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ZEARALENONE-CONTAMINATED CEREALS IN AFRICAN COMMUNITIES, PROBABILISTIC EXPOSURES AND ADVERSE-HEALTH OUTCOMES: A META-ANALYSIS

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ABSTRACT

Zearalenone, a Fusarium spp. mycotoxin is an exposome with estrogenic properties that adversely impact global public health concerns, including African cereal-growing communities. In this study, we used the keywords; "adverse health", "cereals", "zearalenone", and "Africa" to screen published articles from Google Scholar, CrossRef, PubMed and Scopus databases. The returned queries were filtered to obtain 36 relevant articles covering 53 studies. Data including the year of study, zearalenone concentration, number of total samples and total positive samples were extracted from the included papers. The zearalenone concentrations were meta-analyzed to characterize the following: data heterogeneity, weighted averages, effect sizes, and to visualize Forest plots and regression models. The exposures were determined using zearalenone concentrations, mass of cereals ingested, and WHO-recommended body weight according to the EFSA-recommended guidelines. Based on Palisade @Risk probabilistic approaches, the uncertainties of exposures and risks (hazard quotient) were obtained after simulation at 10^5 iterations and benchmarked against PMTDI (0.25 µg/kg). The meta-analysis results presented a zearalenone contamination occurrence of 16% and a high heterogeneity (I^2 =97.9), which indicated high variability in the included articles. Zearalenone concentrations ranging from 0.90 to 1.03×10^3 µg/kg presented high occurrence in rice and rice-based products (75%), while the simulated modal exposures (µg/kg(bw)-d) ranged from 5.33×10^{-3} to 9.70×10^{-2}, the 95th percentile ranged from 1.91 to 31.60. Although the modal exposures among the age-related consumers did not exceed the regulatory threshold (0.25 µg/kg), that for infants (0.10 µg/kg(bw)-d) and toddlers (0.04 µg/kg(bw)-d) were the highest. However, the 95th percentile exposures for all the age-related consumers exceeded the threshold at different intensities, while the infants (31.60 µg/kg(bw)-d) and toddlers (13.11 µg/kg(bw)-d) exposures were significantly (HQ>1) alarming. Control measures are urgently warranted to address this public health concern.

Keywords: zearalenone, probabilistic approach, hazard quotient, cereals, African communities, risk, exposure.

INTRODUCTION

Zearalenone, a Class 3 carcinogen (IARC, 2018), is the main estrogenic mycotoxin produced by *Fusarium spp*. The name is derived from the combination of terms (Urry *et al*., 1966). The "zea" component comes from Maize (Z*ea mays*), whereas the "ral" comes from the **r**esorcylic **a**cid **l**actone portion of its structure. A double bond is also present in the structure of the mycotoxin from which the "en" is derived while the "one" is from the ketone group. Studies have shown that there is inadequate evidence of its carcinogenicity in humans. However, adverse health outcomes are reported in farmed animals fed on zearalenone-contaminated feed (Chen *et al*., 2015; Gajecka *et al*., 2011; Minervini and Aquila, 2008).

A naturally occurring non-steroidal mycoestrogen, zearalenone mainly present in maize and frequently co-occurs with other major mycotoxins such as aflatoxins, fumonisins, ochratoxin A, and deoxynivalenol (Zinedine *et al*., 2007). Zearalenone also present in raw cereals and processed cereal products in different regions globally, including Africa, and is particularly challenging in humid climates. Zearalenone is thermostable; therefore, heat-based processing operations, such as milling and extrusion, do not degrade it (Ropejko and Twarużek, 2021). The increasing global climate change presents the risk of fungal contamination of foods and feed. Thus, mycotoxin contaminations have become a matter of global public health concern.

A large workforce in African communities comprising relatively more women, especially in sub-Saharan Africa (Enete *et al*., 2002), handles the cereal grain commerce (Degraeve *et al*., 2016). Cereal consumption in sub-Saharan Africa contributes half the established per capita kilocalorie intake between 2000 and 2100 kcal/capita per day (Ssepuuya *et al*., 2018). From this amount, local rice, maize, millet, sorghum and barley form a significant staple in their native countries. Handling potentially contaminated cereals may lead to exposure. After exposure and metabolism, zearalenone and its metabolites have been reported to provoke estrogenic responses, causing changes and lesions in the reproductive systems of different female animal species (Chen *et al*., 2015; Gajecka *et al*., 2011; Minervini and Aquila, 2008; Vance *et al*., 2019; Zhang *et al*., 2018). Specifically, zearalenone is transformed in vivo through phase I reactions into its primary metabolites, α-zearalenol (α-ZEL) and β-zearalenol (β-ZEL). Together with these two metabolites, zearalenone competes with human estradiol to bind the estrogen receptors: ERα and ERβ (Alshannaq and Yu, 2017; Zinedine *et al*., 2007). Studies on zearalenone involving human females are scarce, but premature puberty (Rivera-Núñez *et al*., 2019) has been reported. There are also suggestions that exposure to zearalenone-contaminated food in pregnant women might increase health risks for the mother and the young female generation resulting from transgenerational toxicity (Gao *et al*., 2017). Other experts suggest that zearalenone can impact uterine tissue morphology and reduce luteinizing hormone (LH) and progesterone levels (Zhang *et al*., 2014)to correlate the maternal uterus with the fetus, and to explore the development and malformation of fetuses. Pregnant female SD rats were fed diets containing 0.3, 48.5, 97.6, or 146.0 mg/kg ZEN on gestational days (GDs). It has also been reported that zearalenone reduces sperm counts and viability *(Lin et al*., 2021) while impeding spermatogenesis (Yang *et al*., 2018).

On the other hand, animal model studies have reported several adverse outcomes such as immunotoxicity (Cai *et al*., 2020), oxidative stress (Yoon *et al*., 2019), tumorigenesis (Gruber-Dorninger *et al*., 2019)mycotoxin occurrence in feed should be monitored. To this end, we performed a large-scale global survey of mycotoxin contamination in feed

and assessed regional differences and year-to-year variation of mycotoxin occurrence. Concentrations of aflatoxin B1, zearalenone, fumonisins, ochratoxin A, deoxynivalenol, and T-2 toxin were analyzed in 74,821 samples of feed and feed raw materials e.g., maize, wheat, soybean, endocrine-disrupting effects and vulva malformation (Conková *et al*., 2001). The situation is more precarious since some studies have established the presence of zearalenone biomarkers in the blood and urine of females presenting challenges in sexual development (Asci *et al*., 2014; Bandera *et al*., 2011). Meanwhile, the Expert Committee of Joint FAO/WHO communicated a provisional maximum tolerable daily intake (PMTDI) of 0.5 µg/kg(bw)-d for zearalenone in foods meant for human consumption (JECFA, 2013). However, data collected within the decade indicates that human uterine cells could be equally susceptible to zearalenone and its metabolites just as in swine uterine cells (EFSA, 2016). This observation necessitated a review of the threshold to the current PMTDI of 0.25 µg/kg(bw)-d for zearalenone and its derivatives in food (EFSA, 2017b).

The current state of the adverse impact of zearalenone contamination on the African continent among its population, especially in women, is not primarily studied. It may be attributed to the uncertainties and variabilities inherent in the elements of dietary exposure assessment among the diverse communities on the continent. The reasons may include difficulty carrying out epidemiological and other cohort studies to correlate diseases and zearalenone exposure. Studying the level of exposure across African communities will significantly facilitate the determination of zearalenone's exposure patterns in the region, thus providing evidence-based information to strengthen female policy decision-making processes regarding mycoestrogen exposures. It will also especially warrant further investigations into the adverse impact on female reproductive chemistry (Eze and Okonofua, 2015; Lulamba *et al*., 2019). The objective of this study was to systematically review the current state of zearalenone concentrations in cereal-based foods across Africa. The study will also provide insight into using meta-analyzed published data to provide quantified exposure and hazard quotient-based risks of zearalenone ingestion using probabilistic approaches.

MATERIALS AND METHODS

Search strategy and inclusion criteria

Using the Cochrane approaches for systematic reviews, relevant literature searches were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). Research articles for this study met all the inclusion criteria outlined in Figure 1. These criteria include the following properties: The articles must be based on original research conducted in African countries. Additionally, the study should report quantitative data on zearalenone concentrations or occurrence in grains or cereal-based products, along with details such as total sample size and the number of positive samples. Furthermore, the articles published in peer-reviewed journals must be in English, and their full text should be accessible.

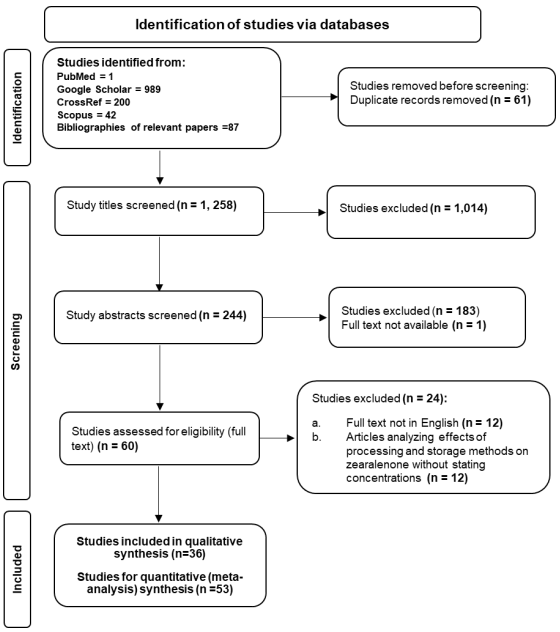

Figure 1. Flow chart showing the article search and selection for inclusion in the systematic review and meta-analysis.

Information search and study selection

In considering a period to assess the current situation of mycotoxin contamination, it was agreed that a minimum of five years or more would yield a fair number of disseminated studies relating to the subject matter. Thus, the search for research articles was limited between 1st January 2015 and 31st December 2020. Data was collected from CrossRef, Google Scholar, PubMed and Scopus repositories. MeSH-terms or Search words used in Google Scholar and CrossRef were: "adverse health" AND "cereals" AND "zearalenone" AND "Africa"; PubMed: "adverse health" AND "cereals" AND "zearalenone"; and Scopus database: "zearalenone" AND "Africa".

In all, the final articles selected provided the following information: the year of study, country of study, cereal type, total sample size (N), positive sample size (n), mean zearalenone concentration, standard deviation (SD), the range of concentrations, and the method of analysis (Supplementary Table S1). The quality of each included article was assessed (Higgins *et al*., 2019) with reference to gold standards, comparability, and outcome criteria (Supplementary Table S2) according to the Newcastle-Ottawa Scale (NOS) quality assessment scale for cross-sectional studies (Supplementary Text T1) (Herzog *et al*., 2013; Modesti *et al*., 2016).

The standardized age ranges approved for food consumption and risk assessment studies (Supplementary Table S3) were obtained from WHO and European Food Safety Authority databases (EFSA, 2012). The consumption data of cereals and cereal-based food products in WHO/GEMS clustered countries (Supplementary Table S4) were obtained from the WHO/GEMS database (WHO/GEMS/FOODS & Program), 2012).

Meta-analyses

Africa is a vast continent, and studies reporting zearalenone concentrations are expected to present varied results due to uncertainties among cereals and cereal-based food products across different ethnic groups. Apart from the sample sizes used by different researchers, the methods of analysis were another source of uncertainty. Therefore, to harmonize the concentrations of zearalenone across the study area, weighted averages of zearalenone concentrations were calculated using the fixed and random effects models (DerSimonian and Kacker, 2007; Jackson *et al*., 2010). To avoid biases introduced by different sample sizes, a system of equations (Equations 2 and 3) was used to determine the effect size (ES) of each study (Borenstein *et al.*, 2011). Subsequently, the occurrence (P) of zearalenone contamination was determined as the ratio of the number of samples presenting contamination (positive samples, p_1) to the total sample size (n_1) collected for the study (Equation 1).

$$P = \frac{p_1}{n_1} \qquad (1)$$

The ES of individual data was determined by first finding the *Hedges' g (δ)* using the estimated standard mean principle (Borenstein *et al*., 2011) ,shown in Equation 2,

$$\delta = \frac{M}{SD} \qquad (2),$$

where M is the reported mean concentration, and SD is the standard deviation of the mean. Equation 3 is then used to correct bias (J) in the estimated standard mean due to sampling error

$$J = 1 - \frac{3}{((4n)-9)\times \delta} \qquad (3),$$

.

where n is the number of positive samples. The effect size is obtained according to Equation 4.

$$ES = \delta \times J \qquad (4)$$

The weighted mean (W_i) of the reported zearalenone concentrations depended on the standard error (SE) Equation 5 (Borenstein *et al*., 2011)from which it was finally determined (Equation 6). In cases where SD was not stated but authors indicated a 95% confidence level, a value of 1.96 was adopted for the SE (Borenstein *et al*., 2011).

$$SE = \frac{SD}{\sqrt{n}} \qquad (5),$$

$$W_i = \frac{1}{SE} \qquad (6),$$

To quantify the variances within one study and between different studies, a Chi-squared (χ^2) test ($p<0.01$) was employed to arrive at the heterogeneity(I^2) of the data collected for the meta-analysis (DerSimonian and Kacker, 2007). The I^2 may range between 0-25%, 26-50% and >50%, indicating low, medium and high variability among studies (Fakhri *et al*., 2019). When I^2 is high for the dataset, further analysis through meta-regression is necessary. A linear regression model was subsequently used to indicate the relationship between the reported zearalenone concentrations, their effect sizes and the year of study. Also, subgroup analyses of I^2 in the data were performed using categorical variable inputs such as countries, WHO/GEMS food cluster classifications, and types of cereals and their products.

The elements used to determine exposure, hazard concentration, mass of food ingested, and body weights are often challenged with uncertainties. Therefore, probabilistic models are best suited to determine such exposure

outcomes based on data variation while harmonizing the estimates during iterations in Monte Carlo simulations. Thus, in this study, the Palisade @Risk software was used to fit the statistical distribution of the zearalenone concentrations collected from the study areas (Supplementary Table S5). The exposure to zearalenone (E_{ZEN}) was quantified (Fakhri *et al*., 2019; Haas *et al*., 1999) according to Equation 7.

$$E_{ZEN} = \frac{C_{ZEN} \times M_f}{B_w} \quad (7),$$

where C_{ZEN} is the concentration of zearalenone (µg/kg), M_f is the mass of cereal-based foods consumed (kg/d), and B_W is the mean body weight (kg) of consumers.

Hazard quotient (HQ)

The hazard quotient (HQ), defined as the ratio of the exposure (E_{ZEN}) of a hazard to its health-based guided reference dose, was determined using Equation 8:

$$HQ = \frac{E_{ZEN}}{R_f D} \quad (8),$$

Where $R_f D$ is the reference dose of zearalenone (0.25 µg/kg(bw)-d) for consumers of all age categories (EFSA, 2016), and significant health risk is implied for consumers when HQ>1 (Fakhri *et al*., 2019; Ofosu *et al*., 2019). Subsequently, zearalenone's probabilistic exposures and health risks were quantified and simulated at 10^5 iterations using Palisade @Risk v 8.1 software (Fakhri *et al*., 2019; Ofosu *et al*., 2019).

RESULTS AND DISCUSSION

Occurrence of zearalenone

Table 1 presents the percentage occurrence of zearalenone in varying cereal types from different African countries and the effect size of each study.

Table 1. Random effects meta-analysis of zearalenone concentrations in grains and cereal-based products in African communities

Countries	No. of studies	[a] Effect Size	95% CI	Frequency	τ^2	I^2	χ^2
Burkina Faso, Ethiopia, Mali, Sudan	1	0.91	[-8.25, -10.08]	3%	-	-	-
Cameroon	3	6.99	[0.90, 13.09]	39%	2.87	98.8%	p<0.01
Egypt	2	3.07	[0.00, 9.83]	18%	20.06	90.4%	p<0.01
Ethiopia	1	21.86	[11.71, 32.02]	96%	-	-	-
Kenya	1	19.16	[7.68, 30.64]	90%	-	-	-
Malawi	1	4.17	[0.00,13.48]	97%	-	-	-
Morocco	3	2.34	[0.00, 8.82]	43%	6.48	98.6%	p<0.01
Nigeria	16	3.91	[1.41, 6.42]	17%	0.50	97%	p<0.01
South Africa	11	3.76	[0.81, 6.71]	19%	0.52	96%	p<0.01
Tanzania	5	2.47	[0.00, 6.59]	10%	0.47	96%	p<0.01
Togo	2	18.36	[10.31, 26.40]	4%	176.44	94%	p<0.01

Tunisia	6	3.38	[0.00, 7.26]	10%	0.04	95%	p<0.01
Zimbabwe	1	1.18	[0.00, 10.35]	15%	-	-	-
Total	**53**						
[b] Cumulative effects		**0.84**	**[0.73, 0.96]**	**16%**	**0.10**	**97.7%**	**p<0.01**

[a] Effect size is the weighted zearalenone concentration per study from countries relative to their sample sizes. [b] occurrence based on the cumulative or total studies.

For this study, the fixed and random effects models yielded a high heterogeneity value (>50), thus indicating significant variances between the reported means of the published works. Thus, a strong representation of zearalenone contamination data across the study area was collected for the meta-analysis (Fakhri *et al*., 2019; Khaneghah *et al*., 2018; Yazar and Omurtag, 2008) Table 2 presents the results of the random effects meta-analysis and occurrence of zearalenone in African countries' cereal-based foods.

Table 2. Occurrence and random effects meta-analysis of zearalenone concentration in cereal and its derived food products.

Cereal foods	Frequency	[a]Effect Size	95% CI	τ^2	I^2
Barley and barley-based	22%	4.43	[0.00, 13.47]	40.94	89%
Maize and maize-based	22%	1.19	[0.99, 1.39]	0.17	96.9%
Millet and millet-based	9%	257.47	[0.00, 767.37]	133814.27	98.8%
Mixed cereal-based	7%	0.34	[0.00, 0.70]	0.08	91.3%
Rice and rice-based	75%	0.22	[0.07, 0.37]	224.31	97.2%
Sorghum and sorghum-based	4%	5.08	[2.86, 7.31]	4.58	96.5%
Wheat and wheat-based	42%	0.74	[0.00, 1.57]	0.67	95.4%
Cumulative effects	**16%**	**0.84**	**[0.73, 0.96]**	**0.10**	**97.7%**

[a]Effect size is the weighted concentration of zearalenone in each category relative to sample size

The cumulative frequency of occurrence of zearalenone in cereal-based products was calculated to be 16% (95 CI =0.04-0.28) for the selected African countries relative to China, where studies conducted over three years recorded high (40.6%) occurrence of zearalenone in maize and maize products (Li *et al*., 2019). A worldwide study of zearalenone contamination in cereal-based foods, covering 34 years, reported a cumulative occurrence of 37% (Khaneghah *et al*., 2018) relative to findings in the current study (16%). A similar percentage occurrence was obtained in a Slovenian study that sampled oats, wheat, maize, rice, and rye, and their products indicated zearalenone as the second-highest contaminant (16%) after deoxynivalenol (Kirinčič et al., 2015). In this study, the zearalenone contamination of cereals was moderately more significant in Malawi (97%) and Kenya (96%) and relatively least (3%) in Burkina Faso, Ethiopia, Mali and Sudan (Supplementary Table S6). The studies that yielded larger effect sizes with smaller confidence intervals contributed significantly to the combined effect of all the studies (Lalkhen and McCluskey, 2008). Such studies were likely to have larger sample sizes,

and their short confidence interval indicates rigorous data and statistically significant findings (Table 1) compared to studies with wider confidence intervals (Lalkhen & McCluskey, 2008; Schabo *et al.*, 2021).

The rank of the weight of effect size for countries that reported zearalenone concentration was in descending order:

Ethiopia>Kenya>Togo>Malawi>Zimbabwe> [Burkina Faso, Ethiopia, Mali, Sudan] >Tanzania>Cameroon>Nigeria>South Africa>Tunisia> Egypt>Morocco.

In this current study, the high heterogeneity (I^2 =97.7%) obtained indicated that the variances observed could not be attributed to sampling error alone (Borenstein, 2016). The heterogeneous nature of the data collected was visualized in Forest plots (Figure 2 and Supplementary Figure S1) to indicate how the effect sizes of different studies overlapped. When the different effect sizes of studies significantly overlap, the data is said to be homogenous and indicates substantial similarity (Dettori *et al.*, 2021). The visualized effect sizes from this meta-analysis overlapped poorly, thus emphasizing the heterogeneity of the data used (Dettori *et al*., 2021; Lewis and Clarke, 2001). This necessitated further analysis (Supplementary Tables S6-S9) of potential sources of the heterogeneity through meta-regression and subgroup analysis (Higgins *et al*., 2019). This observation is similar to other studies presenting high heterogeneity (>50) of mycotoxins in cereals and cereal products (Fakhri *et al*., 2019; Khaneghah *et al*., 2018; Schabo *et al*., 2021) including aflatoxins (AFs). Additionally, the combined-averaged intra-study variance (τ^2=0.10) indicated that the differences in zearalenone concentrations across the study area could not be due to sampling error alone (Borenstein, 2016). The differences in the reported zearalenone occurrence relative to other studies may be attributed to differences in effect sizes of the included studies (Borenstein *et al*., 2011; Higgins *et al*., 2008; Kuroki *et al*., 2017).

When analyzed by cereal types, it was observed that rice and rice-based products presented a high occurrence of zearalenone contamination (75%) relative to wheat and wheat-based food products. This observation suggests that rice could be emerging as a source of zearalenone exposure because its consumption is on the increase in many African communities. Currently, total rice consumption in Africa is estimated at 27-28 million tons per annum and is projected to increase to approximately 36 million tons by 2026 (USDA, 2017). It is observed that zearalenone contamination in maize and its derived products (22%) was similar to its occurrence in barley and barley-based foods (22%). However, sorghum and its derived food products showed a minor occurrence of zearalenone (4%).

The WHO/GEMS Food clusters (Figure 2) countries in terms of cumulative occurrence of zearalenone in cereals and cereal-based products ranked as:

G03 (28%)> G01 (21%) > G05 (19%) > G06 (18%) > G13 (13%).

The highest zearalenone occurrence in cereals was expected to be observed from humid regions or zones where farmers dry harvested cereals in the open air (Badr *et al*., 2016; Hove *et al*., 2016). Indeed, the G03 food cluster zones (Supplementary Table S4) mainly comprise highly humid countries where farmers engage in subsistent agriculture. The observation agrees that zearalenone may accumulate in grains long before harvest, but poor storage conditions after harvesting can exacerbate the contamination (Mally *et al*., 2016) a mycotoxin with high estrogenic activity in vitro and in vivo, is a widespread food contaminant that is commonly detected in maize, wheat, barley, sorghum, rye and other grains. Human exposure estimates

based on analytical data on ZEN occurrence in various food categories and food consumption data suggest that human exposure to ZEN and modified forms of ZEN may be close to or even exceed the tolerable daily intake (TDI). Though the occurrence of zearalenone was highest in G03 food cluster zones (0.28), the most statistically significant zearalenone contamination was from G01 food cluster countries (0.21). This observation can be attributed to the narrow 95% confidence interval around the effect size (Lalkhen and McCluskey, 2008).

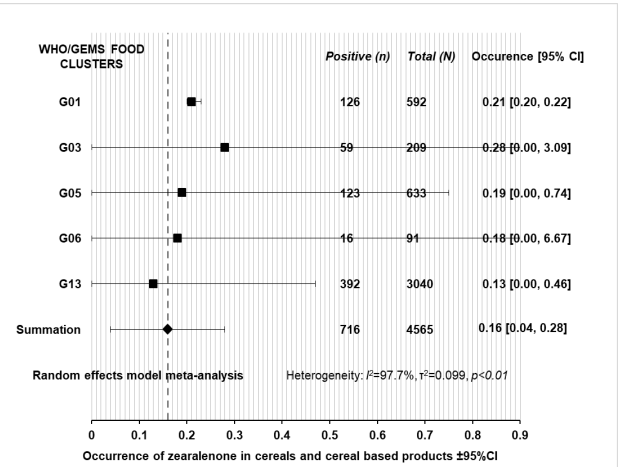

Figure 2. A Forest plot for random-effects meta-analysis of zearalenone occurrence in cereals from Africa by WHO/GEMS food clusters. The dotted line indicates the combined-averaged estimate of zearalenone concentrations.

Similar to other studies (Khaneghah *et al*., 2018; Schabo *et al*., 2021), the summed zearalenone occurrence across the study areas fell on the summed effect line. The 95% confidence interval boundaries of zearalenone occurrence presented cut across the summed effect line, indicating that the true effect sizes of individual studies could lie in the same position as the summed effect size. Thus, there is no significant difference between the summed occurrence for the meta-analysis and the individual effect sizes determined by food cluster zones or studies. A study on mycotoxin contamination of breakfast foods indicated a similar phenomenon (Khaneghah *et al*., 2018). Conversely, another study (Schabo *et al*., 2021) recorded shorter 95% confidence intervals, indicating more reliable concentration data from the studies included in that meta-analysis.

Meta-regression of zearalenone concentrations

It was observed from the linear regression model in Figure 3 and meta-regression in Figure 4a that a weak negative correlation ($p>0.05$) occurred between the year of study and the zearalenone concentrations. There was, however, a significant difference in the effect sizes of reported zearalenone concentrations across the years of study (Figure 4a). Precisely, what is causing the decline in the concentration of zearalenone remains uncertain. There was also a positive correlation between the effect size of zearalenone concentrations for WHO/GEM foods cluster zones, which showed increasing humid conditions (Figure 4b). This observation could be attributed to increasing global warming and weather variations, which inadvertently favors increasing fungal

proliferation and adaptation(Medina *et al*., 2017).

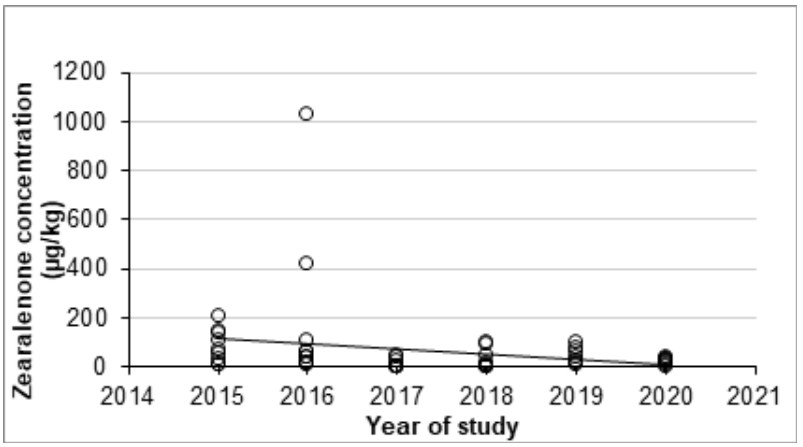

Figure 3. Correlation between zearalenone concentrations and year of study based on a linear regression model.

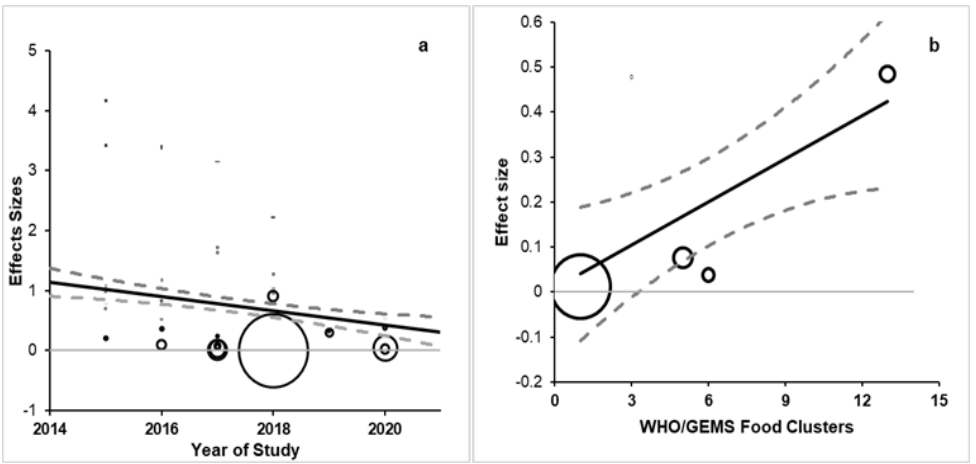

Figure 4. Bubble plot of meta-regression of effect sizes of zearalenone concentrations (a) across years of study and (b) across food clusters.

Again, Figure 4b shows that while the studies on zearalenone concentrations reported from G13 countries were more numerous (26) than those of G03 countries (5), the effect sizes obtained for G13 countries (0.4908) and G03 countries (0.4782) appear similar. The countries in the G13 zone (e.g. Sudan, Ethiopia) and G03 zone (e.g. Togo, Cameroon) generally have low GDPs ranging between $272.14 to $887.28 (Udomkun *et al*., 2017). Thus, these low-income communities may lack technological infrastructure and the will to enforce regulations controlling mycotoxin contamination. Hence, similar outcomes of these concentrations were observed (Alshannaq and Yu, 2017; Schabo *et al*., 2021; Udomkun *et al*., 2017). From Figure 4b, the effect sizes of the occurrence and levels of zearalenone concentrations reported from G13 and G03 countries were larger than

values reported from G01, G05 and G06. The observation bolsters the assertion that in G13 and G03 zones, contaminated grains, rather than being disposed of, will more likely be ingested or fed to animals for financial considerations, primarily if the decision lies in the hands of poor farmers.

Zearalenone concentrations have been reported in wheat flour-based bread and biscuits (Khaneghah et al., 2018), maize porridge (Geary et al., 2016), and Ogi and Ogi baba (Adekoya et al., 2017), fermented maize and sorghum gruels. Studies showing variable zearalenone contamination have also been made on water-based cereal products such as beer and other alcoholic beverages (Afshar et al., 2013; Chilaka et al., 2018; Schabo et al., 2021). A similar report indicated zearalenone concentrations of 9.49 µg/kg and 11.25 µg/kg found in breakfast cereals and bread, respectively (Khaneghah et al., 2018). In Europe, individual studies presented zearalenone concentrations in maize from Croatia (0.9-2.54 µg/kg), Central Italy (nd.-0.38 µg/kg), Western Italy (nd.-0.96 µg/kg) and UK (0.04-1.8 mg/kg) (Yazar and Omurtag, 2008; Zinedine et al., 2007). Comparatively, in South America, zearalenone occurrence in maize as high as 2564.8 µg/kg in Argentina and Brazil (0.0368-0.719 mg/kg) has been reported(Yazar and Omurtag, 2008; Zinedine et al., 2007). In Africa, events of zearalenone in maize have been reported in Egypt (9.8-38.4 mg/kg), Morocco (0.014 -0.017 mg/kg), South Africa (0.05 -8.0 mg/kg) and Côte d'Ivoire (20-50 µg/kg) (Yazar and Omurtag, 2008; Zinedine et al., 2007). Wheat and wheat-based products such as pasta, biscuits and bread are often tested for zearalenone. Levels of zearalenone in wheat and wheat-based products from another meta-analysis reported zearalenone levels in biscuits (9.30 ng/L), bread (11.25 µg/kg), and pasta (5.64 µg/kg) (Khaneghah et al., 2018). Zearalenone concentrations for biscuits, pasta and wheat semolina couscous included in this meta-analysis were reported from Tunisia (9.5-15 µg/kg) and Morocco (0.5-2.0 µg/kg; 22-132.1 µg/kg), respectively. Studies have reported zearalenone in wheat from Germany (1-24 µg/kg), Denmark (1-2 µg/kg), Switzerland (0.01-0.018 mg/kg) and The Netherlands (0.020-0.231 mg/kg) (Yazar and Omurtag, 2008; Zinedine et al., 2007). Although sorghum is cultivated in the Americas, Asia and Africa's Sahel regions (Mundia et al., 2019), its use as a human food source remains relatively confined to sub-Saharan Africa (Khaneghah et al., 2018). In contrast, its use on other continents is restricted in favour of industrial and animal feed use (Hariprasanna and Rakshit, 2016) Studies included in this current meta-analysis reported sorghum zearalenone levels from Nigeria (0-38 µg/kg), Tunisia (3.75-64.52 µg/kg) and Togo (19-24.6 µg/kg).

Mixed cereals usually refer to cereal-based meals that comprise two or more different cereals (Ojuri et al., 2019) with the local staple cereal often present in a higher percentage. The occurrence of zearalenone in mixed cereals has been reported in Malaysia (LOD-58.4 µg/kg), Spain (~32.12 µg/kg), and North America (2.6-8.6 µg/kg) (Khaneghah et al., 2018). Mixed cereals' zearalenone contaminations from African countries presented in this current meta-analysis included Tunisia (0-41 µg/kg), Nigeria (0.6-10.3 µg/kg), and infant cereals sampled in Tunisia (0-44 µg/kg). These concentrations did not differ starkly from reports in other studies.

The different zearalenone concentrations recorded among the cereal-growing communities may be explained by confounding factors such as changes in climate (Al Jabir et al., 2019; Alshannaq and Yu, 2017). Moreover, some studies have reported that cereal samples from subsistent farmers in poorer communities have high levels of mycotoxin contamination (Mngqawa et al., 2016; Owuor et al., 2018; Ssepuuya et al., 2018).

Uncertainty, variability, and elements of dietary zearalenone exposure

Unavoidably, uncertainties and variabilities will be associated with the dietary exposure elements: the concentration of zearalenone, the mass of food consumed, and the body weights of consumers in several African communities. Across the African continent, cereal-based foods are as diverse as the storage techniques for harvested cereals. Among the several papers published, different methods of analyses were used to determine zearalenone concentrations, adding to the uncertainties likely to emerge when a meta-analysis of this scale is carried out. The National Research Council's Science and Judgement in Risk Assessment suggests probabilistic techniques such as Monte Carlo analysis to solve this problem (Maertens *et al*., 2022). In this approach, the distribution of risk is determined from repeated sampling of the probability distributions of variables. Thus, the outcome can be determined within a confidence interval from a distribution of exposure obtained by resampling from empirical distributions of the components of the exposure (NRC, 1994).

The simulation outcomes yielded modelled minimum to maximum zearalenone concentrations ranging from 0.90 to 1.03×10^{3} µg/kg, respectively, in cereals and cereal-based products (Supplementary Table S5). The frequently occurring (modal) concentration was 1.20 µg/kg. Globally, maximum limits ranging from 50 to 200 µg/kg for zearalenone in unprocessed and processed cereal-based foods have been reported (EFSA, 2016), though some regional regulatory bodies set more restrictive limits. In Europe, for example, the maximum limit for zearalenone in cereals is set between 20 and 100 µg/kg, while other countries set 75 µg/kg as the upper bound limit (Lahouar *et al*., 2018). The maximum value of zearalenone obtained from this study in African communities (1.03×10^{3} µg/kg) is undoubtedly higher than what has been set in China (60 µg/kg) for wheat, wheat flour, corn, and cornflour (Li *et al*., 2019). The limits set for processed cereal-based foods for infants and young children (20 µg/kg) and breakfast cereals (50 µg/kg) were significantly lower (EC, 2006) than what was obtained in this study. Again, the Commission's guidance value for cereals (75 µg/kg) and maize (100 µg/kg) intended for direct human consumption were all lower than the maximum value obtained in this study. It is worth noting that while in North America, there is no defined range for zearalenone in cereals meant for food and feed (Alshannaq and Yu, 2017), countries such as Japan, Thailand, South Korea, and Indonesia set their limits depending on food use (Ferre, 2016).

The dietary exposure assessment results are presented in Table 3. The frequently occurring (modal) exposure to zearalenone through cereal diets in the study area ranged from 5.33×10^{-3} - 9.70×10^{-2} µg/kg(bw)-d. Thus, the European Food Safety Authority regulatory limit (<0.25 µg/kg(bw)-d) is higher (EFSA, 2017a).

Table 3. Estimated exposures of dietary zearalenone (E_{ZEN} µg/kg(bw)-day) and [a]Hazard Quotient (HQ) in cereal growing communities in Africa.

	E_{ZEN} (µg/kg(bw)-day)			HQ		
	5th	Mode	95th	5th	Mode	95th
Infants	1.02×10^{-1}	9.70×10^{-2}	31.60	4.07×10^{-1}	3.88×10^{-1}	126.41
Toddlers	4.24×10^{-2}	4.04×10^{-2}	13.11	1.70×10^{-1}	1.62×10^{-1}	52.43
Other children	2.21×10^{-2}	1.89×10^{-2}	6.84	8.85×10^{-2}	7.54×10^{-2}	27.36
Adolescents	1.19×10^{-2}	1.01×10^{-2}	3.65	4.74×10^{-2}	4.05×10^{-2}	14.62
Young adults	8.30×10^{-3}	7.10×10^{-3}	2.57	3.33×10^{-2}	2.85×10^{-2}	10.28
Adults	6.90×10^{-3}	6.60×10^{-3}	2.12	2.76×10^{-2}	2.62×10^{-2}	8.46
Elderly	6.80×10^{-3}	5.80×10^{-3}	2.09	2.72×10^{-2}	2.33×10^{-2}	8.36
Adults: female	7.73×10^{-3}	8.10×10^{-3}	2.33	3.09×10^{-2}	3.23×10^{-2}	9.33
Adults: males	6.21×10^{-3}	5.33×10^{-3}	1.91	2.48×10^{-2}	3.13×10^{-2}	7.66

A hazard quotient equal to or greater than 1 (HQ≥1) indicates a significant risk of adverse health outcomes, while HQ <1 indicates low risk.

However, the 95th percentile exposure was higher (>0.25 µg/kg(bw)-d, Figure 5), suggestive of staple cereal consumers in the study area. Specifically, infants (6-12 mo) and toddlers (1-3 y) were most frequently (modal) exposed to dietary zearalenone relative to the elderly (>65 y), who were frequently (modal) least exposed. Female consumers were also more exposed (2.33 µg/kg(bw)-d) compared to males (1.91 µg/kg(bw)-d). This difference in exposure between adult female and male groups suggests that the burden of adverse estrogenicity would be more significant for females, especially in the younger age groups approaching puberty. There were also isolated cases of heavy exposure (max) ranging between 0.54 mg/kg(bw)-d and 5.47 mg/kg(bw)-d (Supplementary Table S10).

In a recent study in The Netherlands to determine dietary exposure to mycotoxins for 1- and 2-year-old children, a total diet of cereals revealed zearalenone exposure (95th percentile) ranging between 28 and 37 ng/kg(bw)-d (Pustjens *et al.*, 2022).A total diet study was conducted in the Netherlands in which mycotoxins were analysed in foods and beverages consumed by 1- and 2-year-old children. These mycotoxins were aflatoxins, alternaria toxins, citrinin, ergot alkaloids, fumonisins, ochratoxin A, patulin, sterigmatocystin, trichothecenes, and zearalenone. Long-term exposure was calculated by combining concentrations in foods and beverages with consumed amounts of these products. Analysed foods and beverages with a concentration below the detection limit that could contain the mycotoxin, were assigned a concentration equal to half this limit value. To assess if the exposure could result in a possible health risk, the high long-term exposure (95th percentile) was used. Comparatively, the current study's exposure to the same category of consumers shows a higher exposure in African communities. At high consumption (95th percentile), all age-group related consumers are highly exposed, but infants (6-12 mo) were more exposed to dietary zearalenone, followed by toddlers (1-3 y). Thus, younger children, specifically infants, are more at risk of adverse health outcomes.

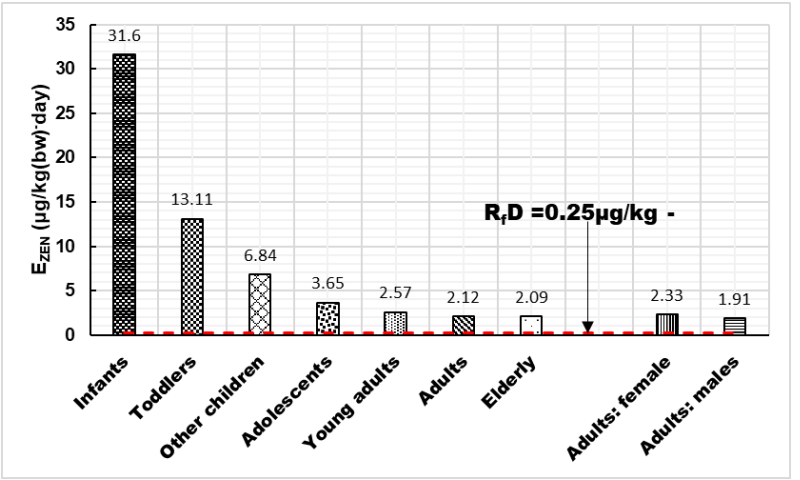

Figure 5. Exposures of zearalenone (95th P) in age-related consumer groups in cereal-growing communities in Africa

These exposures may result from supplementary and weaning foods, many of which are cereal-based (Ojuri *et al*., 2019). Such age groups in the study area will likely develop adverse oestrogenic outcomes if exposure remains unchanged.

Again, human biomonitoring analysis of zearalenone exposure in wheat products among the Chinese population during harvest season presented adolescents as the age group significantly excreting the highest zearalenone biomarkers relative to all others (Zhang *et al*., 2020). Relatively, the dietary exposure of the adolescent group in the current study presented 3.65 µg/kg (bw)-d exposure (95th percentile). Again, this value is higher even when compared to the outdated provisional maximum tolerable daily exposure (0.5 µg/kg (bw)-d) set by the Joint Expert Committee on Food Additives and Contaminants (JECFA, 2013). Age groups approaching puberty are prone to oestrogenic activities, as demonstrated by a study in the US. Indeed, the cross-sectional study involving 163 peri-pubertal girls aged 9 and 10 in New Jersey presented high zearalenone exposures in 55% of urine samples collected (Bandera *et al*., 2011). The experts indicate that subjects with detectable urinary mycoestrogen levels tended to have delayed breast development and were relatively shorter. The exposure to zearalenone (95th percentile) in this study was estimated to be 2.57 µg/kg(bw)-d for young adults (14-18 y) and 2.33 µg/kg(bw)-d for adult females (18-64 y). Adolescent and teenage groups' exposures seem consistently lower across the continents than infants and children. However, younger children are expected to consume lower food masses than teenagers. This disparity is possibly due to the lower body weights of infants and children equally exposed to high concentrations of zearalenone.

Health risk characterization and assessment

Figure 6 presents the 95th percentile hazard quotient for the various consumer groups in the study area. To avoid uncertainty, the heaviest consumers that rely on cereals as staples were used, and all ages exceeded the hazard quotient threshold (HQ=1).

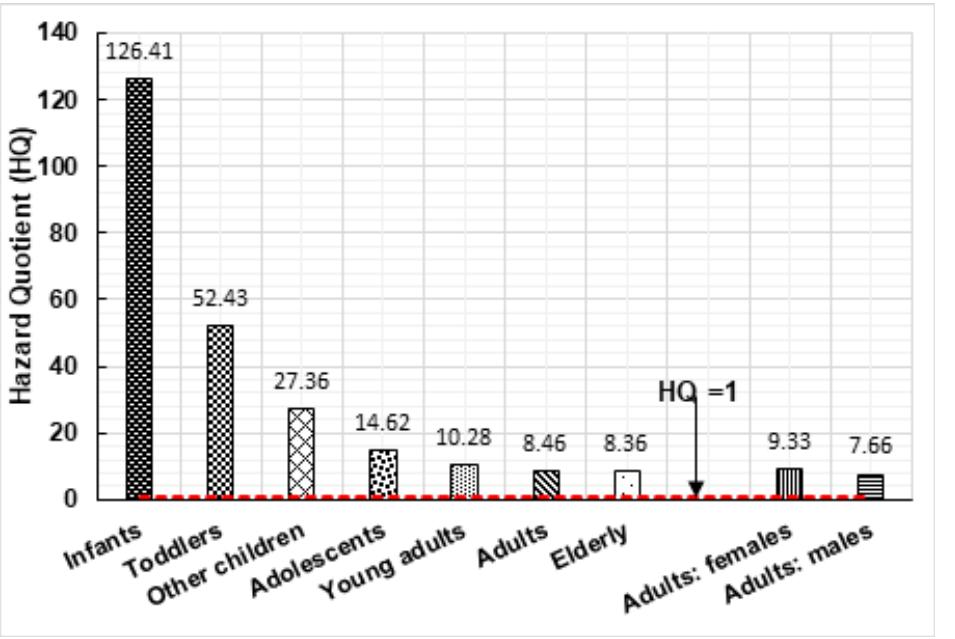

Figure 6. Hazard quotients (95th P) in age-related consumer groups in cereal-growing communities in Africa

This observation was expected since the represented demography had relatively high dietary exposures at 95th percentile across the study area.

A related study on dietary zearalenone exposures in the Yangtze River delta, China, similarly presented a significantly high risk (HQ>1, 95th percentile) to adults (Huang *et al*., 2021) realistic assessments of the risks related to cumulative exposure are limited. This biomonitoring study was conducted to investigate exposure to 23 mycotoxins/ metabolites and their determinants in 227 adults (aged 20-88 years). Conversely, a study in Chile on infants' and children's consumption of cereals presented a non-significant risk at the 95th percentile, suggesting a low public health concern for children (Foerster *et al*., 2022). It is observed that the health risk determined from all these different studies might be associated with uncertainties involving storage conditions, the type of cereals, and prevailing climatic conditions. Interpreting such risk assessment must be carefully done since the health-based guidance value for determining the hazard quotient is described as provisional. While confirmation of a more reliable reference dose is to be used, the exposure of zearalenone in the diets of children and teenagers must be a public health concern since multiple mycotoxins co-occur to present confounding health outcomes.

CONCLUSION

The study aimed to systematically review the occurrence of zearalenone in cereals and cereal-based food products across African communities. The observation revealed a 16% zearalenone contamination in cereal-based foods, similar to zearalenone occurrence in other geographical areas such as Europe and South America, but lower than in the far East. The risk characterization revealed high exposures to all consumer groups in the study area, with infants being the highest

exposed. Although this situation poses a severe health concern, uncertainties could be associated with the health-based guidance value applied in this study. Nevertheless, this study contributes a reliable probabilistic risk characterization approach that presents the zearalenone burden among consumers in African communities. As more reliable health-based guidance values become available, further studies could shed light on zearalenone's margin of exposure to contribute to policies underscoring public health.

Appendix A. Supplementary data

Supplementary data to this article can be found online with DOI: https://doi.org/10.17632/9bncfvb54g.6

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Author Contributions

Naa K-A. Quartey collected data and drafted the initial paper. Isaac W. Ofosu supervised data analysis and substantially edited the drafted manuscript. Gloria M. Ankar-Brewoo and Herman E. Lutterodt drafted some selected manuscript portions. William O. Ellis systematically arranged the text and proofread the manuscript before submission.

Conflict of Interest

Conflict of Interest: None.

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