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A biomarker survey of urinary deoxynivalenol in China: the Shanghai Women's Health Study

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Abstract:	Deoxynivalenol (DON) is a trichothecene mycotoxin found on wheat, maize and barley. In ecological surveys in China, DON and other trichothecenes have been implicated in acute poisoning episodes and linked with the incidence of esophageal cancer. In order to better understand exposure patterns, this pilot survey provided a combined measure of urinary un-metabolised or free DON (fD) and its glucuronide metabolite (DG) in a subset of 60 samples taken from the Shanghai Women's Health Study cohort, China. Samples were collected in 1997/1998 from women age 40–70 years. Urinary fD+DG combined was detected in 58/60 (96.7%)

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5 similar frequency, and a mean level approximately half, of that
6 previously observed for women in the UK. Wheat consumption was
7 approximately 25% of that consumed by western diets; thus DON
8 contamination of wheat may be higher in Shanghai than the UK.
9 The de-epoxy metabolite of DON, a detoxification product observed
10 in animals, was not detected, suggesting that humans may be
11 particularly sensitive to DON due to a more restricted detoxification
12 capacity.
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3 **A biomarker survey of urinary deoxynivalenol in China: the Shanghai Women's**
4 **Health Study**

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27 **Running Title:** Urinary deoxynivalenol in Shanghai
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30 **Key words:** cereal, China, deoxynivalenol, mycotoxin, Shanghai, urinary biomarker.
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34 **Abbreviations**

35 BMI – body mass index

36 DOM-1 – deepoxy- deoxynivalenol

37 DON – deoxynivalenol

38 IAC – immunoaffinity column

39 IS – Internal standard

40 MV – multivariable

41 QC – quality control
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49 **Word count 2963**
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Abstract

Deoxynivalenol (DON) is a trichothecene mycotoxin found on wheat, maize and barley. In ecological surveys in China, DON and other trichothecenes have been implicated in acute poisoning episodes and linked with the incidence of esophageal cancer. In order to better understand exposure patterns, this pilot survey provided a combined measure of urinary un-metabolised or free DON (fD) and its glucuronide metabolite (DG) in a subset of 60 samples taken from the Shanghai Women's Health Study cohort, China. Samples were collected in 1997/1998 from women age 40–70 years. Urinary fD+DG combined was detected in 58/60 (96.7%) samples (mean 5.9ng DON/mg creatinine; range nd – 30.5); a similar frequency, and a mean level approximately half, of that previously observed for women in the UK. Wheat consumption was approximately 25% of that consumed by western diets; thus DON contamination of wheat may be higher in Shanghai than the UK. The de-epoxy metabolite of DON, a detoxification product observed in animals, was not detected, suggesting that humans may be particularly sensitive to DON due to a more restricted detoxification capacity.

Introduction

Fusarium head blight or scab is an economically devastating disease of wheat, barley, and other small grain cereals worldwide (CAST 2003). In addition to the direct crop damage, *Fusarium* species also produce fungal toxins known as mycotoxins (CAST 2003; Canady 2001). These can be present in the absence of visible crop damage and are stable to processing, thus animal feed and food are frequently contaminated (Jackson and Bullerman 1999). In China, *Fusarium* infestation frequently occurs in wheat and barley growing areas in the middle and lower valleys of the Yangtze River, the mountainous areas in southwest China, and the Heilongjiang plain in northeast China (Zhang et al., 2007). One of the major *Fusarium* families of mycotoxins in this region is the type B trichothecenes, including nivalenol, 4-acetylnivalenol, deoxynivalenol (DON), 3-acetyldeoxynivalenol (3-AcDON) and 15-AcDON (Zhang et al., 2007). DON is a potent toxin affecting the immune system (reviewed by Pestka and Smoilinski, 2005; Rotter et al., 1996), the intestinal mucosa (Bouhet and Oswald 2005; Choi et al. 2009; Pinton et al. 2009) and growth in exposed animals (Prelusky 1997; Amuzie and Pestka, 2010). DON and other trichothecenes have also been implicated in acute gastrointestinal illness affecting tens of thousands of people in China over a number of decades (Luo 1994, Pestka and Smolinski 2005). In ecological studies, oesophageal cancer has also been associated with the level of trichothecenes in contaminated cereals (Hsia et al., 1988; Luo et al., 1990), though to date the imprecision of exposure assessment tools has restricted epidemiological investigations.

The combined measurement of un-metabolised or free DON (fD) and its glucuronide conjugate (DG) in urine (urinary fD+DG) has recently been validated as an exposure biomarker for DON intake (Turner et al., 2008a, 2010a). Exposure biomarkers offer improved exposure assessment over more traditional tools. In UK and French adults urinary fD+DG was frequently observed (Turner et al., 2008a, 2008b, 2010a, 2010b; Hepworth et al., 2011), but it is important to understand exposure patterns in more geographically diverse populations. Here we report pilot data from urine samples taken from participants of a population-based cohort of women in Shanghai, where both rice and wheat are dietary staples.

Methods

The Shanghai Women's Health Study methods were described in detail elsewhere (Zheng et al, 2005). Briefly, female residents of Shanghai aged 40-70 years were interviewed between 1997 and 2000. A blood sample and a spot urine sample were collected from the participants at baseline or during the first follow-up. The urine samples were kept cold and processed within 6 hours of collection for long-term storage at -70°C. A subset of sixty urine samples collected between October 1997 and June 1998 were selected to represent samples from a range of both high and low, wheat and rice intake during the past year. The study was approved by the Institutional Review Boards of all participating study centers in China and the United States.

Urinary fD+DG combined was determined essentially according to Turner et al. (2008a) with modifications described by Turner et al., (2010b) for using 1ml of urine. All reagents were purchased from Sigma and were of HPLC grade. In brief, samples were spiked with $^{13}\text{C}_{15}$ -DON as an internal standard, and following enzymic digest of any DON-glucuronide to the parent DON, Wide Bore DON immunoaffinity columns (Vicam Ltd, Watertown, MA) were used to enrich for DON, which was quantified using HPLC (Waters 2795 separations module, Milford, MA) with mass spectrometric detection (Micromass Quattro Micro triple quadrupole mass spectrometer, Manchester, UK). Selective ion recording was used to quantify the individual DON levels by reference to a response-ratio calibration curve generated by Quanlynx software. Samples were run in four batches with two QC's (urine containing 10ng DON/ml) and two negative controls (phosphate buffered saline pH 7.4). Two positive controls and two negative controls were extracted with each batch of tests samples. The mean level for the positive control was 10.4ng DON/ml urine (St. Dev 0.3), and for the negative controls all were non detectable, <0.5ng/ml. In addition, five of the test samples were analysed as blind duplicates. Data are presented as ng DON / ml of urine, in addition to ng DON / mg urinary creatinine. Urine extracts were also quantified

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3 for the de-epoxy metabolite of DON known as DOM-1, using modifications to the LC-MS
4 essentially according to Turner et al., (2010b).
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8 9 Statistical Analysis

10 Statistical analysis was conducted to assess determinants of urinary fD+DG combined.
11 Variables considered were food groups (wheat and rice combined, wheat alone and rice
12 alone), demographics (age, BMI, education), and collection time (time of day, month,
13 year). Urinary DON concentration was natural log transformed prior to statistical analysis.
14 Where numerical data are presented, back transformed values are used for ease of
15 presentation using geometric means (GM) and 95% confidence intervals (95%CI).
16 Univariate analysis was initially conducted to identify variables that may contribute to the
17 multivariate (MV) model of determinants of urinary DON. Multivariate model building
18 included variables with a p-value <0.2 from univariate analysis. Variables were considered
19 significant where $p < 0.05$. Age and BMI were retained in all MV models. Wheat intake
20 was further divided into tertiles.
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32 Results

33 Rice and wheat were the major dietary staples, with significantly ($p < 0.0001$) higher rice
34 intake (mean 162g/day, 95%CI: 147, 176g/day) compared to wheat intake (mean 45g/day,
35 95%CI: 34, 55g/day). fD+DG combined was detected in 58/60 (96.7%) urine samples
36 (mean 4.8ng DON/ml urine; range nd – 29.9; or 5.9ng DON/mg creatinine; range nd –
37 30.5ng/mg). Five samples had a second aliquot analysed separately and blindly, which
38 gave excellent precision. The means (S.D.) for each pair of data were 18.4ng/ml (1.4),
39 4.5ng/ml (0.1), 3.4ng/ml (0.2), 0.6ng/ml (0.5), 0.6ng/ml (0.5), providing additional
40 confidence in the analytical approach. DOM-1 was not detected in any urine samples.
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49 In univariate analysis, urinary DON was not significantly associated with total cereal
50 intake, wheat intake or rice intake ($p > 0.18$ for all) and, for rice only, the association was
51 inverse. Urinary DON was significantly associated with 'the time of day' of urine
52 collection ($p = 0.001$), with higher DON levels later in the day, and 'the month of
53 sampling', with lower DON levels in December and January ($p = 0.018$), and inversely with
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3 BMI ($p=0.016$). In multivariate models adjusting for age and BMI, there remained a
4 significant trend to higher urinary DON in the afternoon collected samples compared to
5 morning collected samples. Month of sampling was not significant in multivariate models.
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7 Where tertiles of 'time of day' were used (median 10am ($n=24$), 3pm ($n=20$) and 5pm
8 ($n=16$)), geometric mean DON levels were higher during the latter time points (4.8ng/mg,
9 95%CI 3.0, 7.6ng/mg, $p=0.007$ and 4.9ng/mg, 95%CI 2.9, 8.4ng/mg, $p=0.005$, for 3pm
10 and 5pm, respectively) compared to the morning collection (1.8ng/mg, 95%CI 1.2, 2.8),
11 see **Figure 1**. When tertiles of wheat intake were included in the MV model there was a
12 non-significant trend to higher urinary DON levels with increasing wheat intake, see
13 **Figure 2**. The adjusted R^2 for the latter model was 0.23.
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23 Discussion

24 In China, there is considerable variation in the amount of wheat, maize and rice
25 consumption by region. In southern China, maize and barley are rarely consumed. Our
26 limited survey of women from Shanghai confirmed this consumption pattern. Rice
27 consumption was by far the predominant cereal consumed and there was a modest
28 negative albeit non significant trend with urinary fD+DG (data not shown), in line with
29 rice not being a major source of DON (CAST 2003). Although wheat was consumed by
30 most individuals (59/60), overall intake was modest (mean 45g/day) compared to the
31 level of consumption in UK adults (mean 187g/day) (Henderson et al., 2002). This
32 generally low intake restricts the power to compare the urinary measure against wheat
33 intake. Despite average wheat intakes being four times lower in Shanghai, mean urinary
34 DON levels were only half that of those in the UK (5.9ng/mg compared to 11.7ng/mg
35 creatinine) (Turner et al., 2008b). This may reflect different levels of contamination of
36 wheat in these two regions, though this apparent discrepancy may also represent
37 differences in study design, especially in sample collection. The observed lower levels of
38 urinary DON in the mid morning may either reflect the pattern of wheat consumption in
39 this population, or may give some insight into the toxicokinetics of DON clearance. In
40 our survey, the median time for urine collection in the morning was 10am, with only one
41 sample collected before 8am, thus the majority of these were likely to be morning spot
42 urines rather than first morning voids. First morning voids would be expected to clear a
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3 high percentage of any residual DON from the previous days DON intake. There was no
4 significant difference in DON levels in early and late afternoon samples, perhaps
5 suggesting a number of hours are required before ingested DON will be transferred to
6 the urine. However, such assumptions need to be treated cautiously as not only the
7 number of samples is small, the 'time of day' patterns of wheat consumptions are not
8 known, and time comparisons are made across different individuals rather than for a
9 given individual.
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17 DOM-1 is formed by gut microbial action on DON rather than mammalian metabolism
18 (Yoshizawa et al., 1986). In part, the species variation in susceptibility to DON toxicity
19 reflects the ability of gut microbes to detoxify DON to DOM-1 (Pestka and Smolinski,
20 2005). The lack of urinary DOM-1 in samples from Shanghai, support an early study of
21 faecal metabolism that suggested that humans lack this putative detoxification route
22 (Sundstol-Eriksen and Pettersson, 2003), and thus may be more sensitive compared to
23 other species. To date DOM-1 has rarely been seen in UK adults (Turner et al., 2010b,
24 2011), but was observed, albeit at modest levels, in French farm workers predominantly
25 involved in cattle handling (Turner et al., 2010b). Overall it does not appear that
26 metabolism to DOM-1 provides protection in women from Shanghai. The potential
27 capacity for DOM-1 metabolism awaits examination in Chinese populations with higher
28 risk of DON exposure, such as those observed in Linxian (Meky et al., 2003).
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40 The variables used within these models explained about 23% of the variation in urinary
41 DON; a value similar to our earlier surveys of cereal intake and urinary DON in the UK
42 (Turner et al., 2008b, 2009) and France (Turner et al., 2010b). These pilot data from
43 Shanghai highlight that, even in a region with modest wheat intake, DON exposure was
44 frequent. It is also important to understand that DON does not occur in isolation from
45 other *Fusarium* mycotoxins. To date, exposure biomarkers for the range of additional
46 mycotoxins that frequently contaminate cereals await development and validation. To
47 fully understand the potential role of mycotoxins in human disease, it will be important
48 to develop validated multi-mycotoxin exposure tools and combine these measures with
49 established risk factors.
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3 **Figure 1. Comparison of urinary DON by time of day of sampling**
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5 Morning: median time 10am; Mid Afternoon: median time 3pm; Late afternoon: median time 5pm
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7 Geometric mean and 95%CI presented in model adjusted for age and BMI, p-values compared to
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9 Morning collection.
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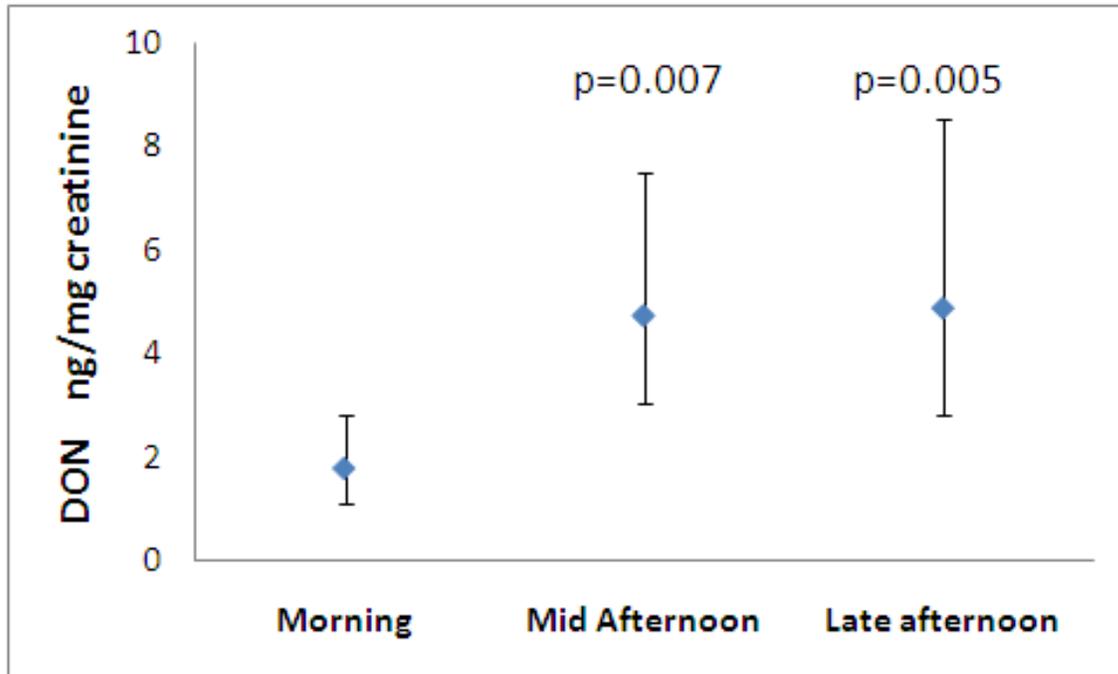
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13 **Figure 2. Comparison of urinary DON by wheat intake groups**
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16 Wheat intake groups Low: 9g/day (95%CI: 7, 11g/day); Medium: 33g/day (95%CI: 28,
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18 38g/day); High: 83g/day (95%CI: 64, 102g/day). Geometric mean and 95%CI presented in
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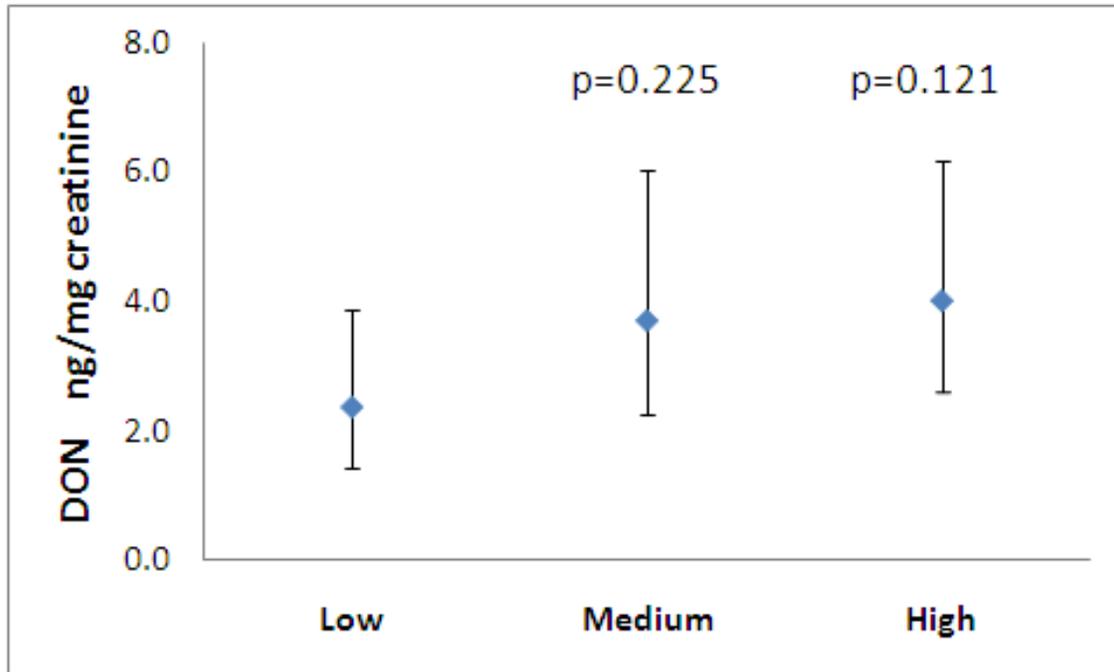
20 model adjusted for age and BMI and 'time of day', p-values compared to Low wheat intake.
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Figure 1



Urinary DON refers to the combined measured of urinary fD+DG

Figure 2



Urinary DON refers to the combined measured of urinary fD+DG