from two separate studies over a period from 2007 to 2014. The first study examined biomarkers of AF exposure in a population at high risk for hepatocellular carcinoma (Johnson et al., 2010), and the second evaluated the potential

chemopreventive effects of calcium montmorillonite clay with the samples from baseline analysis (Pollock et al., 2016). In two other studies, participants from West Texas consisted of healthy volunteers over a period from 2004 to 2010. The first study was a Phase I clinical trial to evaluate the safety of NovaSil clay (Wang et al., 2005), and the second study was designed to evaluate the modulative effects of green tea polyphenols and tai-chi practice on minimizing oxidative damage biomarkers in postmenopausal women with osteopenia (Guoqing Qian et al., 2012). For both populations, the cumulative serum samples totaled 1124, and represented three different time points (2007–2008, 2012–2013, and 2013–2014) for East Texas, and three different time points (2004–2005, 2006–2007, and 2009–2010) for West Texas. All samples were immediately stored at −80 °C freezer after collection and were analyzed shortly afterwards. This study was compliant with human research guidelines from the respective Institutions, and informed consent was acquired from study all participants for the respective studies with the approval of the Institutional Review Boards at Texas Tech University Health Science Center and Texas A&M University.

Quantification of Serum AFB_1-Lysine

Protocols and procedures for sample preparation and adduct concentration and purification, and AFB_1-lysine analysis via HPLC-fluorescence detection using an Agilent 1100 HPLC system were as previously reported (G. Qian et al., 2013). Briefly, 150 μl aliquots from individual serum samples were digested with Pronase according to total protein concentration for each serum sample as determined using the Bradford protein assay for 3 hours in a 37°C water bath. The digest then underwent solid phase extraction using Oasis MAX SPE column (Waters Co., Milford, MA) to obtain purified content eluted in 1 mL methanol containing 2% formic acid. The eluants were then dried using a Labconco Centrivap concentrator (Kansas City, MO), reconstituted with 150 μl 25% methanol, and loaded into vials for injections into HPLC. AFB_1-lysine was detected using an Agilent 1100 HPLC-fluorescence detection system (Agilent Technologies, Wilmington, DE, USA) at wavelengths of 405 and 470 nm for excitation and emission. Chromatographic separations were achieved using a Zorbax Eclipse XDB-C18 reverse phase column (5μm, 4.6 × 250 mm), with a gradient of Buffer A and B (20mM $NH_4H_2PO_4$, pH 7.2, and 100% methanol, respectively), allowing separation within 25 minutes at flow rate of 1.0 ml/min. Injection volume for all samples was 100 μl. Retention time for AFB_1-lysine adduct peak was 13.1 minutes. Typical chromatograms of AFB_1-lysine standard, samples containing low levels of AFB_1-lysine, and samples containing higher levels of AFB_1-lysine, are shown in Supplemental Figure 1. The peaks identified via HPLC-FLD were then further confirmed using an LC/MS/MS technique similar to previous studies (Xue et al., 2016), which confirmed the identity of the peak as that of AFB_1-lysine using HPLC coupled with an Agilent 6546 LC/Q-TOF system (Agilent Technologies, Santa Clara, CA). Results were manually integrated and calculated using an external standard curve, and adjusted by albumin content of corresponding samples, as determined using the BCG albumin assay. The limit of detection was 0.4 pg/mg albumin.

Statistical Analysis

Levels of serum AFB_1-lysine adducts were calculated for the mean ± SD, median, geometric mean, and the detection rate, with box-plot charts using SigmaPlot 13.0 (Systat Software

Inc., San Jose, CA). Cross-sectional one-way analysis of variance was performed to compare the means of the different time points of respective populations. Since the adduct concentrations in serum were not normally distributed, a Kruskal-Wallis test or Wilcoxon rank sum test was used to compare values among the different data groups. Additionally, a Tukey test was performed on log-transformed data values to evaluate differences between pairs of groups. A simple linear regression was also performed using log-adjusted data values to estimate the possible influence of time, with a β coefficient of greater than 0 indicating increase in exposure over time. A P value of 0.05 (two tailed) was considered significant. All statistical tests were performed using SAS ver. 9.4 (SAS Institute, Cary, NC).

Results

In East Texas (Figure 1), serum AFB_1-lysine adduct levels were significantly different among the three time points ($p < 0.0001$). AFB_1-lysine adduct was detectable in 27.33% (47/172) of serum samples collected from 2007–2008, with a median level of 2.35 pg/mg albumin. For the next sampling time point of 2012–2013, the detectability increased to 47.5% (95/200), with a median at 3.07 pg/mg albumin. For the third sampling time of 2013–2014, a 100% detectability was found (398/398) with median at 4.34 pg/mg albumin (Table 1). The overall trend displayed an increase in serum AFB_1-lysine adduct over time ($\beta = 0.3751$, $df = 1$, $p < 0.0001$), with an overall right-ward shift in population distribution of AFB_1-lysine adduct (Figure 2).

Similarly, in West Texas (Figure 3), the serum AFB_1-lysine adduct levels were significantly different among the three time points ($p < 0.0001$). The first sampling time point at 2004–2005 had a very low detectability of 9.26% (5/54), with a median level of 0.63 pg/mg albumin. For the next sampling time point at 2006–2007, the detectability increased to 32.5% (52/160), with median of 2.72 pg/mg albumin. At the third sampling time point at 2009–2010, the detectability reached 100% (140/140) with median of 3.98 pg/mg albumin (Table 1). The overall trend also displayed an increase in serum AFB_1-lysine adduct level over time ($\beta = 0.4511$, $df = 1$, $p < 0.0001$) with an overall right-ward shift in population distribution of AFB_1-lysine adduct levels (Figure 4).

Discussion

The current study examines the human exposure to AFB_1 in both East and West Texas populations using validated biomarkers of exposure (AFB_1-lysine adduct), over various time periods. We found that there is a significant increase in the median level of serum AFB_1-lysine adduct over time, from 2004–2010 in West Texas, and from 2007–2014 in East Texas. Interestingly, the median levels of AFB_1-lysine adduct for both populations, especially during the time groups where 100% detectability was found, with 4.34 pg/mg for East Texas and 3.98 pg/mg for West, are comparable to those reported in some of the high-risk areas, including parts of Africa (Hernandez-Vargas et al., 2015; Natamba et al., 2016; Passarelli et al., 2019). This same observation has been made by Pollock et al. for their baseline, as well as their post-intervention results. They also observed a three-fold increase in detectability when compared to results obtained from an earlier investigation (Johnson et al., 2010; Pollock et al., 2016).

Given the long timespan from the first sample collection, the possible degradation of the biomarker and its impact on the measured quantities is a valid concern. In the current study, all samples were collected, processed, and immediately stored at −80 °C freezer until analysis, and all analyses were performed shortly afterwards, using the same extraction and analytical methods. Previous studies have shown that AFB_1-lysine adduct is quite stable in storage conditions of −80°C freezers up to 30–40 years (Scholl & Groopman, 2008; Wang, 1996). Consequently, the storage time likely would not affect the concentrations in our studies.

AF-related toxicosis and disease etiology has not been considered as a major public health concern in the United States and other developed nations, due to strict regulatory guidelines for food and feed aflatoxin levels. The United States Food and Drug Administration has set an action level of 10–20 μg/kg in human food and 0.5 μg/kg in milk, and has imposed a mycotoxin control program that includes regulatory limits, sampling and analytical procedures, decontamination and/or reduction of risks for contaminated products (Park & Troxell, 2002). It should be noted, however, while a typical sampling protocol ensures that the samples represent the entire lot, fungal and contaminant distribution tend to be heterogeneous and may be missed during sampling, resulting in variations in consumption by the general population (Köppen et al., 2010). While there has been no comprehensive study examining food contamination of AFs in the US since the early 2000s, recent studies have observed contamination levels beyond regulatory limits, posing possible risks of AF exposure. An evaluation for grain products in Georgia found total AF levels (μg/kg) in oats, sorghum, wheat, corn, and peanuts to be 23.48±36.79, 172.34±59.14, 51.81±86.45, 8.44±12.46, and 68.22±95.58, respectively (Seawright, 2016; Seawright et al., 2016). AFs have also been detected in dried red chilies, with toxigenic non-native AF producers detected in chilies from US markets (Singh & Cotty, 2017; Singh & Cotty, 2019). The National Corn Grower's Association has recently put forth the AF Mitigation Center of Excellence Research Program, with priorities focused on amelioration, best-management, biological controls, breeding, testing and transgenic strains (National Corn Growers Association, 2019).

Additionally, consumption of contaminated food may vary by populations, and populations that frequently consume AF-contaminated food items, such as corn, as a staple, may have significantly higher risk compared to the general population. Some have speculated this dietary pattern, where food is more likely to be contaminated by AFs constitutes a large portion of the diet and may be the cause of a disproportionally higher incidence of liver cancer among US Latino populations (Ramirez et al., 2017). One recent study showed that the detection of a specific mutation associated with AF exposure (TP53R249S) among Hispanic HCC patients is associated with development of HCC at a young age and a worse prognosis, indicating a potential role of AFs in liver cancer (Jiao et al., 2018). However, to date there has been no direct evidence linking this dietary pattern, AF exposure, and liver cancer rates in the US. One potential obstacle is confounders such as lifestyle factors, that play a large role in the etiology of liver cancer in United States (Hashem B. El-Serag & Mason, 2000). While we have found a high exposure rate to AFB_1 in a specific high risk population, which is also consistent with the previous report (Pollock et al., 2016), studies

are still warranted to compare other populations at the same time frame to fully evaluate the association between AF exposure and increased liver cancer risk.

Most AFs and other mycotoxin-based assessments in United States have been limited to agricultural commodities, due to the relatively low risks presented (Park & Troxell, 2002; Yoo et al., 2018). An earlier study examining a National Health and Nutrition Examination Survey (NHANES) sample from 1999–2000, was the first attempt at using a biomarker of exposure to examine AFB_1 exposure profile. The study found that only 1% of the samples had detectable levels of AFB_1-lysine adduct, with a geometric mean of 0.842 (95% CI: 0.530–1.34) pg/mg albumin (Schleicher et al., 2013). Consequently, the current study, with high detectability and relatively high levels of AFB_1-lysine adduct found (especially in later time periods), may indicate a significant shift in the exposure profile of the US population. This shift may correspond to a shift in climate pattern, where increasing drought and high temperatures in the Southern and Southwest regions of United States make conditions favorable for fungal growth and mycotoxin contamination (Andreadis & Lettenmaier, 2006; Mitchell et al., 2016; Wu et al., 2011). In Europe, it has been demonstrated that such a shift in climate pattern has considerably increased the contamination rates of mycotoxins, and such a scenario is likely to occur in the United States as well (Moretti et al., 2019; Van der Fels-Klerx et al., 2016; Wu et al., 2011). Examining the drought index and AF biomarker levels, there is correlation ($p=0.0408$) between the severity of drought and exposure level among residents in Bexar County, when comparing data from 2007 and 2013 (Kang, 2016). The United States Drought Monitor data showed that, during the span of 2000–2020, major spikes of prolonged drought events occurred between mid-2003 through mid-2004, early 2005 through early 2007, early 2008 through 2010, 2011 through 2015, and later 2018 (NIDIS, 2020a, 2020b). Among which the drought of 2011 is the most severe, considered the worst in 50 years, with 87.99% of state area classified as D4—exceptional drought, at the peak, and spanning over 4 years with three major spikes and unusually minimal precipitation in between (NIDIS, 2020a; Nielsen-Gammon, 2011). Throughout the span of 2004 and 2014, the major drought events appears to increase in severity (NIDIS, 2020a), seemingly correlating with the conclusion we have drawn regarding human AF exposure, which seem to indicate the role of climate in the increased exposure levels found in our study. It should be noted, however, that the populations examined in our study reside in regions with historically high risk to liver cancer, instead of a broader US general population. It may require additional and more comprehensive studies using biomarkers of exposure to fully assess the potential health risk posed by AFB_1 exposure, as a result of the shift in global climate pattern.

Conclusions

In summary, this observed increase in AF exposure likely represents a shift in dietary AF contamination pattern in the State of Texas, and may warrant further studies on assessment for the potential adverse health effects of such increased exposures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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Abbreviations:

AF	aflatoxin
AFB_1	aflatoxin B_1
HCC	hepatocellular carcinoma

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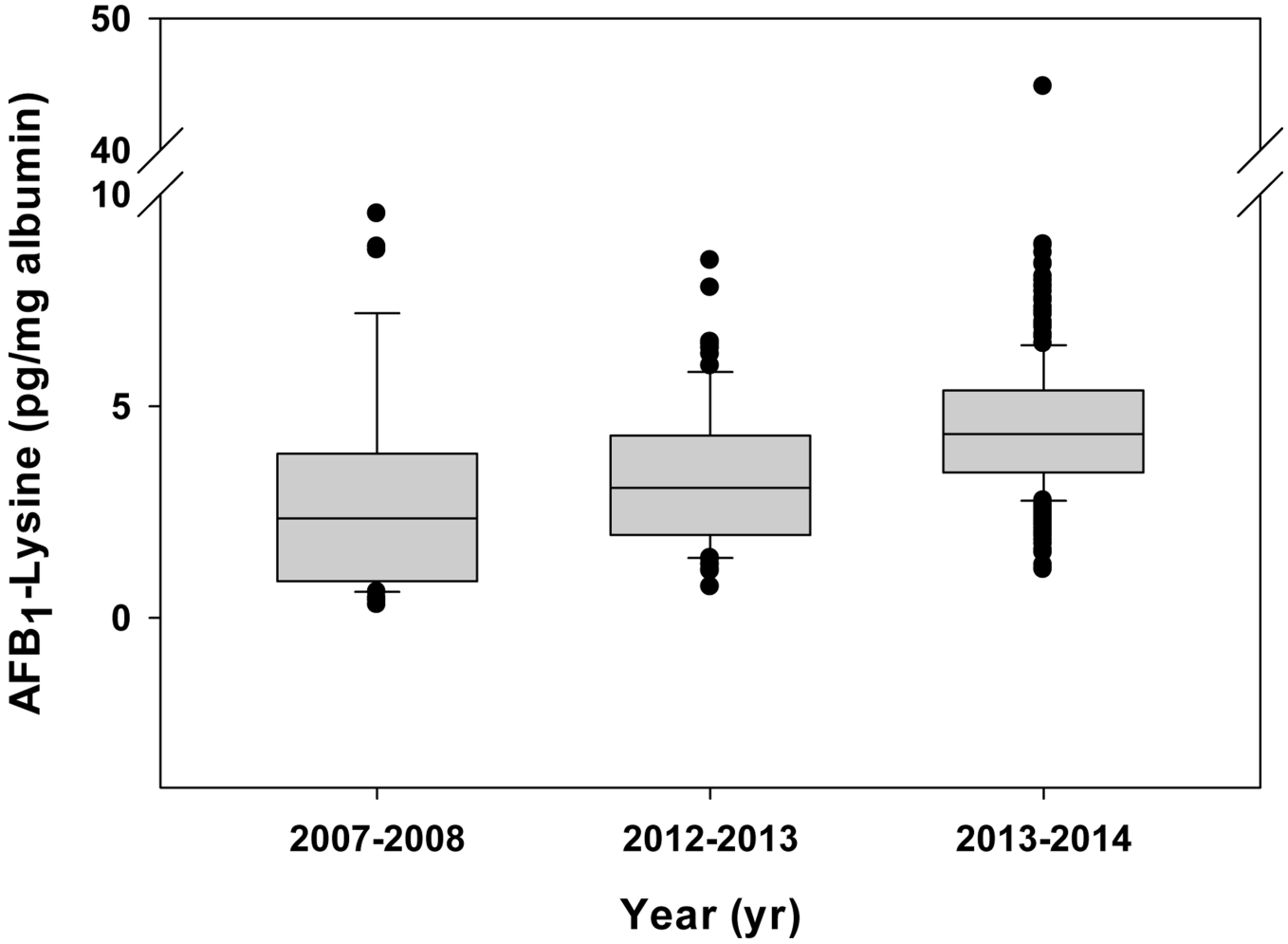

Figure 1:

AFB_1-lysine adduct levels in an East Texas population from 2007 to 2014. The boxes represent the range between the first and third quartile of sample values with the medium line; and the upper and lower bars represent 5% and 95% levels of samples, and dots represent outliers with lower and higher values.

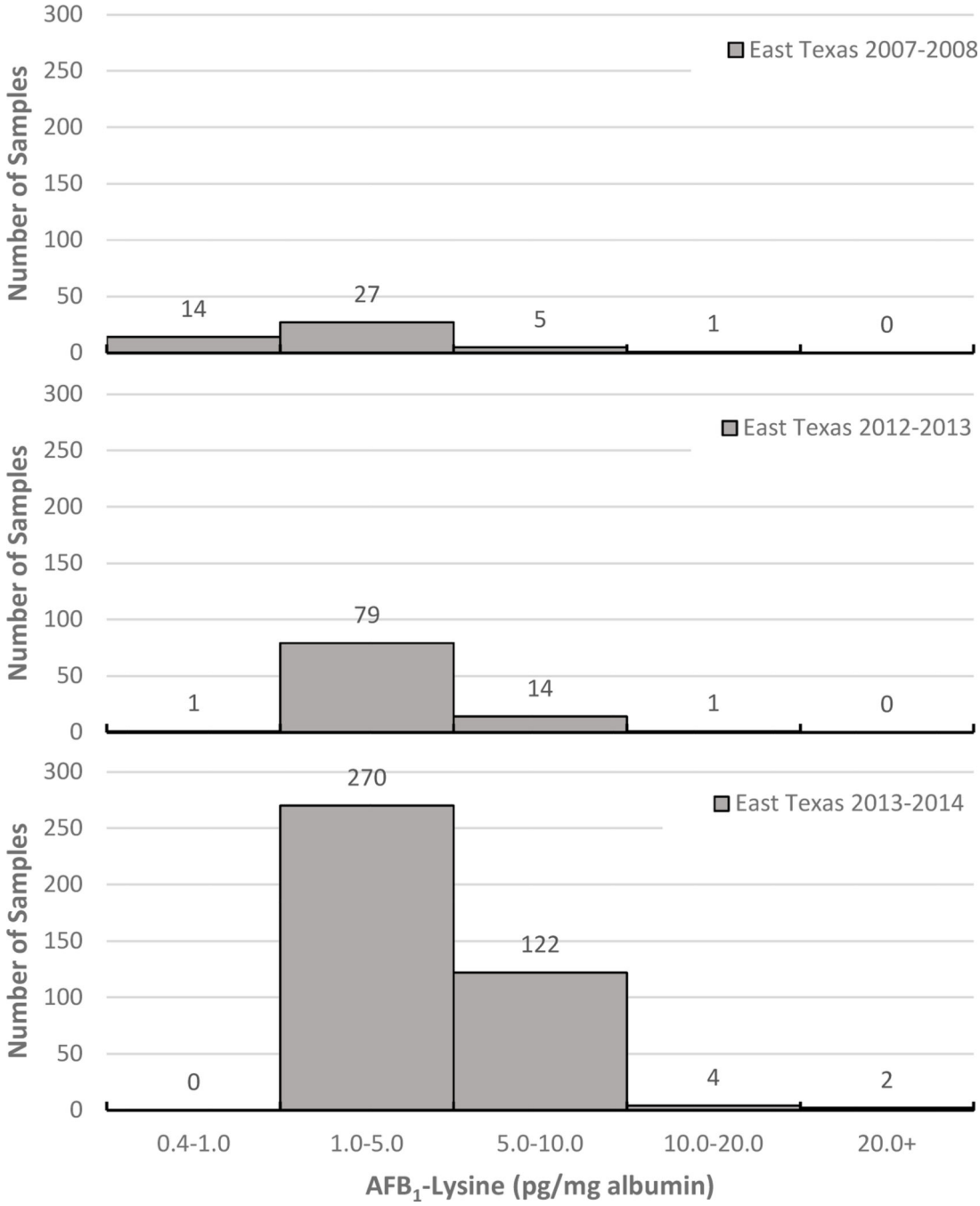

Figure 2:

Frequency distribution of AFB_1-Lysine adduct levels in an East Texas population from 2007 to 2014.

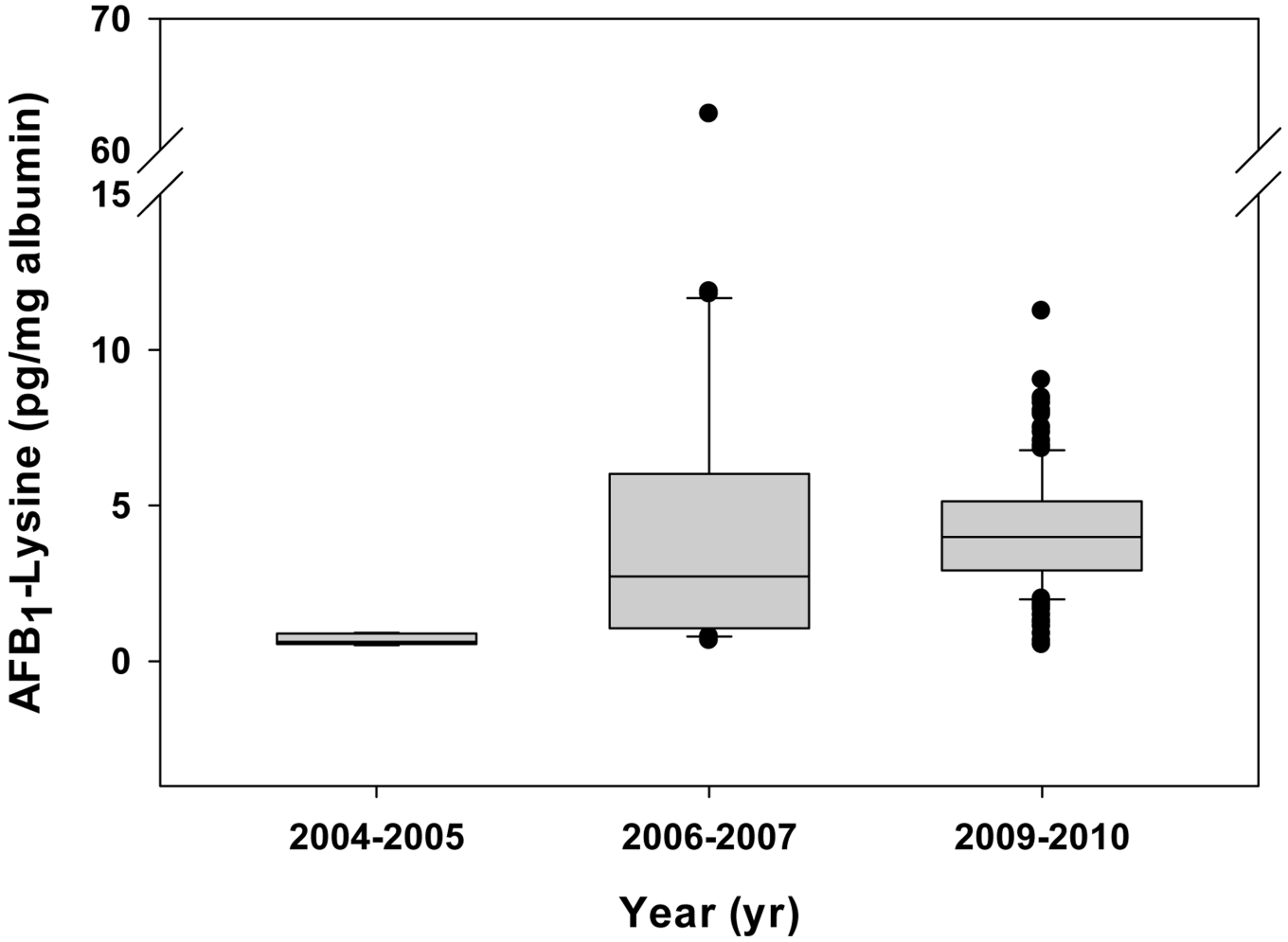

Figure 3:

AFB_1-Lysine adduct levels in a West Texas population from 2004 to 2010. The boxes represent the range between the first and third quartile of sample values with the medium line; and the upper and lower bars represent 5% and 95% levels of samples, and dots represent outliers with lower and higher values.

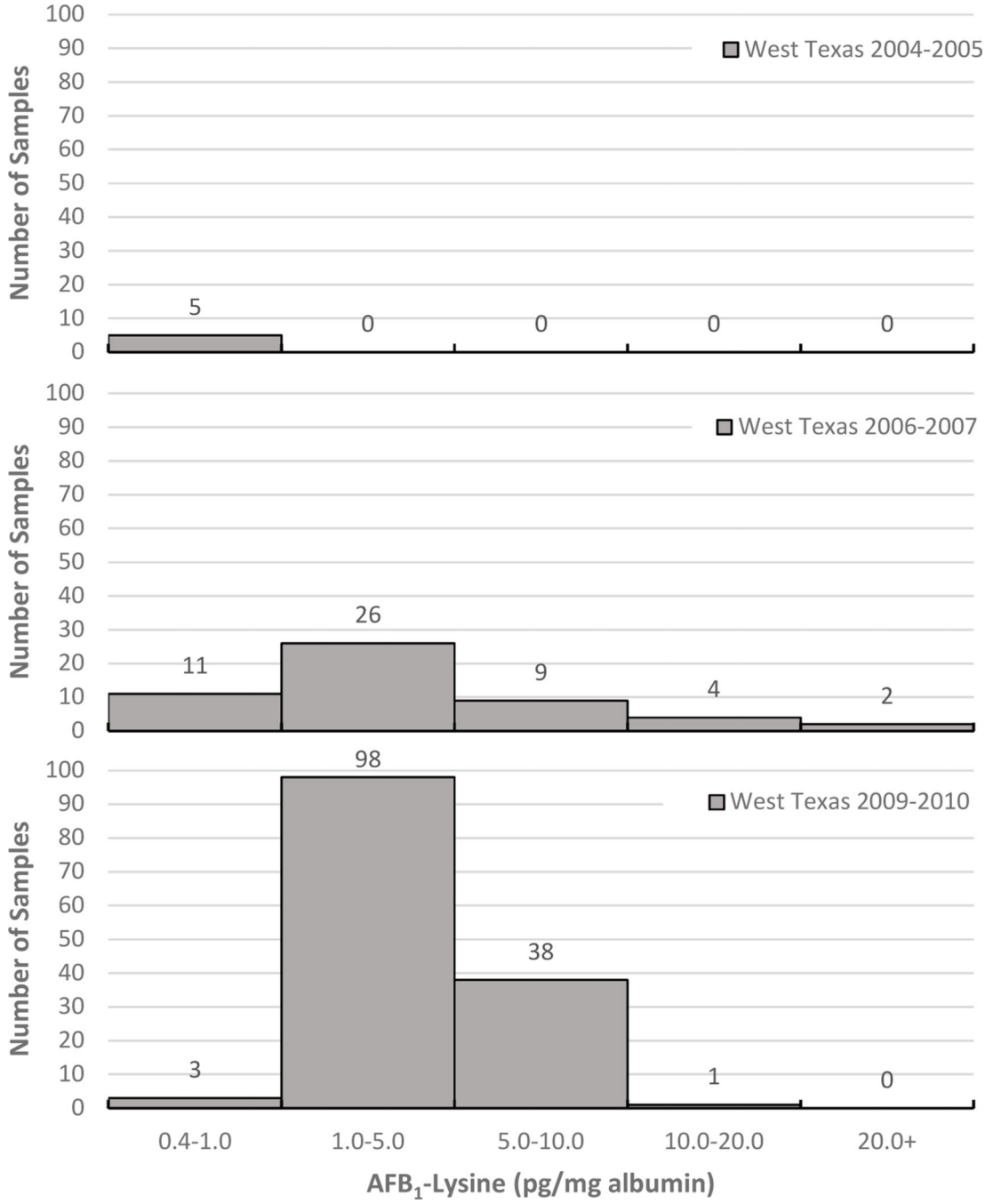

Figure 4:
Frequency distribution of AFB_1-Lysine adduct levels in a West Texas population from 2007 to 2014.

Table 1:

Summary of AFB_1-Lysine Adduct levels (pg/mg albumin) among study participants

Year	% Detectability	Mean [a]	Median [b]	Geometric Mean [c]
West Texas				
2004–2005	9.26 (5/54)	0.70 ± 0.18	0.63 (0.58, 0.88)	0.69 (−0.44, 1.81)
2006–2007	32.50 (52/160)	5.69 ± 10.34	2.72 (1.08, 5.87)	2.88 (2.09, 3.66)
2009–2010	100.00 (140/140)	4.19 ± 1.87	3.98 (2.92, 5.1)	3.74 (3.47, 4.02)
East Texas				
2007–2008	27.33 (47/172)	3.02 ± 3.03	2.35 (0.87, 3.88)	2.01 (1.28, 2.73)
2012–2013	47.50 (95/200)	3.39 ± 1.78	3.07 (1.96, 4.3)	2.97 (2.63, 3.31)
2013–2014	100.00 (398/398)	4.65 ± 2.71	4.34 (3.43, 5.37)	4.28 (4.14, 4.43)

[a] Means are expressed as mean ± standard deviation.

[b] Numerical range in parentheses indicate first and third quartile of data points.

[c] Numerical range in parentheses indicate upper and lower bounds of 95% confidence interval for the geometric mean.