

Article

Investigation of Dietary Mycotoxin Exposure and Colorectal Cancer Risk in a Large-Scale European Cohort

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Featured Application

Mycotoxins are fungal toxins which contaminate crops, food and feed. Climate change alters fungal behaviour and distribution, increasing the risk of exposure to these toxins and exacerbating their potential impacts on health. In this study we investigated associations between dietary mycotoxin exposures and cancer risk in a prospective cohort study and demonstrated positive associations between colorectal cancer incidence and higher mycotoxin exposures. Further research from both observational and experimental studies is needed to confirm these findings and explore their possible impact on public health.

Abstract

Mycotoxins are widely consumed food contaminants. Mechanistic studies support potential carcinogenic effects of mycotoxins in the human intestine, yet no studies have investigated these associations in population-based settings. This study aimed to investigate associations between dietary mycotoxin exposures and colorectal cancer risk. Dietary questionnaire data from the European Prospective Investigation into Cancer and Nutrition (EPIC) were combined with mycotoxin food occurrence data from the European Food Safety Authority (EFSA). Associations between mycotoxin exposures and colorectal cancer (CRC) risk and its anatomical sub-sites were evaluated in multivariable Cox proportional hazards regression models to compute hazard ratios (HR) and their 95% confidence intervals (CI), accounting for potential confounders. Food groups that explained the greatest variation in mycotoxin intakes were cereal-based products, vegetables, non-alcoholic beverages and fruits. For individual mycotoxins, deoxynivalenol (DON) was positively associated with CRC risk (HR top vs. bottom tertiles [T3vsT1] = 1.14; 1.04–1.24), while patulin (PAT) was positively associated with rectal cancer risk only (HR^{T3vsT1} = 1.18; 1.05–1.32). Sensitivity analyses indicated differential results for men versus women with significant positive associations for DON and CRC risk found only in men. In conclusion, dietary mycotoxin exposures may be related to higher CRC risk. Further investigation in independent cohorts and through mechanistic studies is warranted.

Keywords: mycotoxins; epidemiology; prevention; colorectal cancer

1. Introduction

Over recent decades food safety has become of increasing concern to both producers and consumers as a result of increased global availability of food commodities and intensified public awareness on health and food quality [1]. Trace levels of chemical contaminants affect food safety and can originate from natural sources. Mycotoxins are natural fungal toxins which contaminate many of the most frequently consumed foods and feeds worldwide [2–7]. One fungal species is able to produce several different mycotoxins with different physiochemical properties. Eskola et al. (2019) estimated that 60% to 80% of the world's food supply is contaminated by mycotoxins, resulting in widespread human exposure to one or more of this broad group of toxins [8–11]. In terms of chronic toxicity,

mycotoxins are considered more hazardous than synthetic contaminants, food additives, and pesticide residues [7,12].

Mycotoxin exposure has been associated with both acute and chronic human health effects and has been linked to cancer development [12–15]. The International Agency for Research on Cancer (IARC) concluded that aflatoxins B1, B2, G1, G2 and M1 are carcinogenic to humans (Group 1), while others are designated as possibly or probably carcinogenic (Group 2B, e.g., ochratoxin A (OTA) and fumonisin B1 and B2 (FB1 and FB2)) (Supplementary Table S1) [16].

Although mycotoxins such as aflatoxins have been associated with increased risk of hepatocellular carcinoma, particularly in developing countries [14,17], in developed countries chronic multi-mycotoxin exposure may be differentially associated with cancer risk [14,18,19]. Mycotoxins such as deoxynivalenol (DON) and patulin (PAT) are known to be ubiquitously present in European food sources and have been shown to markedly affect epithelial cell integrity and functions [13,20–23]; however, their potential roles in cancer development are not well understood. Notably, in a murine model, low-dose dietary DON at levels near human exposure worsened colitis-associated colorectal cancer (CRC) by increasing epithelial proliferation, tumour burden, and pro-survival signalling [24]. Additionally, *in vitro* studies have shown that patulin induces oxidative stress and apoptosis in colon cancer cells, highlighting its potential role in CRC development [15,25–27].

Together, these experimental findings highlight the colorectum as a biologically plausible target of mycotoxin-induced cellular damage. The ubiquitous presence of mycotoxins in European diets and their suggested deleterious effects on gut health underscore the importance of comprehensively investigating the role of chronic multi-mycotoxin exposure in CRC development. We therefore conducted a population-based analysis of dietary mycotoxin exposure and CRC risk using data from the European Prospective Investigation into Cancer and Nutrition (EPIC) and mycotoxin food occurrence data compiled by the European Food Safety Authority (EFSA). The aim of this research was to explore the association between dietary exposure of single and multiple mycotoxin profiles and incident CRC overall and by cancer subsite. Such research is important to inform first-line hypothesis generation towards informing health safety research and development of relevant public health nutrition strategies.

2. Materials and Methods

2.1. Subjects and Study Design

The analyses were carried out in the large-scale EPIC cohort [28]. EPIC is an ongoing, multicentre prospective cohort study including 521,324 adults (366,521 women; 153,437 men) aged 35–70 years, for whom baseline dietary and lifestyle information was collected. Participants were recruited between 1992 and 2000 across 23 centres in 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. The study rationale, population characteristics, and data-collection procedures have been described previously [28]. All participants provided written informed consent, and the ethical review boards of IARC and all local centres approved the EPIC cohort study. In addition, this study investigating associations between dietary mycotoxin exposures and colorectal cancer risk was approved by the IARC Ethics Committee (IEC) on 27 January 2021 (Registration number: IEC Project 21-07). For the present analysis, we excluded individuals with prevalent or prior cancer at baseline ($n = 25,184$) and those with missing lifestyle or dietary data ($n = 6259$), missing follow-up information ($n = 4148$), or who fell within the highest or lowest 1% of the distribution of the ratio of energy intake to estimated energy requirement ($n = 9573$). Total energy intake (kcal/d) was calculated as the sum of the energy intakes from the consumed foods and

the estimated energy requirement (EER) (kcal/d) is calculated based on the “Energy and protein requirements: the 1985 report of the 1981 Joint FAO/WHO/UNU Expert Consultation” [29] using each individual’s height and weight, as well as their estimated physical activity level. The final analytical dataset therefore comprised 476,160 participants.

2.2. Follow-Up for Cancer Incidence and Vital Status

Incident cancer cases were ascertained using multiple approaches, including record linkage with population-based cancer registries, health insurance databases, pathology registries, and active follow-up of participants. Follow-up closure dates differed by country, ranging from 2009 to 2014. First primary colorectal cancers were treated as cases for the present analysis. Tumours were coded in accordance with the International Classification of Diseases for Oncology (ICD-O) [30]. All incident cancers of the colon (C18) and rectum (C20) were included. Proximal colon cancer comprised tumours of the caecum, appendix, ascending colon, hepatic flexure, transverse colon, and splenic flexure (C18.0–18.5). Distal colon cancer included tumours of the descending and sigmoid colon (C18.6–18.7). Overlapping (C18.8) and unspecified (C18.9) colon lesions were grouped among colon cancers only. Rectal cancer encompassed tumours arising at the rectosigmoid junction (C19) and rectum (C20); anal canal tumours were excluded. An expert panel of pathologists supervised validation of tumour diagnosis and classification, comprising one representative per participating EPIC country and a coordinator.

2.3. Dietary Data and Lifestyle Questionnaires

At baseline, information on physical activity, smoking history, alcohol intake, and educational attainment was obtained using validated, standardised questionnaires. The classification of physical activity was done according to the Cambridge Physical Activity Index. Body weight and height were measured during the baseline examination in all centres except parts of Oxford, France, and Norway, where these measures were self-reported [28].

Dietary intake during the year preceding baseline was assessed at enrolment using validated dietary questionnaires (DQs) tailored to each country/centre [28]. In most centres, DQs were self-administered; however, in Greece, Ragusa (Italy), Naples (Italy), and Spain, data were collected through face-to-face interviews. Detailed quantitative DQs were implemented in northern Italy, the Netherlands, Germany, and Greece, while meal-based questionnaires were used in Spain, France, and Ragusa. Semi-quantitative food-frequency questionnaires (FFQs) were applied in Denmark, Norway, Naples, Umeå (Sweden), and the United Kingdom, whereas, in Malmö (Sweden), a combined approach was used, integrating a short semi-quantitative FFQ with a 7-day record of hot meals [28,31]. The EPIC Nutrient Database (ENDB) was compiled using a highly standardised procedure that adopted nutrient values from the 10 national food composition databases corresponding to the EPIC countries [32].

2.4. Mycotoxin Occurrence Data

In this study, mycotoxin occurrence information provided to EFSA by its member states was linked to EPIC food-consumption data collected through the administered dietary questionnaires. The EFSA databases used for this project contain aggregated occurrence measurements for a wide range of mycotoxins in Europe and were obtained via the European member states (<https://www.efsa.europa.eu/en/topics/topic/chemical-contaminants-food-feed> (accessed on 1 December 2017)). To estimate the amount of each mycotoxin consumed by an individual, the portion size (g) of each food item reported by that participant (from the FFQs) was matched to the corresponding mycotoxin occurrence data for that food [31].

2.4.1. Concentration Scenarios for Sample Values Below the Limit of Detection/Quantification

In contaminant-monitoring programmes, numerical concentration values are typically reported only when measurements exceed the limit of detection (LOD) or the limit of quantification (LOQ); otherwise, results are recorded as <LOD or <LOQ. For EPIC exposure assessments, a middle-bound (MB) concentration scenario was applied for values below the detection limit or below the limit of quantification [33]. Specifically, for commodities (e.g., bread) with at least one sample at or above the LOD/LOQ, non-detect samples were assigned a concentration equal to half the relevant limit value (i.e., LOD/LOQ). For commodities with no samples at or above the LOD/LOQ, all non-detect results were assumed to indicate absence of mycotoxins [31,33]. This approach was selected as a preferable alternative to assigning all results below the detection limit a value of 0.00 µg/kg (the so-called lower-bound scenario) when linking measured concentrations to consumed foods. Nevertheless, the lower-bound scenario was also implemented for sensitivity analyses. The resulting end-user mycotoxin database was subsequently used to evaluate single and combined mycotoxin exposures across the full EPIC cohort and their association with CRC risk.

2.4.2. Mycotoxin Grouping for Analysis

Related mycotoxins were grouped for analysis by summing concentrations of compounds belonging to the same family, based on chemical structure and according to the EFSA hierarchical classification tree. Group definitions were selected to allow inclusion of low-exposure values. An overview of the mycotoxin groupings is provided in Table 1. Selected mycotoxins were additionally considered as individual exposures, including PAT, nivalenol (NIV), diacetoxyscirpenol (DAS), fusarenon-X (FUS-X), and sterigmatocystin (STC). Total mycotoxin exposure was computed by summing the z-scores of concentrations across all individual mycotoxins.

Table 1. Grouping of the different mycotoxins included in the analyses according to the EFSA hierarchical classification tree.

Mycotoxins Groups	Mycotoxins Included in Each Group
Aflatoxins	Aflatoxin B1 (AFB1), Aflatoxin B2 (AFB2), Aflatoxin G1 (AFG1), Aflatoxin G2 (AFG2) and Aflatoxin M1 (AFM1)
Deoxynivalenol and derivatives	DON, 3-acetyl-DON (3ADON), 15-acetyl-DON (15ADON) and deoxynivalenol-3-glucoside (D3G)
Fumonisin	Fumonisin B1 (FB1), Fumonisin B2 (FB2) and Fumonisin B3 (FB3)
Zearalenone and derivatives	The sum of Zearalenone (ZEN), ZEN-derivatives (dv), sum of zearalenols (ZEL), α-zearalenol (α-ZEL), β-zearalenol (β-ZEL) and zearalanone (ZAN)
The <i>Alternaria</i> toxins	Alternariol (AOH), alternariol methylether (AME), altenuene (ALT), tenuazonic acid (TEA), altertoxin (ATX), tenuazonic acid (TEN) and <i>Alternaria alternate</i> f. sp. <i>lycopersici</i> toxins (AAL_toxins)
The Enniatins group	Enniatin A (ENA), enniatin A1 (ENA1), enniatin B (ENB) and enniatin B1 (ENB1)
The Ergot alkaloids group	Ergocornine (Eco), ergocorninine (Econ), ergocristine (Ecr), ergocristinine (Ecrn), α-ergokryptine (Ek), α-ergokryptinine (Ekn), ergometrine (Em), ergometrinine (Emn), ergosine (Es), ergosinine (Esn), ergotamine (Et) and ergotaminine (Etn)
Ochratoxins	Ochratoxin A (OTA)
T2 & HT2 toxins	HT-2 toxin (HT2) and T-2 toxin (T2)
Individual mycotoxins	
Patulin (PAT)	

Table 1. Cont.

Mycotoxins Groups	Mycotoxins Included in Each Group
Moniliformine	
Nivalenol (NIV)	
Diacetoxyscirpenol (DAS)	
Fusarenon-X (FUS-X)	
Sterigmatocystin (STC)	
Citrinin (CIT)	

2.5. Statistical Analysis

Descriptive statistics were used to examine differences in key participant characteristics between CRC cases and non-cases, presenting means and standard deviations (SDs) for continuous variables and proportions for categorical variables. Distributions of mycotoxin exposures were evaluated and summarised using the minimum, maximum, and selected percentiles (P5, P25, P50, P75, and P95).

Associations between dietary mycotoxin exposures (and relevant covariates) and risk of CRC and its anatomical subsites were evaluated using multivariable Cox proportional hazards models, with hazard ratios (HRs) and 95% confidence intervals (CIs) reported. Person-time accrued from recruitment until death, emigration, loss to follow-up, or end of follow-up (EPIC follow-up 1992–2014; median follow-up 15.3 years), whichever occurred first. To account for heterogeneity in questionnaire design and follow-up procedures, all models were stratified by study centre. Models were additionally stratified by age at recruitment (continuous) to permit the baseline hazard to vary across ages. Entry time was defined as age at recruitment and exit time as age at censoring (i.e., age at last follow-up, first incident cancer diagnosis, loss to follow-up, or death, whichever occurred first). For sensitivity analyses, sex-specific models were fitted for men and women. Although estimates were comparable across sexes, mycotoxins may be metabolised differently by sex, which could impact CRC risk. Multivariable adjustment included established or suspected risk factors for each CRC subsite, based on the prior literature (including earlier EPIC reports) and the World Cancer Research Fund/American Institute for Cancer Research [34]. Covariates were retained in the final multivariable models when the β -estimate changed by more than 10%. On this basis, core adjustment variables for all CRC models comprised education (less than university, university graduate, or missing), body mass index (BMI), total energy intake, alcohol intake at recruitment, smoking status (never, former, current, or missing), diabetes (yes, no, or missing), and physical activity (inactive, moderately inactive, moderately active, active, or missing). In addition, the following anthropometric and dietary variables were included in specific models because they altered the β -estimate by >10%: height and intakes of calcium, fibres, and red and processed meat.

Analyses used mycotoxin intakes ($\mu\text{g}/\text{day}$) normalised to body weight (bw), expressed as $\mu\text{g}/\text{kg bw}/\text{day}$. Exposure categories were defined primarily in tertiles for CRC and each subsite; quintile-based analyses were also conducted for overall CRC risk and yielded results consistent with those based on tertiles. Sensitivity analyses additionally examined untransformed mycotoxin exposures reported as $\mu\text{g}/\text{day}$. As noted above, beyond total multi-mycotoxin exposure, mycotoxin-family group exposures were derived by summing concentrations of compounds within families defined by chemical structure.

All statistical analyses were carried out using SAS software (version 9.4). Statistical tests were two-sided, and p -values < 0.01 were considered statistically significant, in accordance with Bonferroni correction.

3. Results

Overall, CRC cases were older and generally reported less healthy lifestyles (e.g., higher alcohol, red and processed meat consumption and smoking status) compared to non-cases (Table 2).

Table 2. Demographic characteristics of the EPIC study participants (30–70 years old) living in 10 European countries with available dietary and biomarker information, recruited from 1992 to 2000 (Total $n = 476,160$).

	Non-Cases		Colorectal Cancer (CRC) Cases	
	469,869		6291	
	Mean	SD	Mean	SD
Body Mass Index (kg/m ²)	25.4	4.3	26.3	4.2
Age at recruitment	51.1	9.9	57.2	7.9
Energy intake (kcal/d)	2075	619	2105	614
Calcium intake (mg/d)	995.0	409.4	985.0	398.5
Fibre (g/d)	22.8	7.7	22.6	7.7
Alcohol at recruitment (g/d)	11.6	16.8	15.0	20.0
Red and processed meat consumption (g/d)	74.6	51.0	83.0	53.0
	N	%	n	%
Sex				
Male	139,522	29.7	2719	30.0
Female	330,347	70.3	3572	70.0
Education				
None	20,633	4.5	293	4.7
Primary school completed	119,864	25.8	1992	32.1
Technical/professional school	104,300	22.5	1564	25.2
Secondary school	96,234	20.7	970	15.6
Longer education (incl. University deg.)	112,201	24.2	1178	19.0
Not specified	10,492	2.3	214	3.4
Physical activity				
Inactive	98,295	20.92	1566	24.9
Moderately inactive	154,754	32.94	2042	32.5
Moderately active	124,075	26.41	1413	22.5
Active	84,033	17.88	1158	18.4
Missing	8712	1.85	112	1.8
Diabetes				
No	419,393	96.6	5274	94.3
Yes	12,275	2.8	246	4.4
Unknown	2252	0.5	72	1.3
Smoking status				
Never	230,537	49.1	2559	40.7
Former	124,704	26.5	2118	33.7
Smoker	105,048	22.4	1516	24.1
Unknown	9580	2.0	98	1.6

Table 3 describes the daily dietary mycotoxin exposures assessed based upon dietary questionnaire data for the full EPIC cohort in the low- and middle-bound scenario (See

Supplementary Table S3 for distributions by country). The mycotoxin exposure distributions indicate that a substantial proportion of the EPIC population was exposed to some of the main mycotoxins present in foods consumed in Europe such as *Fusarium* toxins (Deoxynivalenol and derivatives, T2/HT-2 toxins, Nivalenol, fumonisins and Zearalenone and derivatives), aflatoxins, *Alternaria* toxins (Alternariol, Alternariol monomethyl ether, Altenuene, Tenuazonic acid, Altertoxin I, Tentoxin and *Alternaria alternata* f. sp. *lycopersici* toxins) and total mycotoxins. The potential health risk of these exposure distributions was assessed by plotting the percentages (%) of the EPIC population against the Tolerable Daily Intake (TDI), Tolerable Weekly Intake (TWI) or the Provisional Maximum Tolerable Daily Intake (PMTDI), where available, set by EFSA (with the exception of patulin assessed by the European Commission) (Supplementary Table S2). Taking the middle-bound scenario into account, for most of the mycotoxins, only a small percentage of the population had exposures above the TDI, ranging from 0% for Fumonisins up to 0.15% for Ochratoxins (Supplementary Table S2).

Table 3. Description of the daily dietary mycotoxin exposures assessed based upon dietary questionnaire data for the full EPIC cohort (A—lower-bound results; B—middle-bound results), with N (non-cases) = 469,869 and N (colorectal cancer (CRC) cases) = 6291.

(A) Lower Bound (LB)— $\mu\text{g/kg}$ Body Weight										
Cancer Status	Mycotoxin	Mean	Std	Min	P05	P25	P50	P75	P95	Max
Non-case	Total Mycotoxins	0.32	0.20	3.0×10^{-4}	0.09	0.17	0.27	0.41	0.70	3.28
CRC case	Total Mycotoxins	0.28	0.18	8.2×10^{-3}	0.08	0.16	0.24	0.36	0.63	2.21
Non-case	Ergot alkaloids	0.02	0.05	0.00	0.00	1.4×10^{-3}	6.1×10^{-3}	0.02	0.11	1.57
CRC case	Ergot alkaloids	0.01	0.03	0.00	0.00	4.0×10^{-4}	4.1×10^{-3}	0.01	0.07	0.52
Non-case	Ochratoxins	1.1×10^{-3}	1.4×10^{-3}	0.00	0.00	3.0×10^{-4}	6.0×10^{-4}	1.3×10^{-3}	3.3×10^{-3}	7.0×10^{-3}
CRC case	Ochratoxins	8.0×10^{-3}	1.1×10^{-3}	0.00	0.00	0.00	0.00	1.0×10^{-3}	2.7×10^{-3}	0.04
Non-case	Aflatoxins	0.10	0.13	0.00	5.0×10^{-4}	0.02	0.06	0.14	0.33	3.20
CRC case	Aflatoxins	0.09	0.11	0.00	4.0×10^{-4}	0.00	0.00	0.11	0.31	1.40
Non-case	Patulin	2.4×10^{-3}	7.8×10^{-3}	0.00	0.00	0.00	0.00	0.00	1.2×10^{-3}	2.1×10^{-3}
CRC case	Patulin	3.1×10^{-3}	8.8×10^{-3}	0.00	0.00	0.00	0.00	0.00	0.00	0.13
Non-case	Deoxynivalenol and derivatives	0.07	0.07	0.00	6.9×10^{-3}	0.02	0.05	0.10	0.21	1.35
CRC case	Deoxynivalenol and derivatives	0.07	0.06	0.00	5.7×10^{-3}	0.02	0.05	0.09	0.19	0.65
Non-case	Fumonisins	0.05	0.05	0.00	4.0×10^{-3}	0.02	0.03	0.06	0.13	2.42
CRC case	Fumonisins	0.04	0.06	0.00	2.8×10^{-3}	0.01	0.03	0.06	0.12	1.57
Non-case	T-2/HT-2 toxins	8.0×10^{-4}	3.3×10^{-3}	0.00	0.00	0.00	0.00	0.00	3.8×10^{-3}	0.17
CRC case	T-2/HT-2 toxins	9.0×10^{-4}	3.6×10^{-3}	0.00	0.00	0.00	0.00	0.00	5.6×10^{-3}	0.11
Non-case	Zearalenone and derivatives	0.01	0.02	0.00	1.0×10^{-4}	1.0×10^{-3}	5.6×10^{-3}	0.01	0.05	0.69
CRC case	Zearalenone and derivatives	0.01	0.02	0.00	3.0×10^{-4}	7.0×10^{-3}	6.9×10^{-3}	0.01	0.05	0.29
Non-case	Moniliformine	2.2×10^{-3}	8.9×10^{-3}	0.00	0.00	0.00	0.00	0.00	0.01	0.44
CRC case	Moniliformine	2.3×10^{-3}	9.0×10^{-3}	0.00	0.00	0.00	0.00	1.0×10^{-4}	0.01	0.16
Non-case	<i>Alternaria</i> toxins	6.8×10^{-3}	9.8×10^{-3}	0.00	0.00	1.0×10^{-3}	3.4×10^{-3}	9.1×10^{-3}	0.02	0.40
CRC case	<i>Alternaria</i> toxins	8.6×10^{-3}	0.01	0.00	0.00	1.4×10^{-3}	4.6×10^{-3}	0.01	0.03	0.20
Non-case	Enniatins	0.05	0.05	0.00	3.8×10^{-3}	0.01	0.03	0.06	0.15	0.96
CRC case	Enniatins	0.04	0.04	0.00	3.5×10^{-3}	0.01	0.03	0.05	0.13	0.58

Table 3. Cont.

Cancer Status	Mycotoxin	(B) Medium Bound (MB)— $\mu\text{g/kg}$ Body Weight								
		Mean	Std	Min	P05	P25	P50	P75	P95	Max
Non-case	Total Mycotoxins	1.04	0.48	0.06	0.42	0.70	0.97	1.31	1.94	6.57
CRC case	Total Mycotoxins	0.97	0.44	0.13	0.40	0.65	0.89	1.20	1.78	4.09
Non-case	Ergot alkaloids	0.08	0.07	0.00	7.1×10^{-4}	0.03	0.06	0.10	0.21	1.73
CRC case	Ergot alkaloids	0.06	0.06	0.00	6.3×10^{-4}	0.02	0.05	0.08	0.18	0.55
Non-case	Ochratoxins	2.4×10^{-3}	1.6×10^{-3}	1.0×10^{-4}	9.0×10^{-4}	1.4×10^{-3}	2.0×10^{-3}	2.8×10^{-3}	5.1×10^{-3}	0.07
CRC case	Ochratoxins	2.1×10^{-3}	1.3×10^{-3}	2.0×10^{-4}	8.0×10^{-4}	1.3×10^{-3}	1.8×10^{-3}	2.5×10^{-3}	4.3×10^{-3}	0.05
Non-case	Aflatoxins	0.11	0.13	1.0×10^{-4}	2.9×10^{-3}	0.02	0.07	0.14	0.34	3.20
CRC case	Aflatoxins	0.09	0.11	3.0×10^{-4}	2.6×10^{-3}	0.02	0.05	0.12	0.31	1.41
Non-case	Patulin	0.01	0.01	0.00	3.1×10^{-3}	7.4×10^{-3}	0.01	0.02	0.04	0.29
CRC case	Patulin	0.01	0.01	0.00	2.9×10^{-3}	6.9×10^{-3}	0.01	0.02	0.04	0.17
Non-case	Deoxynivalenol and derivatives	0.24	0.13	3.4×10^{-3}	0.09	0.15	0.22	0.30	0.47	3.09
CRC case	Deoxynivalenol and derivatives	0.22	0.12	0.03	0.08	0.14	0.20	0.28	0.44	1.73
Non-case	Fumonisin	0.24	0.13	0.00	0.09	0.15	0.21	0.29	0.48	2.71
CRC case	Fumonisin	0.22	0.12	0.02	0.09	0.14	0.20	0.28	0.44	1.79
Non-case	T-2/HT-2 toxins	0.02	0.01	0.00	4.9×10^3	0.01	0.02	0.02	0.04	0.21
CRC case	T-2/HT-2 toxins	0.02	0.01	4.0×10^{-4}	4.9×10^3	0.01	0.02	0.02	0.04	0.16
Non-case	Zearalenone and derivatives	0.04	0.02	1.0×10^{-3}	0.01	0.02	0.03	0.04	0.08	0.71
CRC case	Zearalenone and derivatives	0.04	0.02	3.3×10^{-3}	0.01	0.02	0.03	0.04	0.08	0.35
Non-case	Moniliformine	3.4×10^{-3}	9.0×10^{-3}	0.00	0.00	4.0×10^{-4}	1.1×10^{-3}	2.5×10^{-3}	0.01	0.44
CRC case	Moniliformine	3.5×10^{-3}	9.0×10^{-3}	0.00	0.00	5.0×10^{-4}	1.1×10^{-3}	2.4×10^{-3}	0.02	0.17
Non-case	Alternaria toxins	0.20	0.11	0.00	0.05	0.12	0.18	0.26	0.39	1.36
CRC case	Alternaria toxins	0.19	0.10	0.01	0.05	0.12	0.18	0.24	0.37	0.89
Non-case	Enniatins	0.05	0.05	0.00	3.9×10^3	0.01	0.03	0.06	0.15	0.97
CRC case	Enniatins	0.04	0.05	0.00	3.6×10^3	0.01	0.03	0.05	0.13	0.58

Additional analyses identified the main food groups contributing to mycotoxin exposure. The most significant contributors to total mycotoxin intake were cereal and cereal products, vegetables, alcoholic and non-alcoholic beverages (including fruit juices), and fruits. Other food groups showed very low or no detectable levels of mycotoxins, with the exception of zearalenone and its derivatives, which were found in dairy products (Supplementary Table S4).

The associations between cumulative mycotoxin exposures and CRC risk are presented in Table 4. No statistically significant association was found between the sum of all mycotoxins and CRC risk.

Table 4. (A) Hazard ratios (HR) and their 95% confidence intervals (CI) for the associations between mycotoxin exposures ($\mu\text{g}/\text{BW}/\text{day}$) and colorectal cancer risk using a fully adjusted model * (Total $n = 476,160$), using the continuous mycotoxin exposures (per 1-SD increase) as well as tertiles (with trend test). Both colorectal cancer and the different subsites are presented. (B) Results for proximal and distal colon cancers.

(A) Middle Bound Scenario (MB)												
Mycotoxins μg/BW/day	Cases N = 6291	Colorectal			Cases N = 3897	Colon			Cases N = 2094	Rectum		
		HR	95% CI	TrendTest		HR	95% CI	TrendTest		HR	95% CI	TrendTest
Sum of all mycotoxins												
Per 1-SD increase		1.03	0.98–1.08	.		1.04	(0.97–1.10)	.		1.01	(0.93–1.09)	.
T1	2475	1.00	Ref.	.	1567	1.00	Ref.	.	802	1.00	Ref.	.
T2	2086	1.01	0.94–1.08	0.0639	1263	1.00	0.91–1.09	0.0561	706	1.01	0.89–1.14	0.7031
T3	1730	1.10	1.00–1.21	.	1067	1.14	1.00–1.28	.	586	1.03	0.88–1.22	.
Ergot Alkaloids												
Per 1-SD increase		0.97	(0.93–1.01)	.		0.98	(0.93–1.03)	.		0.94	(0.87–1.01)	.
T1	2363	1.00	Ref.	.	1475	1.00	Ref.	.	787	1.00	Ref.	.
T2	2327	0.98	0.92–1.06	0.5247	1436	1.04	0.95–1.14	0.2179	790	0.90	0.80–1.02	0.0086
T3	1601	0.97	0.89–1.06	.	986	1.07	0.96–1.20	.	517	0.81	0.69–0.95	.
Ochratoxins												
Per 1-SD increase		1.02	(0.99–1.06)	.		1.02	(0.97–1.07)	.		1.02	(0.95–1.09)	.
T1	2404	1.00	Ref.	.	1513	1.00	Ref.	.	790	1.00	Ref.	.
T2	2183	1.00	0.93–1.07	0.9737	1368	1.03	0.95–1.12	0.9647	720	0.97	0.87–1.09	0.7435
T3	1704	1.00	0.92–1.08	.	1016	1.00	0.90–1.11	.	584	0.98	0.85–1.12	.
Aflatoxins												
Per 1-SD increase		1.00	(0.96–1.04)	.		0.98	(0.93–1.03)	.		1.04	(0.97–1.11)	.
T1	2547	1.00	Ref.	.	1596	1.00	Ref.	.	833	1.00	Ref.	.
T2	2014	0.98	0.92–1.05	0.6509	1254	0.98	0.90–1.07	0.3214	669	1.01	0.90–1.13	0.4817
T3	1730	0.98	0.90–1.07	.	1047	0.95	0.85–1.05	.	592	1.06	0.91–1.22	.
Patulin												
Per 1-SD increase		1.04	(1.02–1.07)	.		1.03	(1.00–1.07)	.		1.05	(1.00–1.10)	.
T1	2264	1.00	Ref.	.	1470	1.00	Ref.	.	710	1.00	Ref.	.
T2	2087	1.02	0.96–1.09	0.1452	1289	0.98	0.90–1.06	0.5964	696	1.11	0.99–1.23	0.0070
T3	1940	1.05	0.98–1.13	.	1138	0.98	0.90–1.07	.	688	1.18	1.05–1.32	.
Deoxynivalenol and derivatives												
Per 1-SD increase		1.03	(0.99–1.08)	.		1.04	(0.98–1.09)	.		1.02	(0.96–1.09)	.
T1	2452	1.00	Ref.	.	1537	1.00	Ref.	.	800	1.00	Ref.	.
T2	2062	1.03	0.96–1.11	0.0086	1264	1.03	0.95–1.13	0.0270	692	1.02	0.91–1.15	0.2987
T3	1777	1.14	1.04–1.24	.	1096	1.15	1.02–1.29	.	602	1.09	0.93–1.27	.
T-2/HT-2 toxins												
Per 1-SD increase		1.00	(0.96–1.03)	.		0.99	(0.95–1.04)	.		1.00	(0.94–1.06)	.
T1	2160	1.00	Ref.	.	1368	1.00	Ref.	.	699	1.00	Ref.	.
T2	2030	0.98	0.92–1.05	0.8053	1252	0.98	0.90–1.07	0.6958	673	0.98	0.87–1.11	0.9017
T3	2101	0.99	0.91–1.07	.	1277	0.98	0.89–1.08	.	722	0.99	0.86–1.14	.
Fumonisin												
Per 1-SD increase		1.01	(0.97–1.05)	.		1.01	(0.96–1.06)	.		1.01	(0.95–1.08)	.
T1	2423	1.00	Ref.	.	1536	1.00	Ref.	.	780	1.00	Ref.	.
T2	2000	0.96	0.90–1.03	0.5091	1228	0.96	0.88–1.05	0.2704	674	0.95	0.85–1.07	0.5009
T3	1868	1.03	0.95–1.13	.	1133	1.07	0.96–1.20	.	640	0.95	0.82–1.11	.

Table 4. Cont.

Zearalenone and derivatives												
Per 1-SD increase		1.00	(0.96–1.03)	.		1.01	(0.97–1.05)	.		0.98	(0.92–1.03)	.
T1	2242	1.00	Ref.	.	1449	1.00	Ref.	.	697	1.00	Ref.	.
T2	2022	1.00	0.93–1.07	0.9386	1238	1.00	0.92–1.10	0.8427	677	0.98	0.87–1.10	0.9228
T3	2027	1.00	0.92–1.09	.	1210	1.01	0.91–1.12	.	720	0.99	0.86–1.14	.
Moniliformine												
Per 1-SD increase		1.02	(0.99–1.04)	.		1.03	(0.99–1.06)	.		1.00	(0.95–1.04)	.
T1	2032	1.00	Ref.	.	1292	1.00	Ref.	.	630	1.00	Ref.	.
T2	2245	1.01	0.95–1.08	0.0867	1298	0.95	0.87–1.03	0.8184	846	1.15	1.03–1.29	0.0327
T3	2014	0.94	0.88–1.01	.	1307	0.99	0.91–1.08	.	618	0.88	0.77–0.99	.
Alternaria tox- ins												
Per 1-SD increase		1.04	(1.00–1.09)	.		1.05	(0.99–1.11)	.		1.03	(0.95–1.11)	.
T1	2304	1.00	Ref.	.	1443	1.00	Ref.	.	763	1.00	Ref.	.
T2	2181	1.03	0.96–1.10	0.0434	1344	1.01	0.93–1.11	0.2690	729	1.05	0.93–1.18	0.1475
T3	1806	1.10	1.00–1.21	.	1110	1.07	0.95–1.20	.	602	1.13	0.96–1.32	.
Enniatins												
Per 1-SD increase		1.00	(0.97–1.04)	.		1.01	(0.96–1.06)	.		1.00	(0.94–1.06)	.
T1	2312	1.00	Ref.	.	1404	1.00	Ref.	.	764	1.00	Ref.	.
T2	2136	1.03	0.96–1.10	0.3928	1316	1.05	0.96–1.15	0.0989	724	1.02	0.91–1.15	0.5962
T3	1843	1.04	0.95–1.14	.	1177	1.10	0.98–1.24	.	606	0.95	0.81–1.11	.
(B) Middle Bound Scenario (MB)												
Colon Proximal						Colon Distal						
Mycotoxins µg/BW/day	Cases N = 1877	HR	95%CI		TrendTest	Cases N = 1743	HR	95% CI		TrendTest		
Sum of all mycotoxins												
Per 1-SD increase		1.02	(0.93–1.11)		.		1.07	(0.98–1.17)		.		
T1	777	1.00	Ref.		.	697	1.00	Ref.		.		
T2	609	1.00	0.88–1.14		0.2738	563	1.01	0.88–1.15		0.1797		
T3	491	1.11	0.93–1.33		.	483	1.14	0.95–1.37		.		
Ergot Alkaloids												
Per 1-SD increase		0.93	(0.86–1.01)		.		1.02	(0.95–1.10)		.		
T1	745	1.00	Ref.		.	633	1.00	Ref.		.		
T2	677	1.01	0.89–1.15		0.9802	665	1.08	0.94–1.23		0.1373		
T3	455	1.00	0.85–1.17		.	445	1.14	0.96–1.34		.		
Ochratoxins												
Per 1-SD increase		1.01	(0.94–1.08)		.		1.02	(0.95–1.10)		.		
T1	752	1.00	Ref.		.	673	1.00	Ref.		.		
T2	644	1.00	0.89–1.13		0.7495	618	1.05	0.93–1.19		0.7076		
T3	481	0.98	0.84–1.13		.	452	1.03	0.88–1.20		.		
Aflatoxins												
Per 1-SD increase		0.96	(0.89–1.04)		.		1.00	(0.92–1.08)		.		
T1	773	1.00	Ref.		.	718	1.00	Ref.		.		
T2	605	0.98	0.87–1.11		0.1495	568	1.02	0.90–1.15		0.7515		
T3	499	0.88	0.75–1.04		.	457	1.03	0.87–1.21		.		

Table 4. Cont.

Patulin								
Per 1-SD increase		1.00	(0.95–1.06)	.		1.05	(1.00–1.11)	.
T1	710	1.00	Ref.	.	672	1.00	Ref.	.
T2	630	1.00	0.89–1.12	0.5167	570	0.96	0.85–1.08	0.6089
T3	537	0.96	0.84–1.09	.	501	0.97	0.85–1.10	.
Deoxynivalenol and derivatives								
Per 1-SD increase		1.03	(0.95–1.12)	.		1.05	(0.97–1.14)	.
T1	752	1.00	Ref.	.	685	1.00	Ref.	.
T2	626	1.10	0.97–1.25	0.0448	552	1.01	0.89–1.16	0.1434
T3	499	1.19	1.00–1.41	.	506	1.15	0.96–1.37	.
T-2/HT-2 toxins								
Per 1-SD increase		1.01	(0.95–1.08)	.		0.99	(0.93–1.06)	.
T1	620	1.00	Ref.	.	656	1.00	Ref.	.
T2	619	1.10	0.97–1.25	0.1121	535	0.88	0.77–1.00	0.1468
T3	638	1.13	0.97–1.31	.	552	0.89	0.77–1.04	.
Fumonisin								
Per 1-SD increase		1.01	(0.93–1.08)	.		1.03	(0.96–1.10)	.
T1	760	1.00	Ref.	.	684	1.00	Ref.	.
T2	599	0.96	0.85–1.08	0.5982	540	0.96	0.85–1.10	0.4386
T3	518	1.05	0.90–1.24	.	519	1.07	0.91–1.26	.
Zearalenone and derivatives								
Per 1-SD increase		1.01	(0.96–1.07)	.		1.02	(0.96–1.08)	.
T1	657	1.00	Ref.	.	685	1.00	Ref.	.
T2	620	1.09	0.96–1.23	0.5696	520	0.92	0.81–1.05	0.9268
T3	600	1.05	0.90–1.21	.	538	1.01	0.86–1.18	.
Moniliformine								
Per 1-SD increase		1.04	(1.00–1.08)	.		0.99	(0.94–1.05)	.
T1	595	1.00	Ref.	.	587	1.00	Ref.	.
T2	624	0.98	0.87–1.10	0.6974	593	0.94	0.83–1.07	0.8094
T3	658	1.02	0.90–1.16	.	563	0.98	0.86–1.12	.
Alternaria toxins								
Per 1-SD increase		1.04	(0.95–1.13)	.		1.06	(0.98–1.16)	.
T1	708	1.00	Ref.	.	650	1.00	Ref.	.
T2	658	1.06	0.93–1.20	0.3247	585	1.00	0.87–1.14	0.2634
T3	511	1.09	0.92–1.29	.	508	1.11	0.93–1.32	.
Enniatins								
Per 1-SD increase		0.98	(0.91–1.05)	.		1.03	(0.97–1.11)	.
T1	692	1.00	Ref.	.	614	1.00	Ref.	.
T2	624	1.05	0.93–1.19	0.8652	596	1.05	0.92–1.20	0.0920
T3	561	1.01	0.85–1.19	.	533	1.16	0.98–1.38	.

(*) Fully adjusted model: energy intake, BMI, height, alcohol at recruitment, physical activity index, fibre intake, calcium intake, processed meat intake, smoking status, education and diabetes. MB: middle bound; BW: body weight; HR: hazard ratio.

For individual mycotoxin exposures, only DON was statistically significantly positively associated with CRC risk (HR_{T3vsT1} (95%CI) = 1.14 (1.04 to 1.24), p -trend = 0.0086).

When investigating associations by colorectal subsite, PAT was significantly positively associated with rectal cancer risk only (HR_{T3vsT1} (95%CI) =1.18 (1.05 to 1.32), p -trend = 0.007).

Sensitivity analyses showed similar results when using the lower-bound values as for the middle-bound values and when using the mycotoxin exposure expressed as $\mu\text{g}/\text{day}$ instead of $\mu\text{g}/\text{kg bw}/\text{day}$. Analyses by sex (Supplementary Table S5) indicate differential results for men and women, with significant positive associations between mycotoxins and CRC risk only present among men for DON (HR_{T3vsT1} =1.18 (1.03–1.34)) and *Alternaria* toxins (HR_{T3vsT1} = 1.22 (1.06–1.41)).

4. Discussion

The results presented in this study indicate the potential importance of investigating mycotoxin exposures in diverse European populations. These dietary exposure analyses using the EPIC dietary questionnaire data indicate non-negligible exposures to particular mycotoxins in European countries, confirming the results previously published from smaller studies using 24 h dietary recall, serum and urine data on mycotoxin exposures [35]. Our analyses indicate positive associations between CRC risk and higher dietary DON exposure, which is ubiquitously present in European diets. When investigating associations between mycotoxin exposures and the cancer sub-sites, only PAT was found significantly positively associated with rectal cancer risk, while ergot alkaloids were negatively associated with rectal cancer risk. Sensitivity analyses by sex demonstrated significant positive associations for DON and *Alternaria* toxins in relation with CRC risk in men only. These differential results for sex suggest that that mycotoxins may be metabolised differently by sex and that this difference may be relevant for CRC development.

In a recent study using data from the EPIC cohort we showed that dietary exposure to DON was also positively associated with hepatocellular carcinoma incidence [36], underscoring the potential cancer risk due to DON exposure in Europe. DON is an omnipresent mycotoxin of cereal crops in temperate regions of the world, including Europe, and is mainly produced by the *Fusarium* species [37]. For human exposure, cereals and cereal-based products are the main sources of contamination. Following a request by the European Commission, the EFSA CONTAM Panel assessed the risk to animal and human health related to DON, 3ADON, 15ADON and D3G in food and feed and concluded that the estimated mean chronic dietary exposure was high in adolescents and adults and above the tolerable daily intake (TDI) in infants, toddlers and other children, indicating a potential health concern [38,39]. Recently, a comprehensive human intervention study further revealed from urinary biomarker analysis that DON and D3G were rapidly absorbed, distributed, metabolised and excreted in the human body [40,41]. Since 3ADON and 15ADON are largely deacetylated and D3G is cleaved in the intestine to its parent DON, the same metabolic parameters can be expected; however, their intrinsic toxicity differs [41–47].

The mechanisms potentially underlying the association of DON with CRC risk are still unresolved, although several potential pathways of the adverse health effects of mycotoxins on the human gut have recently been suggested on the intestinal barrier function with special focus on mucus and microbiota [21]. Mucus and microbiota are key targets for dietary mycotoxins, although the assessment of induced effects is in early stages. Recently, it was reported that DON exacerbates the genotoxicity of several different genotoxic compounds, including acrylamide [48], colibactin (a toxin produced by pks+ *Escherichia coli* in the gut microbiota) [49], but also drugs such as etoposide, cisplatin and phleomycin, [50] or pesticides such as captan [51]. Research is currently underway to determine the adverse consequences of mycotoxins on gut mucus and microbiota both as individual components and as interconnected players within the gut ecosystem [21].

Therefore, even though DON has not been classified as a carcinogen in humans (IARC Group 3), this mycotoxin may present a potential threat to health, mainly when co-occurring with other mycotoxins in the consumers' diet [52].

PAT is a mycotoxin produced by *Aspergillus* and *Penicillium* species (abundant on the surface of rotten fruits) with suspected carcinogenic properties, though it does not accumulate in the human body [13,15,53]. A provisional maximum tolerable daily intake (PMTDI) for PAT of 0.4 µg/kg bw has been established [54]. An assessment of dietary intake of PAT across the population of EU Member States in 2002 concluded that PAT exposures were below the value indicated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the Scientific Committee on Food (SCF) [55]. Nevertheless, some countries and population groups may yet be importantly exposed to PAT (even though still below the PMTDI), particularly small children consuming larger amounts of fruit compote and juices compared to adults [55]. Apple juice is occasionally heavily contaminated, and continuing efforts are therefore needed to minimise exposure to this mycotoxin by avoiding the use of rotten or mouldy fruits [56,57].

Efforts to elucidate the toxicity mechanism of PAT have focused on protein tyrosine phosphatases (PTPs), which regulate the function of tight junctions (TJs) in colon epithelial cells. A recent study investigating potential mechanisms involved in the increased risk of CRC due to PAT exposures suggests that density-enhanced phosphatase-1 (DEP-1) affects the function of TJs, and that peroxisome proliferator-activated receptor gamma (PPAR γ) might control DEP-1 expression. Therefore, PAT toxicity to cellular functions might be attributable to its ability to down-regulate the expression of DEP-1 and PPAR γ in human colon cancer cells [58]. Dietary PAT exposure potentially increases susceptibility to intestinal absorption of co-exposed pathogens [59]. Although no human studies have reported a link between PAT exposure and rectal cancer risk, similar mechanisms could potentially be involved as for colon and other mycotoxins, though we also acknowledge such a finding could be chance. As for DON, further research is warranted for PAT to elucidate its potential carcinogenic effects on intestinal cells.

Although no statistically significant association was reported between multi-mycotoxin exposure and CRC risk, the positive trend observed when comparing the third tertile with the first tertile (Table 4; HR: 1.10 (1.00–1.21)) for the sum of mycotoxins in relation with CRC risk suggests more in-depth analyses for investigating potential associations between exposures to clusters of mycotoxins and CRC risk. Since mycotoxin exposures disrupt diverse endogenous mechanisms, synergistic interactions between co-exposed mycotoxins may potentially underly the positive trend reported between total mycotoxins exposure and CRC risk. The integrity of protective systems, either macromolecular such as the intestinal epithelium or micro-molecular such as DNA-damage response pathways, may be compromised by mycotoxin exposure. Subsequently, this enables or increases the susceptibility to pathogenic effects from co-exposed compounds [13]. Interestingly, recent research indicated that toxicological effects of multiple mycotoxins differed regarding the type of mycotoxins used for combinations, and a synergistic effect was observed for mixtures containing DON in different cell lines and intestinal explants [52,60–62]. Further research and in particular more prospective studies in humans are imperative to confirm these findings and to disentangle potential mechanisms involved.

Our study has several strengths, including access to the EPIC study database, which is particularly advantageous due to its large sample size, prospective design, and long follow-up period. Additionally, the inclusion of participants from multiple European countries, combined with standardised data collection methods, especially for dietary information, provides a comprehensive and diverse perspective on dietary intake across Europe. In addition, the access to the EFSA mycotoxin occurrence data derived from the European

member states and support and training provided by the EFSA experts are important strengths of this study. Correspondingly, the in-depth independent quality controls that are performed at all the different levels of these analyses support the quality of the results presented in this report.

Some limitations of the study should also be acknowledged. Dietary intake was assessed using self-reported food frequency questionnaires, which are prone to reporting bias and imprecision. Indeed, errors in dietary reporting, insufficient sampling, and dynamic changes in chemical concentrations throughout food processing can cause uncertainties in exposure assessment. In addition, dietary intake was assessed only at baseline and may not reflect long-term intakes [63]. Further, mycotoxin contamination estimates from the EFSA database may vary due to environmental, temporal and geographical factors and heterogeneous distribution, but epidemiological models use point estimates that cannot capture this variability. This may introduce non-differential imprecision that typically attenuates associations toward the null, though potentially also generates false positives if contamination patterns changed systematically over time. Furthermore, due to the lack of conclusive prevalence data in the EFSA database on certain mycotoxins, e.g., CIT and STC, these were excluded from the study to guarantee the quality of the assessments. Missing covariate data was handled via imputation or categorisation, which may have introduced bias, though sensitivity analyses showed consistent results. Generalisability is limited, as the EPIC cohort comprises relatively health-conscious individuals from 10 European countries. Finally, as this is an observational study, bias such as residual confounding and reverse causation cannot be ruled out and no causal relationship can be inferred based on these data.

While external exposure estimates provide an overview of the global mycotoxin burden, only a portion of ingested mycotoxins reaches systemic circulation, making internal exposure assessment through biomarkers essential for accurate risk evaluation. However, data on biomarker profiles remain limited, complicating intake estimations. Mycotoxin exposure cannot be eliminated through diet changes alone, as they are found in nutritionally essential foods. Therefore, practical prevention strategies and sustained monitoring, especially in light of climate-change-driven shifts in fungal contamination, are crucial [15]. Increased awareness and investment are needed to address this often-overlooked public health threat.

5. Conclusions

In conclusion, these analyses show positive associations between CRC risk and dietary exposure to DON and PAT. Nonetheless, no causal relationship can be investigated with our current data and confirmation of these results through additional studies and biomarker-based approaches is essential. Further, investigation into the possible biological mechanisms underlying these suggested associations is also needed. Although DON and PAT have been assigned Group 3 carcinogens (not classifiable as to their carcinogenicity to humans), they may still pose a health risk and further research is warranted.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/app16147205/s1>, Table S1: Mycotoxins classified according to the IARC Monograph that identifies and evaluates environmental causes of cancer in humans; Table S2: Percentage (%) of the EPIC population with external mycotoxin exposures assessed based upon dietary questionnaire data above and below the Tolerable Daily Intake (TDI) levels set by EFSA; Table S3: Description of the external mycotoxin exposures assessed based upon dietary questionnaire data for the full EPIC cohort by country; Table S4: Percentage (%) contributions of mycotoxins to main food groups of the EPIC population; Table S5: Hazard ratios (HR) and their 95% confidence intervals (CI) for the associations between mycotoxin exposures ($\mu\text{g}/\text{BW}/\text{day}$) and colorectal cancer risk

between male and females using a fully adjusted model*. p -value of 0.01 was considered statistically significant (after Bonferroni correction) [38,64–77].

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and approved by the ethical review boards from IARC, and all local centres approved the study. Registration number: IEC Project 21-07, approved by the IARC Ethical Committee on 27 January 2021.

Informed Consent Statement: Written informed consent was obtained from all subjects involved in the study.

Data Availability Statement: EPIC data are available to investigators in the context of research projects that are consistent with the legal and ethical standard practices of IARC/World Health Organization (WHO) and the EPIC Centres. The use of a random sample of anonymised data from the EPIC study can be requested by contacting epic@iarc.fr. For information on the EPIC data access policy and on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at iarc.who.int. Also, information and access to the questionnaires used in EPIC can be requested by contacting epic@iarc.fr.

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Abbreviations

The following abbreviations are used in this manuscript:

EPIC	European Prospective Investigation into Cancer and Nutrition
EFSA	European Food Safety Authority
CRC	colorectal cancer
HR	hazard ratio
CI	confidence intervals
DON	deoxynivalenol
T	tertile
IARC	International Agency for Research on Cancer
OTA	ochratoxin
FB1	fumonisin B1
FB2	fumonisin B2
FB3	fumonisin B3
PAT	patulin
DQ	dietary questionnaires
FFQ	food-frequency questionnaires
ENDB	EPIC Nutrient Database
LOD	limit of detection
LOQ	limit of quantification
NIV	nivalenol
DAS	diacetoxyscirpenol
FUS-X	fusarenon-X
STC	sterigmatocystin
AF	Aflatoxin
3ADON	3-acetyl-DON
15ADON	15-acetyl-DON
D3G	deoxynivalenol-3-glucoside
ZEN	Zearalenone
ZEL	Zearalenol
ZAN	Zearalanone
AOH	Alternariol
AME	alternariol methylether
ALT	altenuene
TEA	tenuazonic acid
ATX	altertoxin
TEN	tenuazonic acid
AAL_toxins	<i>Alternaria alternate</i> f. sp. <i>lycopersici</i> toxins
CIT	citrinin
SD	standard deviation
BMI	Body Mass Index
bw	body weight

TDI	Tolerable Daily Intake
TWI	Tolerable Weekly Intake
PMTDI	Provisional Maximum Tolerable Daily Intake
LB	Lower Bound
MB	Medium Bound
JECFA	Joint FAO/WHO Expert Committee on Food Additives
TJs	tight junctions
DEP-1	density-enhanced phosphatase-1
PPAR γ	peroxisome proliferator-activated receptor gamma

References

1. United Nations. United Nations Sustainable Development Goals. Available online: <http://www.undp.org/sustainable-development-goals> (accessed on 13 July 2016).
2. De Boevre, M.; Diana Di Mavungu, J.; Landschoot, S.; Audenaert, K.; Eeckhout, M.; Maene, P.; Haesaert, G.; De Saeger, S. Natural occurrence of mycotoxins and their masked forms in food and feed products. *World Mycotoxin J.* **2012**, *5*, 207–219. [[CrossRef](#)]
3. Andrade, P.D.; Caldas, E.D. Aflatoxins in cereals: Worldwide occurrence and dietary risk assessment. *World Mycotoxin J.* **2015**, *8*, 415–431. [[CrossRef](#)]
4. Binder, E.M.; Tan, L.M.; Chin, L.J.; Handl, J.; Richard, J. Worldwide occurrence of mycotoxins in commodities, feeds and feed ingredients. *Anim. Feed. Sci. Technol.* **2007**, *137*, 265–282. [[CrossRef](#)]
5. Pittet, A. Natural occurrence of mycotoxins in foods and feeds—an updated review. *Rev. Méd. Vét.* **1998**, *149*, 479–492.
6. Edwards, S.G. Zearalenone risk in European wheat. *World Mycotoxin J.* **2011**, *4*, 433–438. [[CrossRef](#)]
7. Payros, D.; Garofalo, M.; Pierron, A.; Soler-Vasco, L.; Al-Ayoubi, C.; Maruo, V.M.; Alassane-Kpembi, I.; Pinton, P.; Oswald, I.P. Les mycotoxines en alimentation humaine: Un défi pour la recherche. *Cah. Nutr. Diététique* **2021**, *56*, 170–183. [[CrossRef](#)]
8. FAO. *The State of Food and Agriculture*, 27th ed.; FAO: Rome, Italy, 1994.
9. Schatzmayr, G.; Streit, E. Global occurrence of mycotoxins in the food and feed chain: Facts and figures. *World Mycotoxin J.* **2013**, *6*, 213–222. [[CrossRef](#)]
10. Streit, E.; Naehrer, K.; Rodrigues, I.; Schatzmayr, G. Mycotoxin occurrence in feed and feed raw materials worldwide: Long-term analysis with special focus on Europe and Asia. *J. Sci. Food Agric.* **2013**, *93*, 2892–2899. [[CrossRef](#)] [[PubMed](#)]
11. Eskola, M.; Kos, G.; Elliott, C.T.; Hajšlová, J.; Mayar, S.; Krska, R. Worldwide contamination of food-crops with mycotoxins: Validity of the widely cited ‘FAO estimate’ of 25%. *Crit. Rev. Food Sci. Nutr.* **2019**, *60*, 2773–2789. [[CrossRef](#)] [[PubMed](#)]
12. Sulyok, M.; Berthiller, F.; Krska, R.; Schuhmacher, R. Development and validation of a liquid chromatography/tandem mass spectrometric method for the determination of 39 mycotoxins in wheat and maize. *Rapid Commun. Mass Spectrom.* **2006**, *20*, 2649–2659. [[CrossRef](#)] [[PubMed](#)]
13. De Ruyck, K.; De Boevre, M.; Huybrechts, I.; De Saeger, S. Dietary mycotoxins, co-exposure, and carcinogenesis in humans: Short review. *Mutat. Res. Rev. Mutat. Res.* **2015**, *766*, 32–41. [[CrossRef](#)] [[PubMed](#)]
14. Zhang, W.L.; He, H.; Zang, M.Y.; Wu, Q.F.; Zhao, H.; Lu, L.L.; Ma, P.Q.; Zheng, H.W.; Wang, N.J.; Zhang, Y.; et al. Genetic Features of Aflatoxin-Associated Hepatocellular Carcinoma. *Gastroenterology* **2017**, *153*, 249–262.E2. [[CrossRef](#)] [[PubMed](#)]
15. Mafe, A.N.; Büsselberg, D. Mycotoxins in Food: Cancer Risks and Strategies for Control. *Foods* **2024**, *13*, 3502. [[CrossRef](#)] [[PubMed](#)]
16. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Some traditional herbal medicines, some mycotoxins, naphthalene and styrene. *IARC Monogr. Eval. Carcinog. Risks Hum.* **2002**, *82*, 1–556. [[PubMed](#)]
17. Turner, P.C.; Sylla, A.; Diallo, M.S.; Castegnaro, J.J.; Hall, A.J.; Wild, C.P. The role of aflatoxins and hepatitis viruses in the etiopathogenesis of hepatocellular carcinoma: A basis for primary prevention in Guinea-Conakry, West Africa. *J. Gastroenterol. Hepatol.* **2002**, *17*, S441–S448. [[CrossRef](#)] [[PubMed](#)]
18. Chawanthayatham, S.; Valentine, C.C.; Fedeles, B.I.; Fox, E.J.; Loeb, L.A.; Levine, S.S.; Slocum, S.L.; Wogan, G.N.; Croy, R.G.; Essigmann, J.M. Mutational spectra of aflatoxin B1 in vivo establish biomarkers of exposure for human hepatocellular carcinoma. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, E3101–E3109. [[CrossRef](#)] [[PubMed](#)]
19. Huang, M.N.; Yu, W.; Teoh, W.W.; Ardin, M.; Jusaku, A.; Ng, A.W.T.; Boot, A.; Abedi-Ardekani, B.; Villar, S.; Myint, S.S.; et al. Genome-scale mutational signatures of aflatoxin in cells, mice, and human tumors. *Genome Res.* **2017**, *27*, 1475–1486. [[CrossRef](#)] [[PubMed](#)]
20. Bensassi, F.; El Golli-Bennour, E.; Abid-Essefi, S.; Bouaziz, C.; Hajlaoui, M.R.; Bacha, H. Pathway of deoxynivalenol-induced apoptosis in human colon carcinoma cells. *Toxicology* **2009**, *264*, 104–109. [[CrossRef](#)] [[PubMed](#)]
21. Robert, H.; Payros, D.; Pinton, P.; Theodorou, V.; Mercier-Bonin, M.; Oswald, I.P. Impact of mycotoxins on the intestine: Are mucus and microbiota new targets? *J. Toxicol. Environ. Health Part B Crit. Rev.* **2017**, *20*, 249–275. [[CrossRef](#)] [[PubMed](#)]

22. Pinton, P.; Oswald, I.P. Effect of deoxynivalenol and other Type B trichothecenes on the intestine: A review. *Toxins* **2014**, *6*, 1615–1643. [[CrossRef](#)] [[PubMed](#)]
23. Puel, O.; Galtier, P.; Oswald, I.P. Biosynthesis and toxicological effects of patulin. *Toxins* **2010**, *2*, 613–631. [[CrossRef](#)] [[PubMed](#)]
24. Djouina, M.; Waxin, C.; Caboche, S.; Lecointe, K.; Steimle, A.; Beury, D.; Desai, M.S.; Hot, D.; Dubuquoy, L.; Launay, D.; et al. Low dose dietary contamination with deoxynivalenol mycotoxin exacerbates enteritis and colorectal cancer in mice. *Sci. Total Environ.* **2023**, *900*, 165722. [[CrossRef](#)] [[PubMed](#)]
25. Kwon, O.; Soung, N.K.; Thimmegowda, N.R.; Jeong, S.J.; Jang, J.H.; Moon, D.-O.; Chung, J.K.; Lee, K.S.; Kwon, Y.T.; Erikson, R.L.; et al. Patulin induces colorectal cancer cells apoptosis through EGR-1 dependent ATF3 up-regulation. *Cell. Signal.* **2012**, *24*, 943–950. [[CrossRef](#)] [[PubMed](#)]
26. Abastabar, M.; Akbari, A.; Akhtari, J.; Hedayati, M.T.; Shokohi, T.; Mehrad-Majd, H.; Ghalehnoei, H.; Ghasemi, S. In vitro antitumor activity of patulin on cervical and colorectal cancer cell lines. *Curr. Med. Mycol.* **2017**, *3*, 25–29. [[CrossRef](#)] [[PubMed](#)]
27. Bardelčíková, A.; Šoltys, J.; Mojžiš, J. Oxidative Stress, Inflammation and Colorectal Cancer: An Overview. *Antioxidants* **2023**, *12*, 901. [[CrossRef](#)] [[PubMed](#)]
28. Riboli, E.; Hunt, K.J.; Slimani, N.; Ferrari, P.; Norat, T.; Fahey, M.; Charrondiere, U.R.; Hemon, B.; Casagrande, C.; Vignat, J.; et al. European Prospective Investigation into Cancer and Nutrition (EPIC): Study populations and data collection. *Public Health Nutr.* **2002**, *5*, 1113–1124. [[CrossRef](#)] [[PubMed](#)]
29. Livesey, G. Energy and protein requirements the 1985 report of the 1981 Joint FAO/WHO/UNU Expert Consultation. *Nutr. Bull.* **1987**, *12*, 138–149. [[CrossRef](#)]
30. World Health Organization. *International Classification of Diseases for Oncology, Third Edition, First Revision*; World Health Organization: Geneva, Switzerland, 2013.
31. Huybrechts, I.; Nicolas, G.; Jacobs, I.; Skeie, G.; Gunter, M.J.; Ferrari, P.; Ioannidou, S. Dietary-related exposure assessments in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort: An integrated multi-tiered approach using the FoodEx classification system. *Food Addit. Contaminants. Part A Chem. Anal. Control Expo. Risk Assess.* **2025**, *42*, 849–862. [[CrossRef](#)] [[PubMed](#)]
32. Slimani, N.; Deharveng, G.; Unwin, I.; Southgate, D.A.; Vignat, J.; Skeie, G.; Salvini, S.; Parpinel, M.; Moller, A.; Ireland, J.; et al. The EPIC nutrient database project (ENDB): A first attempt to standardize nutrient databases across the 10 European countries participating in the EPIC study. *Eur. J. Clin. Nutr.* **2007**, *61*, 1037–1056. [[CrossRef](#)] [[PubMed](#)]
33. Huybrechts, I.; Sioen, I.; Boon, P.E.; Ruprich, J.; Lafay, L.; Turrini, A.; Amiano, P.; Hirvonen, T.; De Neve, M.; Arcella, D.; et al. Dietary exposure assessments for children in europe (the EXPOCHI project): Rationale, methods and design. *Arch. Public Health* **2011**, *69*, 4. [[CrossRef](#)] [[PubMed](#)]
34. WCRF/AICR. Diet, Nutrition, Physical Activity and Cancer: A Global Perspective. The Third Expert Report. Available online: <https://www.wcrf.org/dietandcancer> (accessed on 20 April 2026).
35. De Ruyck, K.; Huybrechts, I.; Yang, S.; Arcella, D.; Claeys, L.; Abbeddou, S.; De Keyser, W.; De Vries, J.; Ocke, M.; Ruprich, J.; et al. Mycotoxin exposure assessments in a multi-center European validation study by 24-hour dietary recall and biological fluid sampling. *Environ. Int.* **2020**, *137*, 105539. [[CrossRef](#)] [[PubMed](#)]
36. Huybrechts, I.; Jacobs, I.; Biessy, C.; Aglago, E.K.; Jenab, M.; Claeys, L.; Zavadil, J.; Casagrande, C.; Nicolas, G.; Scelo, G.; et al. Associations between dietary mycotoxins exposures and risk of hepatocellular carcinoma in a European cohort. *PLoS ONE* **2024**, *19*, e0315561. [[CrossRef](#)] [[PubMed](#)]
37. Berthiller, F.; Dall'Asta, C.; Corradini, R.; Marchelli, R.; Sulyok, M.; Krska, R.; Adam, G.; Schuhmacher, R. Occurrence of deoxynivalenol and its 3-D-glucoside in wheat and maize. *Food Addit. Contam. Part A-Chem. Anal. Control Expo. Risk Assess.* **2009**, *26*, 507–511. [[CrossRef](#)] [[PubMed](#)]
38. EFSA Panel on Contaminants in the Food Chain (CONTAM); Knutsen, H.K.; Alexander, J.; Barregård, L.; Bignami, M.; Brüschweiler, B.; Ceccatelli, S.; Cottrill, B.; Dinovi, M.; Grasl-Kraupp, B.; et al. Risks to human and animal health related to the presence of deoxynivalenol and its acetylated and modified forms in food and feed. *EFSA J.* **2017**, *15*, 4718. [[CrossRef](#)] [[PubMed](#)]
39. Vin, K.; Rivière, G.; Leconte, S.; Cravedi, J.P.; Fremy, J.M.; Oswald, I.P.; Roudot, A.C.; Vasseur, P.; Jean, J.; Hulin, M.; et al. Dietary exposure to mycotoxins in the French infant total diet study. *Food Chem. Toxicol. Int. J. Publ. Br. Ind. Biol. Res. Assoc.* **2020**, *140*, 111301. [[CrossRef](#)] [[PubMed](#)]
40. Vidal, A.; Claeys, L.; Mengelers, M.; Vanhoorne, V.; Vervaet, C.; Huybrechts, B.; De Saeger, S.; De Boevre, M. Humans significantly metabolize and excrete the mycotoxin deoxynivalenol and its modified form deoxynivalenol-3-glucoside within 24 hours. *Sci. Rep.* **2018**, *8*, 5255. [[CrossRef](#)] [[PubMed](#)]
41. Mengelers, M.Z.; Vidal, M.; De Boevre, A.; De Saeger, M.; Hoogenveen, R. Kinetic analysis of the renal excretion of deoxynivalenol and deoxynivalenol-3-glucoside in humans. *Toxins* **2018**, *11*, 466. [[CrossRef](#)] [[PubMed](#)]
42. Broekaert, N.; Devreese, M.; De Baere, S.; De Backer, P.; Croubels, S. Modified Fusarium mycotoxins unmasked: From occurrence in cereals to animal and human excretion. *Food Chem. Toxicol.* **2015**, *80*, 17–31. [[CrossRef](#)] [[PubMed](#)]

43. Broekaert, N.; Devreese, M.; De Mil, T.; Fraeyman, S.; Antonissen, G.; De Baere, S.; De Backer, P.; Vermeulen, A.; Croubels, S. Oral Bioavailability, Hydrolysis, and Comparative Toxicokinetics of 3-Acetyldeoxynivalenol and 15-Acetyldeoxynivalenol in Broiler Chickens and Pigs. *J. Agric. Food Chem.* **2015**, *63*, 8734–8742. [[CrossRef](#)] [[PubMed](#)]
44. Berthiller, F.; Krska, R.; Domig, K.; Kneifel, W.; Juge, N.; Schuhmacher, R.; Adam, G. Hydrolytic fate of deoxynivalenol-3-glucoside during digestion. *Toxicol. Lett.* **2011**, *206*, 264–267. [[CrossRef](#)] [[PubMed](#)]
45. De Boevre, M.; Graniczowska, K.; De Saeger, S. Metabolism of modified mycotoxins studied through in vitro and in vivo models: An overview. *Toxicol. Lett.* **2015**, *233*, 24–28. [[CrossRef](#)]
46. Suzuki, T.; Iwahashi, Y. Low Toxicity of Deoxynivalenol-3-Glucoside in Microbial Cells. *Toxins* **2015**, *7*, 187–200. [[CrossRef](#)] [[PubMed](#)]
47. Pierron, A.; Mimoun, S.; Murate, L.S.; Loiseau, N.; Lippi, Y.; Bracarense, A.P.; Liaubet, L.; Schatzmayr, G.; Berthiller, F.; Moll, W.D.; et al. Intestinal toxicity of the masked mycotoxin deoxynivalenol-3- β -D-glucoside. *Arch. Toxicol.* **2016**, *90*, 2037–2046. [[CrossRef](#)] [[PubMed](#)]
48. Huertas, C.; Coulibaly, A.B.; Payros, D.; Penary, M.; Puel, S.; Naylies, C.; Payros, G.; Lippi, Y.; Oswald, I.P.; Mirey, G.; et al. Genotoxic interaction between deoxynivalenol and acrylamide. *Food Res. Int.* **2025**, *214*, 116633. [[CrossRef](#)] [[PubMed](#)]
49. Payros, D.; Dobrindt, U.; Martin, P.; Secher, T.; Bracarense, A.; Boury, M.; Laffitte, J.; Pinton, P.; Oswald, E.; Oswald, I.P. The Food Contaminant Deoxynivalenol Exacerbates the Genotoxicity of Gut Microbiota. *mBio* **2017**, *8*, 11. [[CrossRef](#)] [[PubMed](#)]
50. Garofalo, M.; Payros, D.; Oswald, E.; Nougayrède, J.P.; Oswald, I.P. The foodborne contaminant deoxynivalenol exacerbates DNA damage caused by a broad spectrum of genotoxic agents. *Sci. Total Environ.* **2022**, *820*, 153280. [[CrossRef](#)] [[PubMed](#)]
51. Garofalo, M.; Payros, D.; Penary, M.; Oswald, E.; Nougayrède, J.P.; Oswald, I.P. A novel toxic effect of foodborne trichothecenes: The exacerbation of genotoxicity. *Environ. Pollut.* **2023**, *317*, 120625. [[CrossRef](#)] [[PubMed](#)]
52. Sobral, M.M.C.; Faria, M.A.; Cunha, S.C.; Ferreira, I. Toxicological interactions between mycotoxins from ubiquitous fungi: Impact on hepatic and intestinal human epithelial cells. *Chemosphere* **2018**, *202*, 538–548. [[CrossRef](#)] [[PubMed](#)]
53. Ouhibi, S.; Vidal, A.; Gali, R.; Hedhili, A.; De Saeger, S.; De Boevre, M. The mycotoxin patulin: An updated overview on occurrence, toxicity and analytical challenges. *Food Chem. Toxicol.* **2019**, *129*, 249–256. [[CrossRef](#)]
54. JECFA. *Evaluation of Certain Food Additives and Contaminants*; WHO Technical Report Series; TRS 859-JECFA 44/36; WHO: Geneva, Switzerland, 1995.
55. European Commission. *Report of Experts Participating in Task 3.2.8—Assessment of Dietary Intake of Patulin by the Population of EU Member States*; Reports on Tasks for Scientific Cooperation; European Commission: Brussels, Belgium, 2002.
56. De Smet, D.; Dubrue, P.; Van Peteghem, C.; De Saeger, S. Development of a molecularly imprinted polymer for patulin in apple juice. *World Mycotoxin J.* **2011**, *4*, 375–383. [[CrossRef](#)]
57. Baert, K.; De Meulenaer, B.; Kamala, A.; Kasase, C.; Devlieghere, F. Occurrence of patulin in organic, conventional, and handcrafted apple juices marketed in Belgium. *J. Food Prot.* **2006**, *69*, 1371–1378. [[CrossRef](#)] [[PubMed](#)]
58. Katsuyama, A.; Konno, T.; Shimoyama, S.; Kikuchi, H. The mycotoxin patulin decreases expression of density-enhanced phosphatase-1 by down-regulating PPARgamma in human colon cancer cells. *Tohoku J. Exp. Med.* **2014**, *233*, 265–274. [[CrossRef](#)] [[PubMed](#)]
59. Akbari, P.; Braber, S.; Varasteh, S.; Alizadeh, A.; Garssen, J.; Fink-Gremmels, J. The intestinal barrier as an emerging target in the toxicological assessment of mycotoxins. *Arch. Toxicol.* **2017**, *91*, 1007–1029. [[CrossRef](#)] [[PubMed](#)]
60. Alassane-Kpembi, I.; Puel, O.; Pinton, P.; Cossalter, A.M.; Chou, T.C.; Oswald, I.P. Co-exposure to low doses of the food contaminants deoxynivalenol and nivalenol has a synergistic inflammatory effect on intestinal explants. *Arch. Toxicol.* **2017**, *91*, 2677–2687. [[CrossRef](#)] [[PubMed](#)]
61. Alassane-Kpembi, I.; Puel, O.; Oswald, I.P. Toxicological interactions between the mycotoxins deoxynivalenol, nivalenol and their acetylated derivatives in intestinal epithelial cells. *Arch. Toxicol.* **2015**, *89*, 1337–1346. [[CrossRef](#)] [[PubMed](#)]
62. Alassane-Kpembi, I.; Gerez, J.R.; Cossalter, A.M.; Neves, M.; Laffitte, J.; Naylies, C.; Lippi, Y.; Kolf-Clauw, M.; Bracarense, A.P.L.; Pinton, P.; et al. Intestinal toxicity of the type B trichothecene mycotoxin fusarenon-X: Whole transcriptome profiling reveals new signaling pathways. *Sci. Rep.* **2017**, *7*, 7530. [[CrossRef](#)] [[PubMed](#)]
63. Willett, W.C. *Nutritional Epidemiology*, 2nd ed; Oxford University Press: New York, NY, USA, 1998.
64. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risk to Human. Available online: <https://monographs.iarc.who.int/> (accessed on 20 April 2026).
65. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risk to Human, Volume 100F (2012) Chemical Agents and Related Occupations*; IARC: Lyon, France, 2012.
66. International Agency for Research on Cancer. Advisory Group recommendations on priorities for the IARC Monographs. *Lancet Oncol.* **2019**, *20*, 763–764. [[CrossRef](#)] [[PubMed](#)]
67. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risk to Human, Volume 56 (1993) Some Naturally Occurring Substances: Food Items and Constituents, Heterocyclic Aromatic Amines and Mycotoxins*; IARC: Lyon, France, 1993.

68. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risk to Human, Volume 82 (2002) Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene*; IARC: Lyon, France, 2002.
69. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risk to Human, Volume 10 Some Naturally Occurring Substances 1976*; IARC: Lyon, France, 1976.
70. International Agency for Research on Cancer. *IARC Monographs on the Evaluation of Carcinogenic Risk to Human, Volume 40 Some Naturally Occurring and Synthetic Food Components, Furocoumarins and Ultraviolet Radiation 1986*; IARC: Lyon, France, 1986.
71. Arcella, D.; Gómez Ruiz, J.; Innocenti, M.L.; Roldán, R. Human and animal dietary exposure to ergot alkaloids. *EFSA J.* **2017**, *15*, e04902. [[CrossRef](#)] [[PubMed](#)]
72. Schrenk, D.; Bodin, L.; Chipman, J.K.; Del Mazo, J.; Grasl-Kraupp, B.; Hogstrand, C.; Hoogenboom, L.R.; Leblanc, J.C.; Nebbia, C.S.; Nielsen, E.; et al. Risk assessment of ochratoxin A in food. *EFSA J.* **2020**, *18*, e06113. [[CrossRef](#)] [[PubMed](#)]
73. Schrenk, D.; Bignami, M.; Bodin, L.; Chipman, J.K.; Del Mazo, J.; Grasl-Kraupp, B.; Hogstrand, C.; Hoogenboom, L.R.; Leblanc, J.C.; Nebbia, C.S.; et al. Risk assessment of aflatoxins in food. *EFSA J.* **2020**, *18*, e06040. [[CrossRef](#)] [[PubMed](#)]
74. *GEMS/Food-EURO: Second Workshop on Reliable Evaluation of Low-Level Contamination of Food: Report on a Workshop in the Frame of GEMS/Food-EURO, Kulmbach, Federal Republic of Germany, 26-27 May 1995: EUR/HFA Target 22*; Federal Centre for Meat Research, Institut für Chemie und Physik: Kulmbach, Germany, 1995.
75. EFSA Panel on Contaminants in the Food Chain (CONTAM). Scientific Opinion on the risks for animal and public health related to the presence of T-2 and HT-2 toxin in food and feed. *EFSA J.* **2011**, *9*, 2481. [[CrossRef](#)]
76. Knutsen, H.K.; Barregård, L.; Bignami, M.; Brüschweiler, B.; Ceccatelli, S.; Cottrill, B.; Dinovi, M.; Edler, L.; Grasl-Kraupp, B.; Hogstrand, C.; et al. Appropriateness to set a group health-based guidance value for fumonisins and their modified forms. *EFSA J.* **2018**, *16*, e05172. [[CrossRef](#)] [[PubMed](#)]
77. EFSA Panel on Contaminants in the Food Chain (CONTAM). Scientific Opinion on the risks for public health related to the presence of zearalenone in food. *EFSA J.* **2011**, *9*, 2197. [[CrossRef](#)]

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