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Mycotoxin exposure and human cancer risk: A systematic review of epidemiological studies

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Abstract

In recent years, there has been an increasing interest in investigating the carcinogenicity of mycotoxins in humans. This systematic review aims to provide an overview of data linking exposure to different mycotoxins with human cancer risk. Publications (2019 and earlier) of case–control or longitudinal cohort studies were identified in PubMed and EMBASE. These articles were then screened by independent reviewers and their quality was assessed according to the Newcastle–Ottawa scale. Animal, cross-sectional, and molecular studies satisfied criteria for exclusion. In total, 14 articles were included: 13 case–control studies and 1 longitudinal cohort study. Included articles focused on associations of mycotoxin exposure with primary liver, breast, and cervical cancer. Overall, a positive association between the consumption of aflatoxin-contaminated foods and primary liver cancer risk was verified. Two case–control studies in Africa investigated the relationship between zearalenone and its metabolites and breast cancer risk, though conflicting results were reported. Two case–control studies investigated the association between hepatocellular carcinoma and fumonisin B1 exposure, but no significant associations were observed. This systematic review incorporates several clear observations of dose-dependent associations between aflatoxins and liver cancer risk, in keeping with IARC Monograph conclusions. Only few human epidemiological studies investigated the associations between mycotoxin exposures and cancer risk. To close this gap, more in-depth research is needed to unravel evidence for other common mycotoxins, such as deoxynivalenol and ochratoxin A. The link between mycotoxin exposures and cancer risk has mainly been established in experimental studies, and needs to be confirmed in human epidemiological studies to support the evidence-based public health strategies.

KEYWORDS

aflatoxin, cancer, exposure, food, fumonisin, fungal metabolites, mycotoxins

1 | INTRODUCTION

Mycotoxins are fungal secondary metabolites that exert adverse health effects on humans and animals through primarily oral exposure. These fungi widely occur on agricultural crops, such as wheat, maize (corn), and nuts, and their derived food and feed products. In certain climatic conditions, molds are capable of producing more than one mycotoxin, and some mycotoxins are produced by more than one fungal species (Zain, 2011). This consequently results in the coexposure to multiple mycotoxins and the risk of subsequent associated adverse effects, including carcinogenicity. The type of mycotoxin and the level and frequency of exposure (acute or chronic) affect the manifestation of the disease, as well as age, body mass index, gender, concomitant health issues, and possible synergistic effects of other chemicals to which the individual is exposed to (De Ruyck et al., 2015; Peraica et al., 1999). Acute toxicity generally has a rapid onset and an obvious toxic response, while chronic toxicity is characterized by low-dose exposure over a long time-period, which can ultimately result in malignant tumors and other permanent detrimental effects (De Ruyck et al., 2015).

Most of the mycotoxins are easily absorbed from the site of exposure, such as the gastrointestinal (i.e., dietary consumption) or respiratory tract (i.e., inhalation dust), to the circulatory system reaching vital, as the toxin is distributed throughout the body (Adam et al., 2017). Mycotoxins can enter human and animal cells and exert a spectrum of effects, including permanent damage. Through natural cellular processes of transcription and translation, these mutations may manifest or even exacerbate deregulation of cell growth (Adam et al., 2017). Several cellular processes, including DNA replication and protein synthesis, are affected by ochratoxin A (OTA) and deoxynivalenol (DON). Moreover, aflatoxin B1 (AFB1) has been recognized for its carcinogenicity, mostly through genotoxic effects, by the World Health Organization's (WHO) International Agency for Research on Cancer (IARC) Monographs Program (De Ruyck et al., 2015). Table 1 represents the mycotoxins classified by the IARC Monograph evaluation program.

Many mycotoxins exhibit overlapping toxicities in animals, plants, and microorganisms. The individual or intrinsic toxicity has been investigated for numerous mycotoxins, usually in relation to acute pathologies (De Ruyck et al., 2015). Among chronic coexposures to mycotoxins, complex interactions have recently been suggested, possibly resulting in additive or even synergistic effects (De Ruyck et al., 2015). Despite the growing number of studies and evidence, additional in-depth investigations are needed to confirm the ability of each individual and/or combinations of mycotoxins to induce cancer (Adam et al., 2017). The type and mechanism of action of mycotoxins within the biological system determines its role in causing cancer and contributes to other adverse health effects (Adam et al., 2017). In the recent years, there has been an increasing interest in the investigation of mycotoxin-induced carcinogenicity and the underlying mechanisms, using animal models and cultured cell systems. In addition to animal and mechanistic studies, IARC Monographs evaluations (Table 1) put a strong emphasis on human epidemiological studies for carcinogenicity classification (IARC, 1993a, 2012). To investigate mycotoxin-mediated cancer risk in humans, large-scale epidemiological studies are warranted. The main purpose of this systematic review is to summarize the current evidence regarding the relationship between mycotoxins and cancer risk in humans.

2 | MATERIALS AND METHODS

2.1 | Data sources and search strategy

Searches of PubMed and EMBASE (from their commencements to December 2019) were performed, comprising keywords related to mycotoxins ("mycotoxins," " fungal metabolites," "aflatoxin," "ochratoxin," "ergot alkaloids," "patulin," "fusarium," "deoxynivalenol," "diacetoxyscirpenol," "zearalenone," "fusaric acid," "sterigmatocystin," "Alternaria alternata pathotoxin TA," "altertoxin," "tentoxin," "citrinin," "beauvericin," "mycophenolic acid," "enniatins," and "phomopsin") combined with "exposure," "neoplasms," "cancer," and "humans."

MeSH and Emtree terms were used to build up a structured search. To find additional articles, evidence tables and references from earlier publications were examined.

Pubmed Syntax: ("mycotoxin"[All Fields] OR "aflatoxin"[All Fields] OR "ochratoxin"[All Fields] OR "ergot alkaloids"[All Fields] OR "patulin"[All Fields] OR "Fusarium"[All Fields] OR "deoxynivalenol"[All Fields] OR "diacetoxyscirpenol"[All Fields] OR "zearalenone"[All Fields] OR "fusaric acid"[All Fields] OR "sterigmatocystin"[All Fields] OR "Alternaria alternata pathotoxin TA"[All Fields] OR "altertoxin"[All Fields] OR "tentoxin"[All Fields] OR "citrinin"[All Fields] OR "beauvericin"[All Fields] OR "mycophenolic acid"[All Fields] OR "enniatins"[All Fields] OR "phomopsin"[All Fields]) AND ("exposure"[All Fields]) AND ("neoplasms"[All Fields] OR "cancer"[All Fields]) AND "humans"[MeSH Terms].

2.2 | Study selection

2.2.1 | Inclusion criteria

Studies were only included if they investigated the link between mycotoxin exposure and risks of one or more cancer types in humans. Specifically, only cohort studies, and

TABLE 1 Mycotoxins classified according to the IARC Monograph that identifies and evaluates environmental causes of cancer in humans

IARC classification (IARC, 2006)	Mycotoxin (IARC, 2012)	Publication year of IARC Monograph
Group 1: the agent is carcinogenic to humans	AFB1, AFB2, AFG1, AFG2, AFM1	2012 (IARC, 2019; IARC, 2012)
Group 2A: the agent is probably carcinogenic to humans		
Group 2B: the argent is possibly carcinogenic to humans	OTA	1993 (IARC, 1993b)
	FB1, FB2	2002 (IARC Monographs Priorities Group, 2019; IARC, 2002)
	STC	1987 (IARC, 1987a)
	Fusarin C	1993 (IARC, 1993a)
Group 3: the agent is not classifiable as to its carcinogenicity to humans	DON	1993 (IARC, 1993a)
	ZEN	1993 (IARC, 1993a)
	Fusarenone X	1993 (IARC, 1993a)
	CIT	1987 (IARC, 1987b)
	PAT	1987 (IARC, 1987b)
Group 4: the agent is probably not carcinogenic to humans		

Abbreviations: AFB1, aflatoxin B1; AFB2, aflatoxin B2; AFG1, aflatoxin G1; AFG2, aflatoxin G2; AFM1, aflatoxin M1; CIT, citrinin; DON, deoxynivalenol; FB1, fumonisin B1; FB2, fumonisin B2; OTA, ochratoxin A; PAT, patulin; STC, sterigmatocystin; ZEN, zearalenone.

(nested) case–control studies were included. Only articles originally published in English were included.

2.2.2 | Exclusion criteria

The criteria for exclusion of studies were cross-sectional studies, noncohort or noncase–control studies, molecular studies (e.g., animal and cell line studies), and molecular patterns of carcinogenesis studies. Publications that did not focus on the link between mycotoxin exposure and cancer risk but only on mycotoxins or cancer were excluded.

2.2.3 | Type of outcome measurements

Original research on the risk of cancer associated with human exposure to mycotoxins was systematically reviewed and presented here to provide an update on current research in this critical field.

2.3 | Data collection and analysis

2.3.1 | Selection of studies

Three investigators (L.C., C.R., and H.W.) independently selected titles and abstracts from the bibliography retrieved by the search strategy, according to the inclusion and exclusion criteria. Selections from the search strategy were entered in an EndNote library. Full text copies were then obtained for studies that fulfilled the criteria. In case of disagreement between the three investigators or when fulfillment to the criteria was unclear, the opinion of the writing group was requested to reach consensus. The study selection procedure is summarized in Figure 1.

2.3.2 | Quality of the articles

To analyze the quality of the articles, the Newcastle–Ottawa scale (NOS) of quality assessment was used (Ottawa Hospital Reseach Institute, n.d.). This assessment scale consists of three categories (selection, comparability, and exposure); therefore, each study was evaluated on three broad criteria: (a) proper selection of study population, (b) comparability of the study groups, and (c) ascertainment of the exposure or outcome of interest. Each article could receive up to four stars for selection, two stars for comparison, and three stars for exposure. Table A1 presents an overview of the Newcastle–Ottawa criteria used for the quality assessment of case–control and cohort studies.

2.3.3 | Types of mycotoxins and cancer

Mycotoxin exposure and specific cancer sites were considered.

2.3.4 | Data extraction

The following parameters were extracted from the publications and included in the final article selection: length of follow-up, potential confounders taken into account (e.g., age and gender), study type, mycotoxin type, type of matrix, cancer site, location/duration of the study, range of exposure, and analytical detection limit. Table 2 shows the final selection of publications, detailing their characteristics of eligibility.

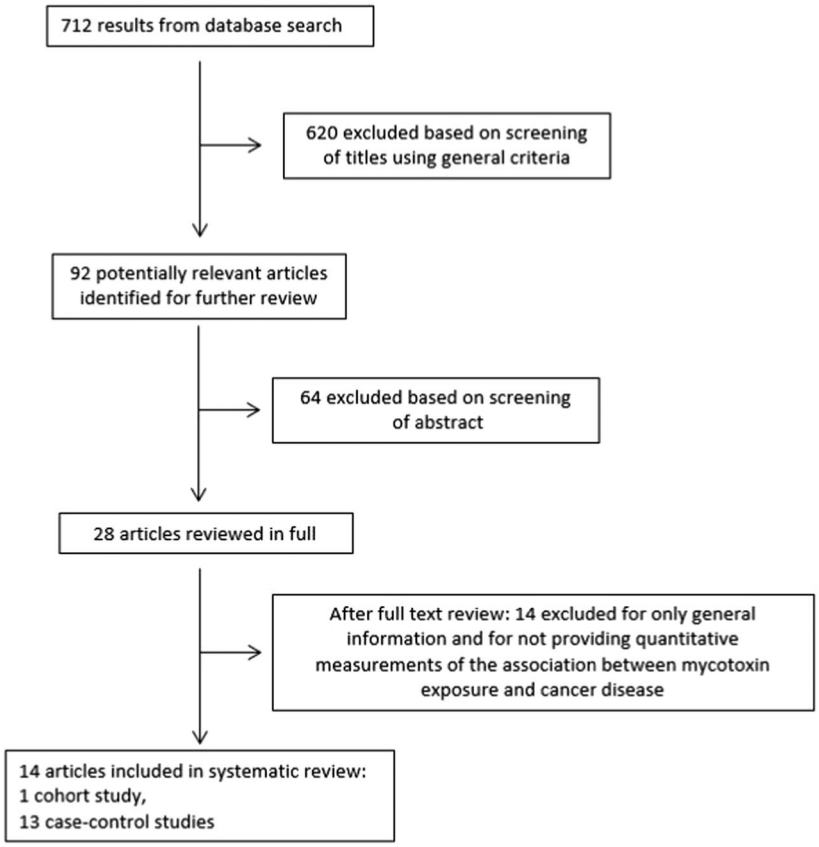

FIGURE 1 Selection of studies for inclusion in the systematic review

3 | RESULTS

3.1 | Study design and population characteristics

A total of 14 articles were finally included in this systematic review. A detailed overview of the different studies and their study design and methods used is given in Table 2. Thirteen studies were case–control studies, including three nested case–control studies, and one study was a longitudinal cohort study. The most frequently studied cancer was primary liver cancer (PLC), followed by breast cancer.

Most of the studies were conducted in Asia ($n = 11$), followed by Africa ($n = 3$). No comparable studies from Europe were found that fulfilled the inclusion criteria.

Aflatoxins (AFs) were the mycotoxins most frequently studied or observed, followed by fumonisin B1 (FB1) and zearalenone (ZEN). Different exposure matrices were examined. The majority of the studies used blood, plasma, or serum ($n = 5$), or urine ($n = 5$), followed by food ($n = 2$) or toenails ($n = 2$) as exposure matrices. Other examined matrices were feces ($n = 1$), liver tissue ($n = 1$), and dust ($n = 1$).

The years of publication ranged from 1982 to 2015, with the majority ($n = 8$) published between 2000 and 2015.

The size of the study populations varied widely. One article had a sample size of only 58 participants, eight articles had a population ranging from 100 to 300, four studies used a population size from 300 to 700, and one study included over 900 subjects. The largest number of subjects was studied in the context of liver cancer ($n = 1{,}102$). All studies covered a population ranging in age between 15 and 74 years.

Table 3 outlines the observed mycotoxins in the selected studies and the different cancer types for which a relationship has been investigated.

Ten studies examined the association between AF and PLC. PLC was divided into hepatocellular carcinoma (HCC) ($n = 7$) and cholangiocarcinoma ($n = 1$); two articles did not further specify the type of PLC. In addition to AF, two articles investigated PLC, namely, HCC, in relation to the FB1 exposure. Three studies examined the carcinogenic effects of ZEN: two with breast cancer and one with cervical cancer.

3.2 | Study quality

The NOS was used to evaluate the quality of each article, as described in Table 2. Overall scores ranged from 0 to 7. Some articles did not give information on the participants nor had an appropriate study design. Most of the articles scored well for selection: five articles received four stars, five articles had three stars, one article had two stars, and one article had one star. Two publications scored zero for selection, mainly due to the lack of information on the selection of controls; however, it remained in the review material based on the relevance of the cancer scope and study size.

TABLE 2 Characteristics of the eligible studies included in the systematic review

№	Source	Population	Study period	Study type	Sex	*N*	Mean age (σ)	Cases	Controls	Study duration	Exposure	MT	LOD; LOQ	Matrix	Cancer site(s)	ORs, RRs	Quality of the article
1	Belhassen et al. (2015)	Tunisia	05/2012–10/2012	Cc	F	110	49.9 (11.0)	69	41	6 months	n/a	α-ZAL	0.2 ng/mL; 0.7 ng/mL	Urine	Breast	OR: 1.54	Selection:** Comparability:* Exposure:*** Total NOS score: 6
2	Bulatao-Jayme, Almero, Castro, Jardeleza, and Salamat (1982)	Philippines	n/a	Cc	B (82.2% M)	180	15-74	90	90	n/a	Dietary	AF	n/a	Urine	PLC	RR: LightAF/Mc HeavyAF: 1/13.9/17	Selection:*** Comparability:* Exposure:** Total NOS score: 6
3	Chao et al. (1994)	Singapore	1991–1992	Cc	n/a	481	n/a	58	423	2 years	n/a	AF	n/a	Blood and liver	PLC: HCC	n/a	Selection: / Comparability: / Exposure: / Total NOS score: 0
4	Chen et al. (2013)	China	1982–2012	Longitudina cohort	B (61.7% M)	652	21-65	n/a	n/a	30 years	Dietary	AF	n/a	Serum	PLC	RR: 7.3 (men with HBV, no AF) RR: 3.4 (men with no HBV, AF) RR: 59.4 (men with HBV, urinary AF-biomarkers)	Selection: / Comparability:* Exposure: / Total NOS score: 1
5	Lai et al. (2014)	China	10/2013–03/2014	Cc	B	218	40.38 (9.32)	68	150	6 months	Environmental	AF	n/a	Dust and serum	PLC: HCC	OR: 5.24	Selection:**** Comparability:** Exposure:* Total NOS score: 7
6	Omer et al. (1998)	Sudan	05/1995–11/1995	Cc	n/a	58	n/a	24	34	7 months	n/a	AF	n/a	Food	PLC: HCC	OR: 7.5	Selection:*** Comparability:** Exposure:* Total NOS score: 6
7	Parkin et al. (1991)	Thailand	1987–1988	Cc	B (68.9% M)	206	54.75 (11.9)	103	103	1 year	Dietary	AF	n/a	Blood and feces	PLC: Cholangio-carcinoma	OR: 1.4	Selection:*** Comparability:** Exposure:* Total NOS score: 6

(Continues)

TABLE 2 (Continued)

№	Source	Population	Study period	Study type	Sex	*N*	Mean age (σ)	Cases	Controls	Study duration	Exposure	MT	LOD; LOQ	Matrix	Cancer site(s)	ORs, RRs	Quality of the article
8	Persson et al. (2012)	China	01/1993–09/2000	Nested cc	B (91.8% M)	551	45 (8.8)	271	280	7 years, 8 months	n/a	FB1	6 pg/L; 20 pg/L	Toenails	PLC: HCC	OR: 1.1	Selection:**** Comparability:** Exposure:* Total NOS score: 7
9	Persson et al. (2012)	China	05/1991–05/2001	Nested cc	B (74.4% M)	219	56 (7.8)	72	147	10 years	n/a	FB1	6 pg/L; 20 pg/L	Toenails	PLC: HCC	OR: 1.47	Selection:**** Comparability:** Exposure:* Total NOS score: 7
10	Pillay et al. (2002)	South Africa	n/a	Cc	F	106	n/a	82	24	n/a	n/a	ZEN	25 ng/mL	Serum	Breast, cervix	n/a	Selection:* Comparability:* Exposure: / Total NOS score: 2
11	Wang et al. (1996)	Taiwan	02/1991–06/1995	Cc	B (89.5% M)	276	n/a	56	220	4 years, 5 months	Environmen	AF	0.01 fm/μg albumin	Blood and urine	PLC: HCC	OR: 7.2	Selection:*** Comparability:** Exposure:* Total NOS score: 6
12	Wu et al. (2008)	Taiwan	02/1991–06/2001	Nested cc	B	364	n/a	74	290	10 years, 5 months	Environmental	AFB1	0.2 ng/mL	Urine	PLC: HCC	OR: 7.5	Selection:**** Comparability:** Exposure:* Total NOS score: 7
13	Wu et al. (2009)	Taiwan	02/1991–06/2004	cc	B (83.3% M)	1.102	n/a	198	904	13 years, 5 months	Environmen	AFB1	n/a	Urine	PLC: HCC	OR: 5.5	Selection:**** Comparability:** Exposure:* Total NOS score: 7
14	Zhang, Wang, Han, & Zhuang (1998)	China	01/1994–10/1995	cc	B (88.0% M)	267	52 (12.6)	152	115	1 year, 10 months	Dietary	AF	n/a	Food	PLC: HCC	OR: 16.44	Selection:*** Comparability:** Exposure:* Total NOS score: 6

Abbreviations: AFB1, aflatoxin B1; AF, aflatoxins; B, both sexes; cc, case–control; F, female; FB1, fumonisin B1; HCC, hepatocellular carcinoma; LOD, limit of detection; LOQ, limit of quantification; M, male; MT, mycotoxin; NOS, Newcastle–Ottawa scale; n/a, not available; OR, odds ratio; PLC, primary liver cancer; RR, relative risk; ZEN, zearalenone; α-ZAL, α-zearalanol; Points assigned for the NOS score were presented as stars (*). One star stands for one point.

TABLE 3 Reviewed mycotoxins and possible links with cancer researched in this study, linked with the cancer subtypes and amount of articles

Mycotoxin	Link with the following cancer(s)	Cancer subtypes
Aflatoxins	Primary liver cancer	7 - hepatocellular carcinoma; 1 - cholangiocarcinoma; 2 - no type specified
Fumonisin B1	Primary liver cancer	2 - hepatocellular carcinoma
Zearalenone	Breast cancer	2
Zearalenone	Cervical cancer	1

For comparability, nine articles scored the maximum of two stars, while four articles received one star. One publication did not obtain any score for comparability. For the third category, exposure, most of the articles had only one star; only one publication had three stars and one received two stars. Low scores on exposure were mostly caused by the confirmation of exposure, which was performed by a nonblinded interview, and did not mention the nonresponse rate.

3.3 | Overall significant findings

Ten studies investigated the associations between AF and liver cancer risk, of which nine suggested a positive, dose-dependent association between the consumption of AF and the risk of developing PLC. On the other hand, only one single article did not find an association between liver cancer and AF intake, hepatitis B infection, and a particular dietary pattern (Parkin et al., 1991).

Two case–control studies in Africa investigated the associations between ZEN and its metabolites, namely, α-zearalenol (α-ZEL), β-zearalenol (β-ZEL), α-zearalanol (α-ZAL), β-zearalanol (β-ZAL), and zearalanone (ZAN), with breast cancer risk. Conflicting results were found, although, the examined biological matrices may not be directly comparable, as one study examined blood and the other urine. Only one article investigated the cervical cancer risk in relation to ZEN exposure. No results were found to suggest a causal relationship between the presence of ZEN in blood and cervical cancer in the study population.

Finally, two studies using a case–control design examined the association between HCC and FB1 exposure. No statistically significant associations were found between FB1 and HCC (Persson et al., 2012).

4 | DISCUSSION

4.1 | Liver cancer

Most publications in this systematic review examined the association between AF and liver cancer. AF, namely, AFB1, aflatoxin B2 (AFB2), aflatoxin G1 (AFG1), aflatoxin G2 (AFG2), and aflatoxin M1 (AFM1), are the only mycotoxins categorized as Group 1 carcinogens by the IARC Monographs (IARC, 2012; IARC, 2019a). Based on the report of the IARC's Monographs Priorities Group, AFs are annotated as medium priority agents for future evaluation by the IARC Monographs with respect to additional cancer sites (IARC, 2019). The included studies confirmed the association between AF-exposure and increased liver cancer risk. These findings further support the World Cancer Research Fund (WCRF)'s conclusions of strong evidence linking AF-contaminated foods with liver cancer risk (Forner et al., 2015)

Experimental animal studies observed carcinogenic effects of AFB1 and AFG1, as opposed to AFB2 and AFG2, where inadequate evidence was found for their carcinogenicity (Baertschi et al., 1989). The liver is the primary target organ for AF with observed liver damage occurring when poultry, fish, rodents, and nonhuman primates were fed with AFB1. On a molecular level, AFB1 induces genetic instability, point mutations, and genetic recombination during mitosis in mammalian cells. Moreover, there is strong evidence that AFB1-induced mutagenicity is due to a direct genotoxic mode of action (IARC, 2012; Knutsen et al., 2018; Zain et al., 2011). AFB1 is metabolized, through oxidation by cytochrome P450 (CYP450), to aflatoxin-8,9-epoxide, which is unstable and highly reactive, and can bind to DNA or proteins (e.g., albumin) (Adam et al., 2017; Bbosa et al., 2013; Eaton & Groopman, 1994; FAO/WHO Expert Committee on Food Additives, 2017; He et al., 2006). Upon reactions with DNA molecules, aflatoxin-8,9-epoxide forms the aflatoxin-N7-guanine-adduct, which during DNA replication causes G:C to T:A transversion mutations (McCull ough & Lloyd, 2019;Huang et al., 2017). If these mutations occur in important cancer-related genes (oncogenes or tumor suppressor genes), they can lead to the increased proliferation of abnormal cells, ultimately resulting in the development of cancer.

AFs have been linked to HCC incidence in low- and middle income countries, through the consumption of subsistence-farmed agricultural crops (Turner et al., 2002; IARC, 2015). In contrast to the majority of findings from this systematic review, one reviewed study reported no evidence for an association of liver cancer with AF intake, hepatitis

B infection, or any dietary pattern (Parkin et al., 1991). The study focused on cholangiocarcinoma, a malignant tumor in the bile ducts, whereas the association of AF with liver cancer is usually studied in the context of HCC (Forner et al., 2015). This suggests that a diverse causation for different subtypes of liver cancer, that is, unspecified PLC, HCC, and cholangiocarcinoma, could explain the heterogeneity among study results (Forner et al., 2015). There are inadequate high-quality studies, supporting the contradictory result of the described study, which is why these results need to be interpreted with caution (Parkin et al., 1991).

Articles included in the review corrected their analyses by using different confounders. According to the literature and an overview provided by the WCRF, factors influencing liver cancer risk include overweight or obesity, alcohol consumption, fish, or other AF-contaminated foods, coffee drinking, physical activity, liver cirrhosis, chronic viral hepatitis B/C, chronic use of oral contraceptives containing high levels of estroprogestatives, or smoking, in human epidemiological studies. The different use of confounders can critically influence the result obtained by human epidemiological studies (Forner et al., 2015).

Most of the studies included used blood as an exposure matrix and adjusted for smoking status, but only some studies adjusted for hepatitis B virus (HBV) and hepatitis C virus (HCV) as confounders or effect modifiers (Forner et al., 2015). The Western Pacific and African Regions have the highest hepatitis B prevalence, with 6.2% and 6.1% of the adult population infected, respectively. Three percent (3.3%) of the general population of the WHO-delineated Eastern Mediterranean is infected, followed by 2.0% of South-East Asia and 1.6% of the European Region. Only 0.7% of the WHO Region of the Americas is infected (Parkin et al., 2018; World Health Organisation, 2017). HBV and HCV infections account for the majority of cirrhosis and PLC throughout most of the world (Perz et al., 2006). The synergistic effect of HBV infection and AF-exposure might be explained by a virus-induced increase in CYP450, which converts AF to its reactive metabolite (Forner et al., 2015; Hernandez-Vargas et al., 2015).

No statistically significant association was reported in the two included case–control studies examining the association between HCC and FB1 exposure. FB1 (IARC Group 2B) has the potential to alter protein synthesis, and DNA synthesis can be inhibited by higher concentrations *in vitro* in intestinal cells (IARC, 2002; Kouadio et al., 2005; Rheeder et al., 2002). An animal bioassay in rats ($n = 25$) confirmed the hepatocarcinogenicity and hepatotoxicity of FB1 (Adam et al., 2017; Gelderblom et al., 1991; Howard et al., 2001). This finding is not yet confirmed in humans. A high evaluation priority is recommended for FB1 because substantial new information has become available since the previous IARC Monographs evaluation (IARC, 2019). Evidence has been presented for the inhibition of ceramide synthase in people in Guatemala who consume corn-based foods with a high FB1 content (Riley et al., 2015). It coincides with a high incidence of liver cancer in individuals from this region, although this is confounded by the presence of AFB1 (Torres et al., 2015). Recent work further demonstrated that urinary FB1 may be used to assess ongoing exposure to FB1 in population-based studies. The improved exposure assessment may increase the power of current and future epidemiological studies to uncover relationships between FB1 exposure and the development of preneoplastic lesions and/or cancer (Riley et al., 2015; Torres et al., 2015). Furthermore, an elevation of phosphorylated sphingoid bases in mouse embryonic fibroblasts treated with FB1 has been associated with decreased histone deacetylase activity and an increased acetylation of histone lysines (Gardner et al., 2016; IARC, 2019b).

Besides the more common biological matrices, two studies from China incorporated by this systematic review used toenails as an exposure matrix (Persson et al., 2012). Toenails have not been generally validated as a reliable matrix for exposure assessment of FB1, and no other studies have investigated the half-life of FB1 in nails, or the association between measurable FB1 in nails and HCC. Inhibition of ceramide synthase by exposure to FB results in increased sphingolipid levels in serum, which can be used as a biomarker of exposure (Desai et al., 2002; Persson et al., 2012). Due to the lack of validated FB1 biomarkers of exposure and based on rodent models, an allometrically projected serum half-life of 128 min in humans, there have been few human studies to date investigating the relationship between FB1 and HCC (Delongchamp & Young, 2001; Persson et al., 2012; Riley et al., 2012; Shephard et al., 2007). Recent human urinary analyses of fumonisins identified FB1 as the most prevalent form, ahead of FB2 and fumonisin B3 (FB3) (Vidal et al., 2018). Studies in rodents and laboratory primates showed that FB1 levels could be observed in hair after exposure (Sewram et al., 2001), and may be a useful alternative for human exposure assessment (Persson et al., 2012; Sewram et al., 2003).

4.2 | Breast cancer

Two publications that investigated the association between ZEN and breast cancer, both conducted in Africa, gave conflicting results (Belhassen et al., 2015; Pillay et al., 2002). One study in North-Africa (Tunisia) investigated the link between urinary ZEN concentrations and breast cancer risk. The results suggested a possible role for α-ZAL in breast cancer development (Belhassen et al., 2015). α-ZAL can originate from ZEN-metabolism or dietary consumption, which is not yet a thoroughly characterized vector, as α-ZAL can be found in meat when used as a growth promoter for cattle (Stephany et al., 2009). Its diastereomers β-ZAL and

ZAN are the metabolites of α-ZAL after ingestion by humans. In addition, α-ZAL can be conjugated with glucuronic or sulfonic acid (Belhassen et al., 2015). ZEN shares structural similarity with the hormone 17β-estradiol, thereby exerting affinity to estrogen receptors, which can affect the fertility in both humans and livestock (Adam et al., 2017). Different estrogenic potencies were observed *in vivo* for ZEN and its metabolites. To account for these differences, molar potency factors relative to ZEN (relative potency factors, RPFs) were calculated and applied to exposure estimates of the respective ZEN-metabolites. RPFs were given on a molar basis for ZEN (reference 1.0) and its metabolites as proposed by the EFSA CONTAM Panel, with α-ZAL RPF 4.0, and α-zearalenol (α-ZEL) up to RPF 60 (Knutsen et al., 2017). These findings further support the idea that ZEN and its metabolites may play a role in reproductive organ cancer in both humans and animals (Adam et al., 2017; Pillay et al., 2002). ZEN was also found to be carcinogenic in mice, causing hepatocellular adenomas and pituitary tumors (Pfohl-Leszkowicz et al., 1995; National Toxicology Program, 1982; Eriksen et al., 1998). Additional epidemiological studies with reliable exposure assessment are required to confirm its potential carcinogenicity in humans (Eriksen et al., 1998). However, the presence of mycotoxin biomarkers in blood did not indicate a causal relationship between exposure to these mycoestrogens and breast cancer in a study in South-Africa (Pillay et al., 2002).

4.3 | Cervical cancer

One epidemiological study in South-Africa investigated the relationship between ZEN and cervical cancer but reported no association (Pillay et al., 2002). Nevertheless, caution is required when interpreting these results, as the NOS score of the article is only 2, out of 9 stars that could be obtained. One star was given in the category for proper selection of study population and one in the category for comparability of the study groups (Table 2). Hence, it could be hypothesized that ZEN is involved in causing cancer of genitalia in humans, since ZEN exerts estrogenic activity in many animal species, and forms DNA adducts in genitalia of mice, rats, and domestic animals, such as horses (Eriksen et al., 1998; Pillay et al., 2002). Therefore, more high-quality research needs to be undertaken to specifically unravel the association between ZEN and cervical cancer.

4.4 | Strengths and limitations of the systematic review

This structured systematic review of mycotoxin exposure and human cancer risk is the first of its kind in epidemiology. PubMed and EMBASE were both comprehensive queried, and the article selection was performed by three independent reviewers. Finally, the quality of the articles was scaled using the NOS of quality assessment.

However, this systematic review was prone to some limitations. First, the comparability of study results was limited because of differences in choice of biological matrix used for exposure assessments, the study population demographics, regionality, and each study's approach to confounding factors. Second, the data extraction was not done in duplicate. Finally, the quality of the studies included was considered relatively limited. The studies evaluating the risk of liver cancer were mainly assessed as good quality. Nevertheless, 2 out of the 12 studies on liver cancer were of low quality, for example, Chao et al. (1994) did not report LOD/LOQ and OR/RR-values. The two breast cancer studies had contrasting results and quality scores, whereas the single investigation into cervical cancer risk was of low quality. The deductions and conclusions of some of these studies can, therefore, be questioned and may warrant reinvestigation.

4.5 | Implications for future research and perspectives

Most studies investigating the associations between mycotoxins exposures and cancer risk have focused on AF, while the majority of mycotoxins (e.g., DON, citrinin [CIT], patulin [PAT], ZEN, T-2 toxin [T-2], nivalenol [NIV], and fusarenon-X [FUX]) are classified as IARC Group 3 compounds due to lacking information from both animal and human carcinogenicity. For FB1, OTA, and STC (Group 2B), sufficient evidence of carcinogenicity in experimental animal studies exists, but inadequate data on humans (IARC, 2012). Overall, these studies highlight the need for additional high-quality animal and human studies to clarify their contribution to cancer development. Moreover, the influence and causative character of (emerging) mycotoxins needs to be investigated with respect to additional cancer sites.

To date, no human epidemiological studies have reliably confirmed the involvement of mycotoxins, except AFs, in cancer development. This is reflected in the findings of the IARC Monograph evaluations (Table 1) (IARC, 1993a 2012). Consequently, there is clearly an urgent demand for more human epidemiological studies. In addition, the currently available literature is based on limited sample sizes and variable study designs, which lower their overall quality and complicates the comparison of published results. To tackle this issue, comprehensively designed, large-scale prospective cohort studies should be considered as one of the most reliable and promising avenues for future research.

The countries with the highest incidence of cancer are found in Oceania, Europe, and North-America (World Cancer Research Fund, n.d.). This review did not cover any studies investigating the associations between mycotoxin exposures and cancer risk on these continents. Future studies,

particularly case–control studies, are therefore recommended in these three continents that remain under-represented in the literature of the field.

More research on reliable exposure matrices, methods of exposure assessment, validated biomarkers of exposure and effect, and their toxicokinetics needs to be undertaken. Currently, only human biomarkers for AF and DON have been validated (Ayelign et al., 2017; Mengelers et al., 2019; Vidal, Claeys et al. 2018; Vidal et al., 2018). Prior studies have noted the importance of multiple days of weighted diet records to provide an optimal assessment of dietary factors (Yuan et al., 2018). However, aggregation and heterogeneity of mycotoxin patterns in agricultural products are commonplace, which effectively leads to unpredictable mixtures of possible mycotoxin contamination in foods (Turner et al., 2012). A recent study assessed multimycotoxin exposure by 24-hr dietary recalls and biological fluid sampling in a multicenter European validation study. Multimycotoxin exposures, calculated by intersecting quantities of consumed foods with representative contaminant levels, indicated a probability of exposure, which may be valid over a period contemporary to the contamination data. Comparatively, the use of biological sampling to assess mycotoxin dietary exposure enables far higher resolution exposure assessments at the individual level, though only within a short time window around the moment of sample collection. Therefore, future research should further invest in optimizing the assessments of mycotoxin exposures for epidemiological investigations (De Ruyck et al., 2020).

So far, the few studies investigating the potential effects of mycotoxin exposures on cancer risk focused on exposures of single mycotoxins and their acute health effects; however, *in vivo* studies using farm animals illustrated a complex set of possible synergistic, additive, subadditive, or antagonistic effects on animal health when mycotoxin mixtures were administered (Bensassi et al., 2014; De Ruyck et al., 2015; Grenier et al., 2011; Speijers et al., 2004). When chronically exposed to multiple mycotoxins, complex interactions may lead to any number of the aforementioned effects (Bensassi et al., 2014; De Ruyck et al., 2015; Grenier et al., 2011). For example, CIT acts synergistically with OTA on the kidneys of single comb White Leghorn pullets (Glahn et al., 1988; Speijers et al., 2004). Furthermore, when rats are exposed to ZEN and other mycotoxins, simultaneously antagonistic toxic effects have been reported in the liver and kidneys (Bensassi et al., 2014; De Ruyck et al., 2015; Halabi et al., 1998). After coexposure to ZEN and OTA in animals, it was noticed that OTA-induced kidney damage was further antagonized by the coexposure (Grenier et al., 2011). Finally, in contrast to the individual exposures, either additive or antagonistic effects on serum immunoglobulins were observed after coexposure of mice to ZEN and DON (Forsell et al., 1986).

To date, several European regulations and recommendations have been published to minimize mycotoxin concentrations allowed in food and feed (The Commission of the European Communities, 2006; Zain et al., 2011). However, only individual exposures are taken into account for these regulations. The complex dynamics of risks arising from coexposure to multiple mycotoxins (or even other contaminants) are still a convoluted matter (Steinkellner et al., 2019). Hence, further research investigating the potential effect of mycotoxin coexposures on cancer risk is needed to facilitate more targeted prevention strategies.

5 | CONCLUSIONS

This systematic literature review of epidemiological studies assessing the relationship between mycotoxin exposure and cancer risk confirmed associations between AF and liver cancer risk in humans, building on previously published IARC Monograph evaluations. Few human studies have specifically addressed the associations between mycotoxin exposures and cancer risk, even though ample evidence exists linking these mycotoxins to negative health effects by a range of mechanisms, including genotoxicity. Well-designed prospective cohort studies represent an important strategy to address potential causal associations and ensure the quality of the collected data, which appears to be a major caveat of existing studies. Additionally, many emerging mycotoxins remain generally uninvestigated with respect to health outcomes at all, and this too requires urgent attention, particularly in the real-world contexts of both highly variable and highly parallel exposures. Mycotoxins are understood to be ubiquitously present in agriculture, and may be chronically consumed by large majorities of human populations all around the world, while having demonstrated myriad toxic capabilities. Yet, even the tools of assessment used for estimating mycotoxin exposure, such as dietary intake assessments or biological sampling, do themselves require further investigation and validation. Finally, to strengthen the evidence calling for implementation of relevant public health strategies, the latest human epidemiological as well as experimental studies must be integrated with current legal regulations and recommendations as a high priority.

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DISCLAIMER

The authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization.

The authors alone are responsible for the views expressed in this article and do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization.

AUTHOR CONTRIBUTIONS

M.D.B. and I.H. were responsible for primary conceptualization of the review. L.C., I.H., C.R., and K.D.R. drafted the review manuscript. L.C., C.R., K.D.R, and H.W. contributed to the search syntax in PubMed and EMBASE, design and development of the manuscript. J.Z., M.G., B.F., M.K., S.D.S, M.D.B., and I.H. edited the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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APPENDIX

TABLE A1 Newcastle–Ottawa criteria used for quality assessment

	Case–control studies	Cohort studies
Selection	**Proper selection of study population**	**Proper selection of study population**
1	Case definition adequate	Representative of exposed cohort
2	Representativeness of the cases	Selection of the nonexposed cohort
3	Selection of controls	Ascertainment of exposure
4	Definition of controls	Demonstration that outcome of interest was not present at start of the study
Comparability	**Comparability of the study groups**	**Comparability of cohorts on the basis of the design or analysis**
5	Studies that controlled for the most important factor	Studies that controlled for the most important factor
6	Studies that controlled for any additional factor	Studies that controlled for any additional factor
Exposure	**Ascertainment of the exposure or outcome of interest**	**Ascertainment of the exposure or outcome of interest**
7	Ascertainment of exposure	Assessment of outcome
8	Same method of ascertainment for cases and controls	Assessment of follow-up duration in terms of outcomes
9	Nonresponse rate	Adequate follow-up of cohorts