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1           **Comprehensive dietary and internal exposure assessment of**  
2 **deoxynivalenol contamination in a Chinese population using duplicate**  
3 **diet studies and urinary biomarkers**

4  
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16 **Abstract**

17 This study assessed the exposure of a considerably large Chinese population sample  
18 from the Anhui Province, China, to deoxynivalenol (DON) based on their dietary  
19 intake and urinary biomarkers. This is the first study to compare between both  
20 procedures of DON exposure detection (diet study and human bio-monitoring  
21 approach) within the same population. Food and urine samples were collected from  
22 199 healthy participants. The highest concentrations of DON and its derivatives were  
23 detected in wheat-based products. Both DON and its metabolite, DOM-1, were found  
24 in the urine samples. Total (free + conjugated) DON was detected in 99% of the  
25 samples, with a mean concentration at  $109.21 \text{ ng mL}^{-1}$ . The mean estimated dietary  
26 intake (EDI) level calculated from food consumption and contamination data was  
27 obtained as  $2.54 \pm 1.63 \text{ } \mu\text{g kg}^{-1} \text{ bw d}^{-1}$ , while the mean probable daily intake (PDI)  
28 based on urinary biomarkers was estimated to be  $3.96 \pm 4.20 \text{ } \mu\text{g kg}^{-1} \text{ bw d}^{-1}$ . A  
29 significant correlation was evidenced between EDI and PDI, both exceeding the  
30 provisional maximum tolerable daily intake. Elevated contaminant levels were  
31 observed in the adolescent group compared to children, adults, and elders, thereby  
32 indicating a potential health risk in them. The excretion rate of adolescents was  
33 approximately 2.5 times that of adult participants, possibly indicative of higher  
34 metabolic activity, which needs further in-depth investigation.

35 **Keywords**

36 deoxynivalenol; duplicate diet study; human bio-monitoring; urinary biomarkers;  
37 exposure assessment

## 38 **1. Introduction**

39 Deoxynivalenol (DON), a trichothecene mycotoxin produced by *Fusarium*  
40 *graminearum* and *F. culmorum*, is a predominant contaminant of wheat, maize, and  
41 barley throughout the world (Ali et al., 2016). Research has suggested that DON  
42 exposure in animals can prove to be toxic and cause serious problems such as emesis,  
43 anorexia, decreased body weight gain, cardiotoxicity, and immunotoxicity, as well as,  
44 impaired reproduction and development resulting from maternal toxicity (Payros et al.,  
45 2016). In view of the presence of widespread DON contamination in food and its  
46 toxic effects, many organisations and countries have set DON limit standards. In 2011,  
47 the Joint FAO/WHO Expert Committee on Food Additives (JECFA) conducted a  
48 series of risk assessments and established a provisional maximum tolerable daily  
49 intake (PMTDI) of 1  $\mu\text{g kg}^{-1}$  bw d<sup>-1</sup> for DON and its acetylated derivatives,  
50 3-acetyl-deoxynivalenol (3A-DON) and 15-acetyl-deoxynivalenol (15A-DON)  
51 (WHO, 2011). As per the Commission Regulation (EC) No. 1126/2007, the maximum  
52 DON levels in various foodstuffs were set as: unprocessed durum wheat and oats  
53 (1750  $\mu\text{g kg}^{-1}$ ), soft wheat (1250  $\mu\text{g kg}^{-1}$ ), bread, pastries, biscuits, cereal snacks and  
54 breakfast cereals (500  $\mu\text{g kg}^{-1}$ ), products such as dry pasta, cereals, cereal flour, bran,  
55 and germ meant for direct human consumption (750  $\mu\text{g kg}^{-1}$ ), and processed  
56 cereal-based baby foods and foods for young children (200  $\mu\text{g kg}^{-1}$ ). In China, the  
57 DON limit standards in grain and its products have been determined as 1000  $\mu\text{g kg}^{-1}$   
58 ((National Health Commission of PRC, 2017).

59 Deoxynivalenol contamination in crops is a common phenomenon reported across  
60 the world, including in countries like China, Japan, and the United States. Given its  
61 toxicity in animals and the potential health concerns in humans, it is necessary to  
62 conduct accurate DON exposure assessments. The two primary procedures for this  
63 include dietary exposure and biomarker-based exposure methods. As humans and  
64 animals are exposed to DON mainly by ingestion of contaminated food (Ali,  
65 Blaszkewicz, & Degen, 2016), calculation of the exposure levels based on food  
66 contamination levels and food consumption data has been well recognised as an  
67 effective and reliable way to assess human exposure to such mycotoxins via food. The  
68 exposure assessment of DON has been conducted in several countries and regions,  
69 such as the total diet studies (TDSs), in France (Siro, Frey, & Leblanc, 2013),  
70 Spain (Eduardo, María, Tania, Cristina, & Félix, 2013), Netherlands (Sprong et al.,  
71 2016), and China (Wu et al., 2015; Wu, Zhao, & Li, 2018). Biomarker-based  
72 exposure measurement in case of DON is essentially obtained using urinary  
73 biomarkers (considering the metabolic transformation of DON), and the  
74 concentrations of urinary DON can thus be employed to accurately assess their  
75 exposure risk in humans. Following ingestion, DON quickly disappears from the  
76 bloodstream and is excreted to the urine in the form of non-metabolised free DON, its  
77 phase I metabolite, de-epoxy-deoxynivalenol (DOM-1), and glucuronide conjugates  
78 (DON-GlcA) like DON-3-glucuronide (DON-3-GlcA) and DON-15-glucuronide  
79 (DON-15-GlcA). In humans, most of the ingested DON is metabolised as DON-GlcA  
80 (phase II metabolism), the process being catalysed by UDP-glucuronosyl-transferase.

81 In addition, the gut microbiota present in human intestine has been found to detoxify a  
82 small portion of DON to DOM-1, and conversion to glucuronide conjugates, which  
83 are then excreted in the urine (Gratz, Duncan, & Richardson, 2014). This approach  
84 has been adopted for internal exposure assessment of DON in some countries  
85 including Europe (UK, France, Croatia, Austria, Germany, Italy, Belgian, Spain,  
86 Swedish) (Cirlini et al., 2016; Föllmann, Ali et al., 2016; Gerding, Cramer, & Humpf,  
87 2014; Hepworth et al., 2012; Heyndrickx et al., 2015; Huybrechts, Martins,  
88 Debongnie, Uhlig, & Callebaut, 2015; Papageorgiou et al., 2018a; Papageorgiou et al.,  
89 2018b; Rodriguez-Carrasco, Molto, Manes, & Berrada, 2014; Rodriguez-Carrasco,  
90 Manes, Berrada, & Font, 2015; Šarkanj et al., 2013; Solfrizzo, Gambacorta, &  
91 Visconti, 2014; Turner et al., 2008a; Turner et al., 2008b; Turner et al., 2010a; Turner  
92 et al., 2011; Warth et al., 2012; Wallin et al., 2015; Warth et al., 2016; Wells et al.,  
93 2016; Wells et al., 2017), Africa (South Africa, Egypt, Cameroon, Tanzania) (Abia et  
94 al., 2013; Gong, Shirima, Srey, Kimanya, & Routledge, 2015; Piekkola et al., 2012;  
95 Shephard et al., 2013; Srey, Kimanya, Routledge, Shirima, & Gong, 2014) , and Asia  
96 (Bangladesh and Shanghai, Yunnan, Henan, Anhui of China) (Ali, Blaszkewicz,  
97 Nahid, Rahman, & Degen, 2015; Ali, Blaszkewicz, & Degen, 2016; Ali,  
98 Manirujjaman, Rana, & Degen, 2020; Deng et al., 2018; Meko et al., 2003; Turner et  
99 al., 2011) .

100 The purpose of this study was to assess the dietary intake and biomarker-based  
101 exposure of DON among the residents of Anhui province in China, using the  
102 duplicate diet method and human bio-monitoring approach. The study groups

103 comprised of children, adolescents, adults, and elders of both genders. Such  
104 diversified age groups were selected in order to understand the relation between the  
105 dietary intake and internal exposure of DON, and whether gender and age played a  
106 differential role in influencing it. Although several studies have investigated this  
107 relationship, few have focused on adolescents and children. This study is the first  
108 detailed analysis of the correlation and difference between dietary and internal DON  
109 exposure in a considerably large population sample from a high-exposure area in  
110 China.

## 111 **2. Materials and Methods**

### 112 *2.1 Chemicals and reagents*

113 Mycotoxin standards for DON (100  $\mu\text{g mL}^{-1}$ ), DOM-1 (50  $\mu\text{g mL}^{-1}$ ), 3A-DON (100  
114  $\mu\text{g mL}^{-1}$ ), 15A-DON (100  $\mu\text{g mL}^{-1}$ ), DON-3-G (50  $\mu\text{g mL}^{-1}$ ), and  $^{13}\text{C}_{15}$ -DON (10  $\mu\text{g}$   
115  $\text{mL}^{-1}$ ) were purchased from Biopure (Tulln, Austria), while the enzyme  
116  $\beta$ -glucuronidase (Type IX from *E. coli*) was obtained from Sigma-Aldrich (MO,  
117 USA). LC-MS gradient grade water, acetonitrile, methanol, formic acid, and  
118 ammonium acetate were commercially obtained from Fisher Scientific (Leicestershire,  
119 United Kingdom). All other chemicals and reagents used in this study were of  
120 analytical grade or better. The Oasis PRiME HLB 96-well  $\mu$ Elution plate (3 mg/30  $\mu\text{m}$ )  
121 was product of Waters (Milford, MA, USA). A mixed standard containing 10  $\mu\text{g mL}^{-1}$   
122 of each of the analytes was prepared in ACN/H<sub>2</sub>O (50/50, v/v) and stored at 4 °C, and  
123 working dilutions of the mixed standards were freshly prepared for each run in  
124 methanol/H<sub>2</sub>O (20/80, v/v). Similarly, the enzyme solution containing 2000 U  $\text{mL}^{-1}$  of

125  $\beta$ -glucuronidase was also prepared freshly on each day of experimentation in a  
126 phosphate buffer (0.075 mol L<sup>-1</sup>, pH 6.8).

## 127 ***2.2 Study design and population samples***

128 This study was carried out in 2016 in select rural areas of the Anhui Province (i.e.,  
129 Hao and Gao villages, Yingshang County, Fuyang City), located in east China. A  
130 sample of 199 healthy volunteers (96 male and 103 female) from 74 families offering  
131 homemade meals in Fuyang City were randomly chosen for the study and divided into  
132 four age groups. Each family was given a family code and each family member was  
133 further assigned a member code. All the participants were healthy volunteers. A short  
134 medical check-up of the participants revealed no acute or chronic illnesses, except for  
135 some infections of the upper respiratory tract. All participants consumed a mixed diet,  
136 and none of them were on a special diet. The dietary DON intakes were measured by  
137 the duplicate diet portion method, according to the WHO Guidelines (WHO, 1985).  
138 Each individual's physiological information, food samples, and urine sample were  
139 labelled with his/her unique number.

140 Samples of all cereal foods consumed by each participant during a single day  
141 (entire day) within the study period were collected and transported to the laboratory  
142 via the cold chain. In addition, we recorded the names and weights of all the food  
143 items consumed. The collected food samples were then weighed, homogenised, and  
144 subjected to analysis for detection of DON and DON metabolites. There were 244  
145 duplicate diet food samples, which mainly included cereal products such as steamed  
146 buns, noodles, rice porridges, boiled rice, baba (local pancakes made with glutinous

147 flour), baked pancakes, deep-fried dough sticks, cookies, dumplings, crispy rice,  
148 sangza soup (crispy noodle soup), beer, steamed twisted rolls, cornmeal porridge, and  
149 sweet potato porridge. Among these foods, 63 steamed buns, 64 noodles, 72 rice  
150 porridges, 25 boiled rice, 7 baba, 3 dumplings, and 10 other foods were served.  
151 Second-day morning urine samples were collected from each participant and  
152 immediately transported to the laboratory, where it was stored frozen at -70 °C until  
153 further analysis. The protocol of this study was approved by the ethics committee of  
154 the China National Center for Food Safety Risk Assessment (No. 2016030063), and  
155 all the experiments were performed according to the approved guidelines and  
156 regulations. In the case of minors who participated in this study, informed consent  
157 from their parents or guardians were duly sought.

### 158 *2.3 Analytical procedure of DON assessment in food and urine samples*

159 The collected food and urine samples were thoroughly thawed and homogenised,  
160 wherein the urine samples were centrifuged at 5000×g for 15 min to remove any  
161 debris.

162 The presence of DON and its derivatives (deoxynivalenol-3-glucoside (DON-3-G),  
163 3-and 15-acetyldeoxynivalenol (3A-DON and 15A-DON) and DOM-1 in the  
164 collected food samples was analysed using the method specified by Wu (2015). The  
165 internal standard ( $^{13}\text{C}_{15}$ -DON, 1 mg L<sup>-1</sup>) was mixed into 2.0 g of the sample, followed  
166 by extraction with 10 mL ACN/H<sub>2</sub>O (86/14, v/v) with rigorous shaking for 1.5 h  
167 before centrifugation at 9000×g for 15 min. The supernatant (5 mL) was further

168 cleaned via MultiSep®226 multifunctional column. The analytes were dried with N<sub>2</sub>  
169 and dissolved with 1 mL of ACN/H<sub>2</sub>O (20/80, v/v) prior to LC-MS/MS analysis.

170 The analysis of urinary DON was performed based on our previous work- Deng et  
171 al. (2018). The urine samples were spiked with the internal standard, <sup>13</sup>C<sub>15</sub>-DON, and  
172 then 1 mL of the sample was digested with 2000 U of β-glucuronidase. The mixture  
173 was incubated in a shaking water bath at 37 °C for 18 h for digestion. After being  
174 cleaned via Oasis® PRiME HLB μElution Plate, the sample was analysed using  
175 LC-MS/MS.

176 The identification and quantification of the contaminants was performed in an  
177 ACQUITY UPLC™ I-Class system (Waters, MA, USA) connected to a Xevo® TQ-S  
178 tandem quadrupole mass spectrometer (Waters, MA, USA), equipped with an  
179 electrospray ionisation (ESI) source. Chromatographic separation of DON and its  
180 metabolites was accomplished on a CORTECS™ UPLC® C18 Column (2.1×100 mm,  
181 1.6 μm, Waters, MA, USA), detected under a multi reaction monitoring (MRM) mode,  
182 and quantified by the isotope internal standard.

## 183 ***2.4 Dietary exposure assessment of DON***

### 184 *2.4.1 Estimated intake of DON from food*

185 The estimated daily intakes (EDI) of DON were calculated based on the food  
186 consumption data of the surveyed population and concentrations of DON, 3A-DON,  
187 and 15A-DON in the food samples. The formula is as follows (Wu, 2015):

$$188 \quad EDI = \frac{\sum c \times m}{w}$$

189 where  $C$  = total concentration of DON, 3A-DON, and 15A-DON in food sample ( $\mu\text{g}$   
190  $\text{kg}^{-1}$ ),  $m$  = food consumption ( $\text{kg d}^{-1}$ ),  $W$  = the individual body weight of each  
191 participant (kg).

#### 192 *2.4.2 Probable intake of DON based on biomarkers present in daily urine excretion*

193 The probable daily intake (PDI) of DON was calculated using urinary biomarkers  
194 based on the formula:

$$195 \quad PDI = \frac{C \times V \times 100}{W \times E}$$

196 where  $C$  = total DON concentration ( $\mu\text{g L}^{-1}$ ),  $V$  = daily urine excretion (L),  $W$  = body  
197 weight of each participant (kg),  $E$  = excretion rate (%). In the calculation, the mean  
198 daily urine excretion was assumed to be 0.5 L for children and 1.5 L for adults (Gong et  
199 al, 2015; Haga and Sakata, 2010). The excretion rate was considered to be 68%, with  
200 52% as DON-glucuronides and 16% as free DON (Warth et al., 2013).

#### 201 *2.5 Statistical analysis*

202 If the concentration of DON and its derivatives in the food and urine samples were  
203 below the limit of detection (LOD), then a value of half their respective LODs were  
204 considered for the statistical analysis (Haga et al., 2010; Piekkola et al., 2014). The  
205 independent sample t-test and ANOVA was employed to test for significant  
206 differences between the sub-groups at  $p < 0.05$ . Furthermore, the correlations of total  
207 DON with free DON and total DOM-1, and of EDI with PDI were analysed using the  
208 Spearman's rank correlation coefficient. All statistical analyses were conducted using  
209 SPSS, version 19 (SPSS, Chicago, IL, USA).

### 210 **3. Results and Discussion**

### 211 ***3.1 Demographic characteristics***

212 The demographic characteristics of the participants are shown in Table 1. The 199  
213 healthy volunteers (96 male, 103 female), aged between 4 to 80 years, from 74  
214 households were divided into four groups. The children's group was aged  $\leq 12$  years;  
215 adolescents, 13-18 years; adults, 19-65; and elderly,  $> 65$  years.

### 216 ***3.2 Duplicate diet analysis***

#### 217 ***3.2.1 Food consumption***

218 The duplicate diet food samples collected from the study area were analysed for  
219 DON and its derivatives using the LC-MS method. Figure 1 presents the average  
220 consumption of each food category in the participants, calculated from their  
221 individual consumption data. Mean intake of steamed buns, noodles, rice porridges,  
222 boiled rice, baba, baked pancake, dumplings, deep-fried dough stick, crispy rice,  
223 sangza soup (crispy noodle soup), beer, steamed twisted rolls, cookies, cornmeal  
224 porridge, and sweet potato porridge was obtained as 205.19, 436.13, 544.87, 115.82,  
225 16.11, 3.12, 32.40, 1.32, 1.70, 3.74, 2.51, 2.83, 0.25, 2.50, and 18.63 g d<sup>-1</sup>,  
226 respectively. In China, the results of the fifth Chinese total diet study shows that the  
227 main cereal foods consumption of Chinese population are (924.62 g d<sup>-1</sup>), beverages  
228 and water (891.58 g d<sup>-1</sup>), vegetables (404.92 g d<sup>-1</sup>), meats (95.77 g d<sup>-1</sup>), legumes  
229 (87.55 g d<sup>-1</sup>), potatoes (81.36 g d<sup>-1</sup>) (Wu, 2015). Wheat and rice constitute the staple  
230 foods, although there may be regional variations in the consumption pattern. Similarly,  
231 in this study, steamed buns, noodles, rice porridges, boiled rice were observed to be  
232 the main types of staple food, of which rice porridge marked the highest consumption.

233 In the eastern region of China, there has been a decrease in the consumption of  
234 maize since the 1980s. Similar changes in the consumption pattern could be observed  
235 in the Anhui rural areas during our survey using the duplicate diet method.  
236 Consequently, the intake of maize and other coarse cereals were less, as compared to  
237 rice and wheat, which were the predominant cereals.

### 238 *3.2.2 Concentrations of DON in food samples*

239 Table 2 lists the mean and median concentrations, of DON and its derivatives  
240 (DOM-1, DON-3-G, 3A-DON, and 15A-DON), their concentration ranges, and  
241 detection rate in the duplicate diet food samples. As can be seen from the table, the  
242 mean concentration of DON at  $151.7 \pm 223.0 \mu\text{g kg}^{-1}$  (ND  $\sim 1770 \mu\text{g kg}^{-1}$ ) was the  
243 highest, followed by DON-3-G levels at  $18.32 \pm 30.63 \mu\text{g kg}^{-1}$  (ND  $\sim 297.8 \mu\text{g kg}^{-1}$ ).  
244 Similarly, DON was the main contaminated toxin in terms of the detection rate,  
245 followed by DON-3-G and DOM-1, while 3A-DON and 15A-DON displayed the  
246 lowest rates.

247 Figure 2 shows the mean concentrations of DON and its derivatives in each food  
248 category. As can be observed, the concentrations of these contaminants in wheat  
249 (steamed buns, noodles, dumplings, and other wheat products) and glutinous rice  
250 products (baba) were significantly higher than in rice products (rice porridge, boiled  
251 rice, etc.). Furthermore, within the wheat products, steamed buns revealed higher  
252 concentrations than dumplings and noodles.

253 Data from across the world has shown that DON and its derivatives (DON-3-G,  
254 3A-DON and 15A-DON) mainly contaminate wheat, barley, oats, and maize, as

255 opposed to lesser contamination in rice and sorghum (Lu and Yang, 2015). In wheat  
256 and its associated products, the concentrations of DON, DON-3-G, 3A-DON, and  
257 15A-DON are largely affected during the processing stage (Kostelanska et al., 2011;  
258 Pacin et al., 2010; Wu & Wang, 2016). Previously published data has suggested that  
259 DON concentration in steamed buns increased by nearly twice than its initial content  
260 in flour, while that of DON-3-G decreased significantly as it (and other derivatives)  
261 converted to DON (Zhang & Wang, 2014). Wu and Wang (2016) have reported that  
262 throughout the Chinese steamed bread making process, DON remains stable, while  
263 3-ADON and 15-ADON get partially deacetylated and transform to DON during  
264 kneading (54.1–60.0% and 59.3–77.5%, respectively), fermentation (64.0–76.9% and  
265 78.2–91.6%, respectively), and steaming (47.2–52.7% and 52.4–61.9%, respectively).  
266 On the contrary, during the process of cooking noodles, DON migrates to the cooking  
267 water given its high water solubility, thereby accounting for reduced concentrations of  
268 DON and DON-3-G in the cooked noodles (Moazami Farahany & Jinap, 2011).

269 In accordance with the findings of studies conducted both in China and elsewhere,  
270 all the dietary food samples examined in this study exhibited DON and DON-3-G as  
271 the most prevalent forms among the DON-related compounds. Of the 244 dietary  
272 samples collected in this study, the detection rate of DON was obtained as 70.5%  
273 ( $151.7 \pm 223.0 \mu\text{g kg}^{-1}$ ), and that of DON-3-G as 54.9% ( $18.32 \pm 30.63 \mu\text{g kg}^{-1}$ ).  
274 Another similar study in Anhui Province based upon 709 grain samples collected  
275 from 2010 to 2014 obtained 100% detection rate for DON (Jin et al., 2016). These  
276 results demonstrate the higher prevalence of DON in cereals in Anhui Province. The

277 contamination levels were observed to vary between different years, wherein the years  
278 with more rainfall exhibited higher than usual levels. Hence, this highlights the  
279 necessity for stronger surveillance and control of DON and its derivatives in cereals.

### 280 ***3.3 Estimated dietary intake of DON from food***

#### 281 *3.3.1 Dietary intake of DON*

282 The Estimated dietary intake (EDI) of DON was calculated based on concentrations  
283 of DON, 3A-DON, and 15A-DON in food and food consumption data and expressed  
284 as  $\mu\text{g kg}^{-1} \text{ bw d}^{-1}$ . As mentioned earlier, during the analysis, if the concentrations were  
285 below the LOD, then a value of 1/2 LOD was used to produce the estimates. The EDI  
286 of DON thus obtained ranged between 0.16 and  $9.78\mu\text{g kg}^{-1} \text{ bw d}^{-1}$ , with the mean  
287 level  $2.54\pm 1.63\mu\text{g kg}^{-1} \text{ bw d}^{-1}$ , and 171 of the 199 participants (85.9%) exceeded the  
288 PMTDI value set by JECFA ( $1\mu\text{g kg}^{-1} \text{ bw d}^{-1}$ ).

289 Amongst the four age groups, children had the highest EDI, with the mean value at  
290  $2.68 \pm 1.92\mu\text{g kg}^{-1} \text{ bw d}^{-1}$ , respectively, but no significant difference was present with  
291 other three groups ( $P>0.05$ ) (Table 3). Similarly, no significant difference could be  
292 found with regards to gender in all the age groups. As can be seen in Table 3, the mean  
293 EDI calculated over the total number of participants was estimated to be  $2.54\pm 1.63\mu\text{g}$   
294  $\text{kg}^{-1} \text{ bw d}^{-1}$ , wherein both values exceeded the PMTDI. This indicated a high potential  
295 risk for the subjects.

#### 296 *3.3.2 Food contribution to dietary exposure*

297 The contributions of food categories to the dietary intake of DON were investigated  
298 (Figure 3). Although the surveyed population in this study exhibited higher

299 consumption of rice and rice porridge, these food items accounted for only 4% and 1%  
300 of the dietary exposure sources of DON, respectively. In contrast, steamed buns and  
301 noodles accounted for 62% and 20%, respectively. The contribution of noodles to  
302 DON dietary exposure was lower than that of steamed buns, despite its consumption  
303 being higher, thereby showing consistency with the findings of previous studies.

### 304 **3.4 Human bio-monitoring**

#### 305 *3.4.1 Urinary DON biomarkers in the subjects*

306 As was described in the methods, urinary DON as biomarkers were used in this  
307 study to detect the prevalence of free and total (free + conjugated) DON and its  
308 metabolites in a select population of the Anhui province. This study also evaluated the  
309 occurrence of free DON (fDON) and DOM-1 (fDOM-1) by eliminating the  
310  $\beta$ -glucuronidase digestion step. Of the collected urine samples, 95.0% (n=189/199)  
311 showed positive detection for fDON and 14.6% (n=29/199) for fDOM-1. The mean  
312 fDON level was 22.47 ng mL<sup>-1</sup> (range being below the LOD at 173.2 ng mL<sup>-1</sup>), while  
313 fDOM-1 exhibited low levels in few of the samples with a mean of 0.18 ng mL<sup>-1</sup>.  
314 Following enzymatic hydrolysis, urinary tDON was determined in 99.0% (n=197/199)  
315 of the samples, with a mean value of 109.2 ng mL<sup>-1</sup> (<LOD range at 583.6 ng mL<sup>-1</sup>).  
316 The detection rate obtained for tDOM-1 was 45.2% (n=90/199), with its mean  
317 concentration being 3.01 ng mL<sup>-1</sup> (<LOD, range = 110.8 ng mL<sup>-1</sup>) (Table 4). Thus, it  
318 was observed that the concentration of DON and DOM-1 increased substantially upon  
319 treatment with  $\beta$ -glucuronidase, indicating that glucuronide conjugates are the main  
320 metabolites of both DON and DOM-1. This is consistent with the findings of previous

321 studies (Chen et al., 2017; Warth et al., 2012; Turner et al., 2011).

322 Table 5 summarises the results of recent human bio-monitoring studies of urine  
323 samples, wherein it is evident that the major metabolites of DON are DON-3-GlcA,  
324 DON-15-GlcA, and DOM-1. Recently, the presence of DON-3-sulfate as a phase II  
325 metabolite of DON has also been detected in human urine, and its concentration in the  
326 excreted urine after 24 h was found to be approximately 4% of the initial DON intake  
327 (Warth et al., 2016). Therefore, only  $\beta$ -glucuronidase was used in this study, where  
328 the results can represent most of the DON urinary metabolites.

329 Human exposure to DON through contaminated food has been widely reported  
330 from across the world (Asia, Europe, and Africa), as well as from different provinces  
331 of China. In China, DON biomarker levels in urine have been reported in healthy  
332 residents from Shanghai, Yunnan, and Henan. Nevertheless, the DON biomarker  
333 levels pertaining to the Anhui province determined in our study are by far the highest.  
334 These magnified levels indicate the regional and temporal variability of DON  
335 exposure in the Chinese population. China has five main climatic zones, each with  
336 diverse dietary habits and possibilities of food contamination, which ultimately  
337 differentially influences the exposure to DON. Bangladesh, another Asian country,  
338 also reported lower tDON values than those presented here. In addition, the overall  
339 tDON values acquired in this study were notably higher than all those reported  
340 previously from other regions, including Europe and Africa, excepting the results  
341 obtained for pregnant women in Croatia (Šarkanj et al., 2013). We believe that the  
342 urinary DON concentrations found in this study may well be the highest levels to be

343 recorded in Chinese populations, which could be partially attributed to the large  
344 consumption of cereals in this area.

345 So far, the data on the occurrence of DOM-1 in humans are still limited. While  
346 some studies detected urinary tDOM-1 following enzymatic hydrolysis by  
347  $\beta$ -glucuronidase at very low levels (Föllmann, 2016; Turner et al., 2010b; Turner et al.,  
348 2011), others did not find any presence (Hepworth et al., 2012; Papageorgiou et al.,  
349 2018a). Conversely, in our study, tDOM-1 was detected in 45.2% of the samples,  
350 which is in agreement with the findings of Henan province in China (30.5%), France  
351 (34%), Belgium (25%), and Germany (40%, 50%); but higher than that in Sweden  
352 (8%), Spain (3.7%), UK (3%), and Egypt (2%) (Ali et al., 2015; Deng et al., 2018;  
353 Huybrechts et al., 2015). Research has indicated that the production of DOM-1 may  
354 be due to the degradation of DON (detoxification) by intestinal microorganisms  
355 (Chen et al., 2017; Gratz et al., 2013). In a previously published work, Deng et al.  
356 (2018) first identified the occurrence of fDOM-1 in human urine. In this study,  
357 fDOM-1 was detected in 14.6% of the samples (mean 0.18 ng mL<sup>-1</sup>). We also  
358 discovered that the surveyed population had higher levels of tDOM-1 in their urine,  
359 which might be attributed to the higher level of DON intake.

#### 360 *3.4.2 Influence of gender and age on the biomarkers*

361 The tDON and tDOM-1 occurrence in urine were further analysed for gender and  
362 age influences. There was no significant difference in the levels of either tDON or  
363 tDOM-1 according to the gender. With respect to the age of the participants, the mean  
364 concentration of tDON was about 1.5-fold higher in adolescents ( $175.5 \pm 151.8$  ng

365 mL<sup>-1</sup>) and children (141.1 ± 107.3 ng mL<sup>-1</sup>) than in adults (91.16 ± 96.39 ng mL<sup>-1</sup>)  
366 and the elderly group (79.04 ± 6.49 ng mL<sup>-1</sup>), with significant differences between the  
367 four groups (Table 6). However, the tDOM-1 levels did not exhibit any significant  
368 difference.

369 Recent studies have found significant gender-based variations in animal response to  
370 DON exposure, but few studies have elucidated this in humans. In animals, including  
371 mice and pigs, males were more sensitive to DON exposure than females. In humans,  
372 no such significant gender-based differences have been found, as apparent from  
373 studies conducted over various populations in Tanzania, the UK, and Italy (Gong et  
374 al., 2015; Solfrizzo et al., 2014; Srey et al., 2014; Turner et al., 2010b), although  
375 countries like Spain and Cameroon did display notable variations (Ediage et al., 2012;  
376 Rodriguez-Carrasco et al., 2014). However, the small sample size of these studies  
377 may not reflect the influence of gender differences in DON exposure in a statistical  
378 significant or reliable manner. In contrast, this study used a larger sample size of 199  
379 urine samples to evaluate the gender differences, wherein the results verify an absence  
380 of significant variation with respect to both tDON and tDOM-1 exposures.

381 There is very little data on DON exposure in children and adolescents, although  
382 they should receive more attention given their high food intake in terms of per  
383 kilogram of body weight and possible differences in metabolism compared to adults.  
384 As evident in Table 6, the mean concentrations of tDON were higher in adolescents  
385 and children (though with no significant difference between them, p=0.526) as  
386 compared to the means in adults and the elderly (p=0.001). This is similar to the

387 Spanish data provided by Rodriguez-Carrasco et al. (2014). However, in the UK, the  
388 mean tDON concentration was higher in children (41.6 ng mg<sup>-1</sup> creatinine) than in  
389 adolescents (21.0 ng mg<sup>-1</sup> creatinine) (Papageorgiou et al., 2018a). In Bangladesh, the  
390 average DON level was about 2-fold higher in infant (3.8 ± 2.9, max 6.8 ng mg<sup>-1</sup>) than  
391 in children urines (1.6 ± 1.8, max 8.6 ng mg<sup>-1</sup>) (Ali et al., 2020), probably owing to  
392 the smaller body size and higher relative dietary intake of DON contaminated  
393 foodstuff of infants compared with children. Regarding the analysis of DOM-1 in this  
394 study, no significant gender and age differences were revealed, but its occurrence in  
395 the excreted urine was similar amongst all members of the same family. This could  
396 possibly be related to the similar gut microbiota composition of the family members  
397 given their shared environment and diet, and thus identical intestinal degradation of  
398 DON to DOM-1.

399 The correlation comparison between different urinary biomarkers demonstrated  
400 significant relation between the levels of fDON and tDON (Figure 4a, r=0.890,  
401 P<0.01). Free DON accounts for only 20.1% of tDON, which indicates that about 80%  
402 of the tDON is present as conjugated forms (mainly D-3-GlcA and D-15-GlcA). This  
403 is in accordance with the findings of previous studies (Maul et al., 2012; Warth et al.,  
404 2012). These results confirm that the content of tDON post enzymatic pre-treatment  
405 tends to be much higher than in the absence of hydrolysis. Thus, compared to fDON,  
406 tDON proved to be a more important urinary biomarker in reflecting the dietary  
407 exposure to DON. On the contrary, a weak correlation existed between tDOM-1 and

408 tDON (Figure 4b,  $r=0.019$ ,  $p<0.01$ ) in the 90 positive samples, where urinary tDOM-1  
409 concentration was only 8.59% of the tDON level.

### 410 ***3.5 Estimated dietary DON intake assessed from urinary biomarkers***

411 As can be seen in Table 7, the mean PDI of the participants in total were estimated as  
412  $3.96\pm 4.20 \mu\text{g kg}^{-1} \text{ bw d}^{-1}$ , both exceeding the PMTDI. About 80% of the participants  
413 exceeded the PMTDI set by JECFA ( $1\mu\text{g kg}^{-1} \text{ bw d}^{-1}$ ) (Warth, et al., 2013).  
414 Adolescents exhibited the highest PDI, with a mean of  $7.49 \pm 6.63\mu\text{g kg}^{-1} \text{ bw d}^{-1}$ ,  
415 respectively, and 89.3% exceeding the PMTDI. Their values were also notably higher  
416 than the other three age groups ( $P<0.05$ ). Children (mean =  $4.21 \pm 3.51\mu\text{g kg}^{-1} \text{ bw d}^{-1}$ ),  
417 adults ( $3.22 \pm 3.31\mu\text{g kg}^{-1} \text{ bw d}^{-1}$ ), and elderly ( $3.03 \pm 3.05\mu\text{g kg}^{-1} \text{ bw d}^{-1}$ ) showed  
418 relatively lower PDI, with no significant difference ( $P>0.05$ ). Thus, the overall  
419 obtained results indicate a high potential risk of exposure to DON via foodstuffs in  
420 this area.

### 421 ***3.6 Relationship between dietary intake and DON exposure***

422 The EDI of DON obtained in this study  $2.54\pm 1.63\mu\text{g kg}^{-1} \text{ bw d}^{-1}$  was slightly higher  
423 than that reported from Lebanon ( $1.56\mu\text{g kg}^{-1} \text{ bw d}^{-1}$ ) and the United states ( $1.50\mu\text{g}$   
424  $\text{kg}^{-1} \text{ bw d}^{-1}$ ); near similar to Norway ( $2.6\mu\text{g kg}^{-1} \text{ bw d}^{-1}$ ); and significantly higher than  
425 that reported from most other countries, such as Denmark, the United Kingdom,  
426 Belgium, Germany, France, Austria, Netherlands, Portugal, Canada, and Ireland,  
427 where the values ranged from 0.17 to  $0.37\mu\text{g kg}^{-1} \text{ bw d}^{-1}$  (Raad et al., 2014; Sirot et al.,  
428 2013). Likewise, the mean PDI acquired here  $3.96\pm 4.20\mu\text{g kg}^{-1} \text{ bw d}^{-1}$  was slightly  
429 lower than that reported from Belgium ( $5.9\mu\text{g kg}^{-1} \text{ bw d}^{-1}$ ) and close to Croatia ( $4.1\mu\text{g}$   
430  $\text{kg}^{-1} \text{ bw d}^{-1}$ ), while significantly higher than countries such as Germany ( $0.3\mu\text{g kg}^{-1}$

431 bw d<sup>-1</sup>) and Haiti (0.27µg kg<sup>-1</sup> bw d<sup>-1</sup>) (Gerding et al., 2015; Gerding et al., 2014;  
432 Šarkanj et al., 2013).

433 We also discovered that the level of DON through internal exposure was higher  
434 than the dietary exposure levels (Table 8). There may be two possible reasons for this.  
435 Firstly, we had collected morning urine samples for this study and the DON  
436 concentrations tend to be approximately two times higher in the morning urine  
437 compared to a 24-hour urine sample. This may lead to an overestimation of the  
438 internal exposure (Warth et al., 2013). The second reason could be that all the  
439 volunteers in this study live in the rural areas of the Anhui province, where they  
440 continue to be exposed to DON related compounds through unintended environmental  
441 and occupational conditions in addition to the dietary sources of exposure. The  
442 majority of the study population had DON exposure exceeding the PMTDI. It is  
443 possibly related to the local food consumption pattern. The consumption of cereals in  
444 this area (1387 g/d) was higher than the national average (924.6 g/d from the 5<sup>th</sup>  
445 China Total Diet Study). Besides, the climate might be another reason. In 2016, the  
446 average annual precipitation of Anhui Province was nearly 40% more than usual, the  
447 highest since 1961. That might lead to an increase in mycotoxin production both in  
448 field and during storage.

449 With respect to dietary exposure, there were no significant differences in terms of  
450 gender or age, as opposed to internal exposure, where significant dissimilarity was  
451 observed between the adolescent group and the others. It has been reported by  
452 previous studies that a substantial amount of dietary DON can be rapidly excreted

453 within 24 h. Accordingly, an average excretion rate of 68% (including 52% as  
454 DON-glucuronides and 16% as free DON) in humans was used for the calculations in  
455 this study. The ratio of  $EDI_{\text{adolescents}}/EDI_{\text{adults}}$  was thus achieved as 0.912, and 2.325  
456 for  $PDI_{\text{adolescents}}/PDI_{\text{adults}}$  was. This implies that the excretion rate of adolescents is  
457 approximately 2.5 times that of adult participants. Further investigations, which take  
458 into account age-specific excretion rates, may needed to be performed for accurate  
459 internal exposure assessment. Phase II metabolism of DON in humans lead to the  
460 formation of a substantial amount of DON-glucuronides, which is also excreted in  
461 urine. The fDON to tDON ratio may reflect the metabolic efficiency of each  
462 individual; the corresponding ratios obtained in this study for adolescent and adult  
463 groups being 25.95 and 22.91, respectively. This reflects a higher metabolic activity  
464 in adolescents than in adults, which could be responsible for the high excretion rate in  
465 adolescents. More attention would need to be focussed on this aspect in future studies.

466 Significant positive correlation was found between the EDI and PDI levels of DON,  
467 thereby reflecting the relation between dietary and internal exposures (Figure 5,  
468  $r=0.306$ ,  $P<0.001$ ). Thus, it can be concluded that both food-based dietary exposure  
469 and biomarker-based internal exposure assessments can be used to evaluate human  
470 exposure to DON.

#### 471 **4. Conclusions**

472 In conclusion, this study investigated the association between dietary and  
473 biomarker-based exposure to DON in humans in a high-risk area of China using the  
474 duplicate diet method and bio-monitoring approaches. The correlation between these

475 two approaches have seldom been studied previously, especially in the case of DON.  
476 Our study is the first DON exposure assessment from the perspective of both dietary  
477 exposure and human bio-monitoring conducted over a considerably large sample  
478 population. The results obtained from the duplicate diet study ascertain DON to be the  
479 predominant analyte in food samples. The cereal sources of wheat and glutinous rice  
480 are contaminated with relatively higher DON levels, with wheat contributing to over  
481 80% of the DON intake. DON and DOM-1 were also frequently detected in the urine  
482 samples, though in lesser amounts. Total DON with a mean concentration of 109.2ng  
483 mL<sup>-1</sup> was detected in 99% of the samples, which was higher than in most populations  
484 previously studied. There were no significant differences based on gender or age in  
485 dietary exposure, while internal exposure exhibited significant variations between the  
486 adolescent group and the others, but the same did not appear with respect to gender.  
487 The PDI of DON estimated from urinary biomarker levels was higher in adolescents  
488 than in children, adults, and elders. The excretion rate of adolescents was also found  
489 to be approximately 2.5 times that of adult participants. These conditions need to be  
490 further investigated, wherein age-specific excretion rates may assist accurate internal  
491 exposure assessments. Significant positive correlation was observed between the EDI  
492 and PDI, and 85.9% (data from the EDI) and 79.4% (data from the PDI) of the study  
493 population had DON exposures exceeding the PMTDI, indicating a potential health  
494 risk in the surveyed area. Effective measures, including rigorous control procedures  
495 and enhanced monitoring, need to be undertaken to reduce such risks.

496

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501 **Conflict of interest**

502 The authors declare that there is no conflict of interest.

503

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732 **Figure Captions**

733 **Figure 1** Mean weights of each food consumed per day ( $\text{g d}^{-1}$ )

734 **Figure 2** Mean concentrations of DONs ( $\mu\text{g kg}^{-1}$ )

735 **Figure 3** Distribution of various food sources of dietary DON and its derivatives in  
736 the examined Anhui food samples.

737 **Figure 4** Scatterplot of urinary fDON (a) and tDOM-1 (b) against urinary tDON

738 **Figure 5** Scatterplot of DON dietary exposure and DON internal exposure

739

**Table 1** Demographic characteristics of the subjects (mean  $\pm$  SD (range))

Variables	Children	Adolescents	Adults	Elderly
	Age $\leq$ 12	12<Age $\leq$ 18	18<Age $\leq$ 65	Age>65
Number of subjects	37	28	83	51
Male	16	15	40	25
Female	21	13	43	26
Age (years)	6.8 $\pm$ 2.3	14.5 $\pm$ 1.3	42.3 $\pm$ 14.0	70.4 $\pm$ 3.7
Body Weight (kg)	25.0 $\pm$ 7.2 (13-50)	53.1 $\pm$ 10.2 (36-75)	62.2 $\pm$ 9.0 (40-85)	58.7 $\pm$ 10.2 (44-104)
BMI (kg/m <sup>2</sup> )	17.7 $\pm$ 4.3	20.2 $\pm$ 3.3	22.6 $\pm$ 2.9	22.4 $\pm$ 3.0

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**Table 2** Levels of DON and derivatives in food samples ( $\mu\text{g kg}^{-1}$ )

	Positive	Mean $\pm$ SD ( $\mu\text{g kg}^{-1}$ )	Median ( $\mu\text{g kg}^{-1}$ )	Range ( $\mu\text{g kg}^{-1}$ )
DON	172 (70.5%)	151.7 $\pm$ 223.0	30.92	ND~1770
DOM-1	133 (54.5%)	1.10 $\pm$ 1.65	0.15	ND~12.97
DON-3-G	134 (54.9%)	18.32 $\pm$ 30.63	2.44	ND~297.8
3A-DON	15 (6.1%)	0.50 $\pm$ 0.47	0.35	ND~3.73
15A-DON	1 (0.4%)	0.84 $\pm$ 0.44	0.70	ND~5.05

743 ND, level below LOD; positive samples refer to the levels higher than LOD.

744

**Table 3** Estimated Dietary Intake of DON across the four examined age groups

Age	Gender	Mean ( $\pm$ SD)	Median	Range	Exceeding PMTDI
		$\mu\text{g kg}^{-1}$ bw	$\mu\text{g kg}^{-1}$ bw d <sup>-1</sup>	$\mu\text{g kg}^{-1}$ bw d <sup>-1</sup>	n (%)
Age $\leq$ 12	M(16)	2.23 ( $\pm$ 1.99)	1.78	0.25-6.50	11(68.8)
	F(21)	3.02 ( $\pm$ 1.79)	2.98	0.32-7.56	18(85.7)
	37	2.68 ( $\pm$ 1.92)	2.19	0.25-7.56	29(78.4)
12 < Age $\leq$ 18	M(15)	2.26 ( $\pm$ 1.18)	2.06	0.61-5.12	14(93.3)
	F(13)	2.47 ( $\pm$ 1.21)	2.11	0.75-4.72	11(84.6)
	28	2.36 ( $\pm$ 1.20)	2.08	0.61-5.12	25(89.3)
18 < Age $\leq$ 65	M(40)	2.71 ( $\pm$ 1.75)	2.14	0.59-7.36	36(90.0)
	F(43)	2.48 ( $\pm$ 1.88)	2.04	0.16-9.78	36(83.7)
	83	2.59 ( $\pm$ 1.82)	2.11	0.16-9.78	72(86.7)
Age > 65	M(25)	2.64 ( $\pm$ 1.21)	2.35	0.92-6.09	24(96.0)
	F(26)	2.31 ( $\pm$ 1.15)	2.10	0.72-4.81	21(80.8)
	51	2.31 ( $\pm$ 1.19)	2.23	0.72-6.09	45(88.2)
Total	199	2.54 ( $\pm$ 1.63)	2.19	0.16-9.78	171(85.9)

747

**Table 4** Summary of free and total DON and it's metabolites in 199 urine samples

compound	Free				Total			
	positive	mean	median	range	positive	mean	median	range
	n(%)	$\mu\text{g L}^{-1}$	$\mu\text{g L}^{-1}$	$\mu\text{g L}^{-1}$	n(%)	$\mu\text{g L}^{-1}$	$\mu\text{g L}^{-1}$	$\mu\text{g L}^{-1}$
DON	189(95.0)	22.47	12.00	ND- 173.3	197(99.0)	109.2	77.47	ND-583.6
DOM-1	29(14.6)	0.18	ND	ND-11.06	90(45.2)	3.01	ND	ND-110.8

748

**Table 5 Occurrence of DON and its metabolites in human urine**

Countries	Sample(n)	Gender	Age	Positive n (Analyte)	Mean/median, ng mL <sup>-1</sup>	range, ng mL <sup>-1</sup>	References
<b>Europe</b>							
UK	25	16(M) 9(F)	21-59	25 (DON)	7.2(Geometric mean)	4.9-10.5 creatinine	Turner et al., 2008a
UK	300	-	-	296(DON)	9.42 µg/day	ND-65.97 µg/day	Turner et al., 2008b
France	76	-	23-74	75(DON)	6.8	0.8-28.8	Turner et al., 2010a
				26(DOM-1)	0.2	0.2-2.8	
UK	35	17(M) 18(F)	20-59	23 (DON+DON- GlcA)	17.8/13.8	5.0-78.2	Turner et al., 2011
				23 (DON)	2.4	0.5-9.3	
				1 (DOM-1)	0.3	<LOD -0.8	
UK	85	pregnant	16-44	85(DON)	10.3 creatinine	0.5-116.7	Hepworth et al., 2012
				0(DOM-1)	<LOD	<LOD	
UK	42	pregnant	20-38	On 1 day: 37 (DON+ DON-GlcA)	29.7	<LOD-436.0	Wells et al., 2016
				On 2 day: 35 (DON+ DON-GlcA)	28.7	<LOD-167.0	
				0 (DOM-1)	<LOD	<LOD	
				0 (DOM-GlcA)	<LOD	<LOD	
UK	63	11(vegetarian M)	-	On 1 day: (tDON)	13.6	<LOD-39.1	Wells et al., 2017
			-	On 2 day: (tDON)	14.5	<LOD-55.4	
		21(vegetarian F)		On 1 day: 17 (tDON)	31.1	<LOD-135.0	
				On 2 day: 19 (tDON)	22.9	<LOD-60.5	
		16 (Adult M)	18-64	On 1 day: (tDON)	13.1	2.20-29.4	
				On 2 day: (tDON)	18.1	5.10-58.8	
		15 (Adult F)	18-64	On 1 day: (tDON)	12.4	3.30-40.6	

UK	40	20(M) 20(F)	3-9	On 2 day: (tDON)	14.2	0.90-36.0	Papageorgiou et al., 2018a
				On 1 day: (tDON)	M: 22.5 F: 38.2	M:1.2-86.5 F:3.0-138.0	
UK	39	19(M) 20(F)	10-17	On 2 day: (tDON)	M: 20.6 F: 35.4	M:4.1-52.0 F:1.4-140.9	Papageorgiou et al., 2018b
				On 1 day: (tDON)	M: 20.6 F: 26.0	M:1.6-52.5 F:3.1-104.3	
UK	20	10(M) 10(F)	≥65	On 2 day: (tDON)	M: 27.0 F: 28.8	M:2.9-66.3 F: <LOD -67.2	Papageorgiou et al., 2018b
				On 1 day: 9, 9 (tDON)	M: 26.7 F: 8.0	M: <LOD -186.0 F: <LOD -28.8	
				7, 9 (fDON)	M: 5.0 F: 0.8	M: <LOD -42.0 F:0.1-1.8	
				9, 9 (DON-GlcA)	M: 21.7 F: 7.3	M: <LOD -144.0 F: <LOD -27.0	
				0, 0 (DOM-1)	M: <LOD F: <LOD	M: <LOD F: <LOD	
				On 2 day: 9, 9 (tDON)	M: 20.1 F: 8.8	M: <LOD -65.1 F: <LOD -17.5	
Croatia	40	pregnant	26-33	6, 7 (fDON)	M: 2.2 F: 1.0	M: <LOD -11.8 F: <LOD -3.3	Šarkanj et al., 2013
				9, 9 (DON-GlcA)	M: 17.8 F: 7.8	M: <LOD -53.3 F: <LOD -14.2	
				0, 0 (DOM-1)	M: <LOD F: <LOD	M: <LOD F: <LOD	
				39 (DON-15GlcA)	120.4/55.2	<LOD-1237.7	
Croatia	40	pregnant	26-33	33 (DON-3GlcA)	28.8/10.0	<LOD-298.1	Warth et al., 2016
				31 (fDON)	18.3/6.7	<LOD-275.0	
				28 (DON-3-sulfate)	4.5	<LOD-58.0	
Austria	27	-	20-63	tDON: 6(fDON)+26(DON-GlcA's)	20.4/2.4	<LOQ-63	Warth et al., 2012
Germany	101	44(M)	20-30	30 (fDON)	5.3/3.38	5.97-31.31	Gerding et al., 2014
				84 (DON-GlcA)	15.51/9.41	2.95-139.37	
Italy	52	26(M) 26(F)	3-85	50 (fDON)	11.89 /10.32	<LOD -67.36	Solfrizzo et al., 2014
Italy	55	celiac patient	-	4 (fDON)	0.22/0.00	<LOQ-8.94	Cirlini et al., 2016
				5 (DON-GlcA)	0.22/0.00	<LOQ-5.59	
				4 (fDON)	0.17/0.00	<LOQ-2.41	
Italy	50	healthy subject	-	5 (DON-GlcA)	0.17/0.00	<LOQ-5.84	Huybrechts et al.,
				32 (DON-15GlcA)	82.62	3.00 -420	
Belgian	32	-	-				

				29 ((DON-3GlcA)	10.65	<LOQ-550	2015
				8 (DOM-GlcA)	4.60	0.80-16.4	
				23 (DON)	0.436	<LOD -3.00	
Belgian	239	-	19-65	238 (DON-15GlcA)	53.8/31.2	<LOQ-460.8	Heyndrickx et al., 2015
				184 ((DON-3GlcA)	7.5/4.4	<LOQ-126.2	
				53 (DOM-GlcA)	16.9/5.8	<LOD -172.0	
				89 (DON)	3.9/1.7	<LOD -129.8	
	155	-	3-12	155 (DON-15GlcA)	58.4/42.6	4.6-301.7	
				141 ((DON-3GlcA)	10.6/7.8	<LOQ-53.0	
				26 (DOM-GlcA)	91.7/24.0	<LOD -526.1	
				109 (DON)	5.2/3.9	<LOD -27.4	
Spain	54	16	8-14	9 (DON)	DON:27.8 creatinine	<LOD -84.5	Rodriguez-Carrasco, 2014
		16	18-28	1 (DOM-1)	DOM-1:1.3	<LOD -1.3	
		22	>28	12 (DON) 0 (DOM-1)	creatinine	<LOD -69.1	
				16 (DON) 0 (DOM-1)	DON:32.9 creatinine	<LOD -56.9	
					DON:14.8 creatinine		
Spain	1	Male	26	1(fDON)	18.8	18.8	Rodriguez-Carrasco, 2015
Swedish	252	-	-	158 (DON)	3.37	-	Wallin et al., 2015
				20 (DOM-1)	0.18	-	
Germany	30	13(Male control)	-	13 (DON)	6.85/6.794	1.013-14.634	Föllmann et al., 2016
				5 (DOM-1)	0.085/0.05	LOD -0.184	
		12(Male worker)		12 (DON)	6.50/5.395	3.275-13.82	
				7 (DOM-1)	0.105/0.114	LOD -0.216	
		5(Male worker)		5 (DON)	8.084/9.326	0.85-10.395	
				3 (DOM-1)	0.11/0.11	LOD -0.228	

**Africa**

South Africa	53	Male	19-97	7 (DON)	1.52	<LOD -21.3	Shephard et al., 2013
Egypt	93	pregnant	18-40	63 (DON)	2.8(Geometric mean)	2.1-3.6	Piekkola et al., 2012
Cameroon	145	Male	18-58	8 (fDON)	<LOD	<LOD	Abia et al., 2013
				62 (DON-15GlcA)	5.49	<LOD -96.2	
				16 (DON-3GlcA)	3.93	<LOD -22.5	
				62 (tDON)	5.93	<LOD -74.69	
Tanzania	166	-	6-14 months	32 (tDON):Vist1	1.1	0.8-1.4	Srey et al., 2014
				40 (tDON):Vist2	2.3	1.7-3.2	
				38 (tDON):Vist3	5.7	4.1-7.9	
Tanzania	141	Children: 50 Mothers: 50 Fathers: 50		(DON)	15.4	10.2-23.3	Gong et al., 2015
				(DON)	45.0	31.8-63.6	
				(DON)	42.0	30.9-56.9	

**Asia**

Bangladesh	54	pregnant	18-36	28 (fDON)	0.86/0.19	<LOD -7.16	Ali et al., 2015
				0 (DOM-1)	<LOD	<LOD	
Bangladesh	62	31(M) 31(F)	22-60	Summer: 17((fDON)	0.17/<LOD	<LOD -1.78	Ali et al., 2016
				0 (DOM-1)	<LOD	<LOD	
Bangladesh	154	Infants:49	1-12 months	3 (fDON)	3.8/3.67	<LOD -6.8	Ali et al., 2020
				0 (DOM-1)	<LOD	<LOD	
		Children:105	1-6 years	37 (fDON)	1.6/1.0	<LOD -8.6	
				0 (DOM-1)	<LOD	<LOD	
China (Shanghai)	60	Female	40-70	0 (DOM-1)	5.9 creatintine	<LOD -30.5	Turner et al., 2011
China (Yunnan)	15	-	-	(DON)	Linxian: 37	14-94	Meky et al., 2003
					Gejiu: 12	4-18	
China (Henan)	150	56 (M) 95 (F)	2-78	140 (fDON)	8.25/5.48	<LOD -47.0	Deng et al., 2018
				3 (fDOM-1)	0.052/0.05	<LOD -0.23	
				151 (tDON)	47.6/32.5	1.36 -247.0	

China (Anhui)	199	96 (M) 103 (F)	46 (tDOM -1)	0.28/0.05	<LOD -6.43	This study
			189 (fDON)	22.47	<LOD -173.2	
			29 (fDOM-1)	0.18	<LOD -11.06	
			197 (tDON)	109.2	<LOD -583.6	
			90 (tDOM-1)	3.01	<LOD -110.8	



**Table 7** PDI of DON by 4 age groups

Age	Gender	Mean ( $\pm$ SD) $\mu\text{g kg}^{-1} \text{bw}$	Median $\mu\text{g kg}^{-1} \text{bw d}^{-1}$	Range $\mu\text{g kg}^{-1} \text{bw d}^{-1}$	Exceeding PMTDI n(%)
Age $\leq$ 12	M (16)	3.55 ( $\pm$ 3.56)	1.70	0.86-14.73	13(81.3)
	F (21)	4.71 ( $\pm$ 3.38)	4.15	0.69-14.80	19(90.5)
	37	4.21 ( $\pm$ 3.51)	3.54	0.69-14.80	32(86.5)
12<Age $\leq$ 18	M (15)	7.21 ( $\pm$ 6.17)	4.58	0.57-23.41	13(86.7)
	F (13)	7.80 ( $\pm$ 7.10)	4.97	0.62-26.66	12(92.3)
	28	7.49 ( $\pm$ 6.63)	4.89	0.57-26.66	25(89.3)
18<Age $\leq$ 65	M (40)	3.14 ( $\pm$ 3.43)	2.43	0.20-16.96	29(72.5)
	F (43)	3.29 ( $\pm$ 3.19)	1.98	0.01-15.51	31(72.1)
	83	3.22 ( $\pm$ 3.31)	2.07	0.01-16.96	60(72.3)
Age>65	M (25)	3.87 ( $\pm$ 3.82)	2.63	0.76-18.66	23(92.0)
	F (26)	2.23 ( $\pm$ 1.71)	2.02	0.01-6.78	18(69.2)
	51	3.03 ( $\pm$ 3.05)	2.30	0.01-18.66	41(80.4)
Total	199	3.96 ( $\pm$ 4.20)	2.71	0.01-26.66	158(79.4)

755

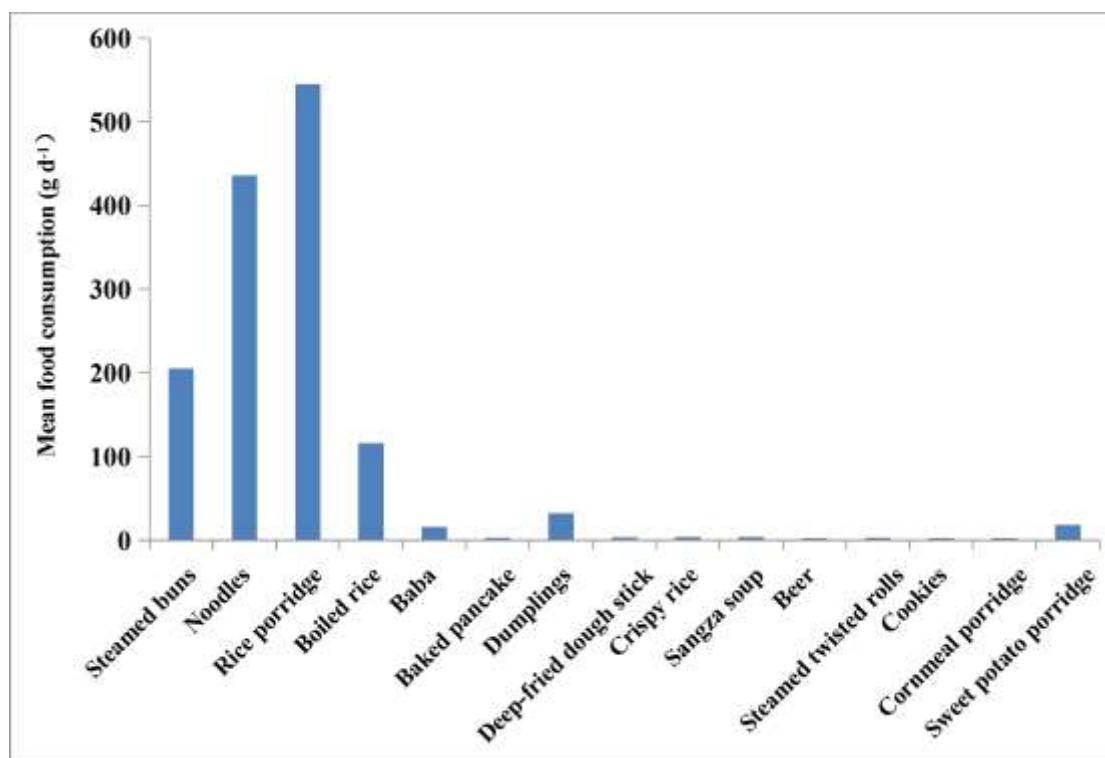
**Table 8** Comparison of dietary and internal exposure ( $\mu\text{g kg}^{-1} \text{bw d}^{-1}$ )

	Percentiles (95%CI)					Exceeding
	Mean $\pm$ SD	P50	P75	P95	Range	PMTDI
EDI	2.54 $\pm$ 1.63	2.19	3.36	6.01	0.16~9.78	171 (85.9%)
PDI with excretion rate correction	3.96 $\pm$ 4.20	2.71	5.11	11.78	0.008~26.7	158 (79.4%)

756

757

Figure 1

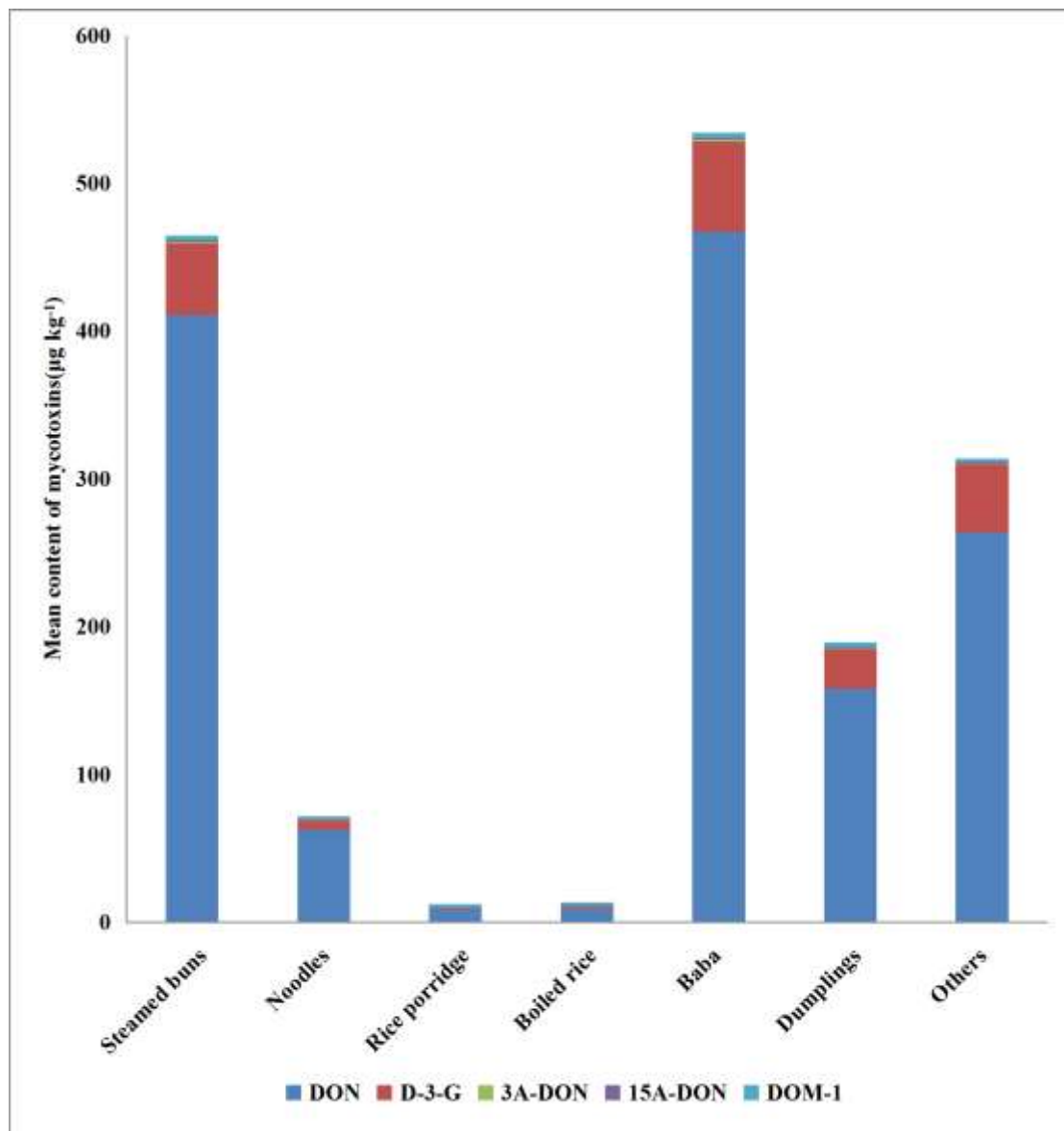


758

759

760 **Figure 2**

761

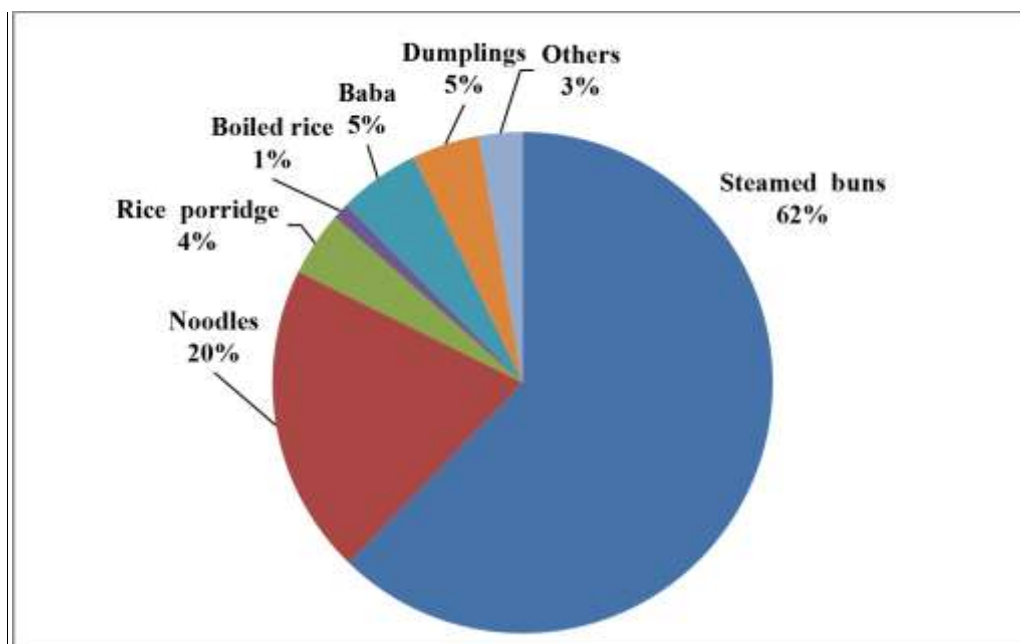


762

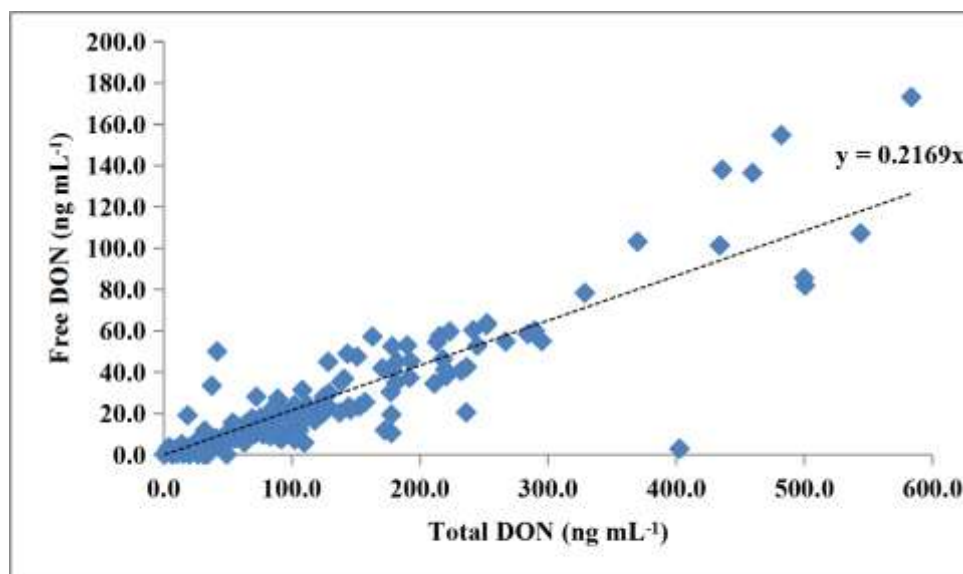
763

764

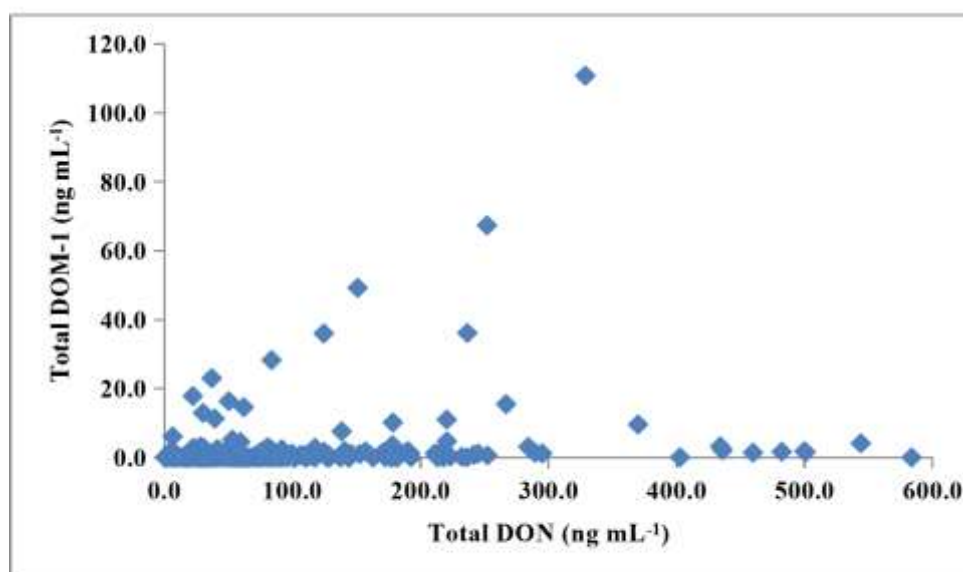
**Figure 3**



765

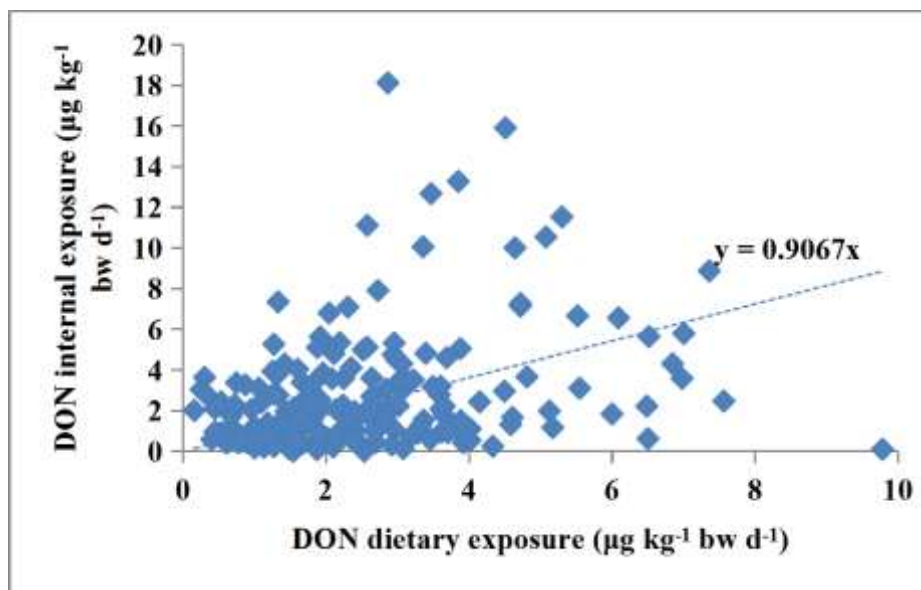


(a)



(b)

768 **Figure 5**



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