IOWA STATE UNIVERSITY
Digital Repository

Food Science and Human Nutrition Publications | Food Science and Human Nutrition

11-2017

Mycotoxins

Suzanne Hendrich
Iowa State University, shendric@iastate.edu

Follow this and additional works at: http://lib.dr.iastate.edu/fshn_ag_pubs


Part of the Food Chemistry Commons, Food Processing Commons, and the Human and Clinical Nutrition Commons

The complete bibliographic information for this item can be found at http://lib.dr.iastate.edu/fshn_ag_pubs/163. For information on how to cite this item, please visit http://lib.dr.iastate.edu/howtocite.html.

This Article is brought to you for free and open access by the Food Science and Human Nutrition at Iowa State University Digital Repository. It has been accepted for inclusion in Food Science and Human Nutrition Publications by an authorized administrator of Iowa State University Digital Repository. For more information, please contact digirep@iastate.edu.

www.manaraa.com

Mycotoxins

Abstract
Mycotoxins, toxins produced by fungi that commonly contaminate food crops, remain an important global food safety concern. Aflatoxins and fumonisins mainly pose a cancer risk, whereas deoxynivalenol poses a risk to gastrointestinal and immune function. Ochratoxin A poses a risk for kidney disease. Grains and some legumes are the predominant sources of these toxins, but they vary in the range of foods that they contaminate. For example, fumonisins occur mainly in corn, whereas deoxynivalenol is mainly found in wheat, barley and corn. Aflatoxins are mainly found in peanuts and corn. The nature of the fungi that produce each toxin seems to be the main determinant of which crop species will be the main sources of the mycotoxins.

Disciplines
Food Chemistry | Food Processing | Food Science | Human and Clinical Nutrition

Comments
This is a book chapter from *Food Toxicology Current Advances and Future Challenges*, 2017. Posted with permission.

This article is available at Iowa State University Digital Repository: http://lib.dr.iastate.edu/fshn_ag_pubs/163

www.manaraa.com

Mycotoxins

Suzanne Hendrich

CONTENTS

18.1 INTRODUCTION

Mycotoxins, toxins produced by fungi that commonly contaminate food crops, remain an important global food safety concern. Aflatoxins and fumonisins mainly pose a cancer risk, whereas deoxynivalenol poses a risk to gastrointestinal and immune function. Ochratoxin A poses a risk for kidney disease. Grains and some legumes are the predominant sources of these toxins, but they vary in the range of foods that they contaminate. For example, fumonisins occur mainly in corn, whereas deoxynivalenol is mainly found in wheat, barley and corn. Aflatoxins are mainly found in peanuts and corn. The nature of the fungi that produce each toxin seems to be the main determinant of which crop species will be the main sources of the mycotoxins.

Aflatoxins, most importantly aflatoxin B1 (AFB1), are produced, and named for *Aspergillus flavus*, but other *Aspergillus* species also produce aflatoxins, especially *A. parasiticus*. Crosses of these two fungi produce greater amounts of aflatoxins than do either parent species, but the two species are typically isolated from each other, with *A. flavus* infecting peanuts, corn, cottonseed and tree nuts and *A. parasiticus* infecting mainly peanuts [1]. Aflatoxin B1 is a human liver carcinogen, and is also involved in impairing growth, development and immune function of children in regions with significant aflatoxin contamination of staple foods [2].

www.manaraa.com

Fumonisins are produced by at least 15 Fusarium species, especially *F. verticillioides*, *F. proliferatum* and *F. subglutinans*. These fungi are corn pathogens, causing stalk rot as well as potentially harmful levels of the predominant fumonisin, B1 in corn kernels [3]. Fumonisin B1 has been associated with human esophageal cancer and neural tube defects [3], especially in regions where corn is a staple food and where contamination of corn by this toxin is not well-recognized and managed. *In vivo* studies of *Fusarium* mycotoxins have been reviewed recently, showing a broad array of effects across many species[4].

Deoxynivalenol (DON) is mainly produced by *Fusarium graminearum*, and also by *F. culmorum* [5]. These fungi cause *Fusarium* head blight in wheat, a main source of this toxin. Other cereals such as barley and corn, can also be significant DON sources. DON is linked with immune dysfunction and gastroenteritis, hence its prior common name, vomitoxin[6].

Ochratoxins are produced by *Aspergillus ochraceus, A. carbonarius and Penicillium verrucosum*. *A. ochraceus* grows and produces ochratoxin mainly in stored grains under dry conditions and in moderate temperatures. *A. carbonarius* grows in grapes, so ochratoxins may be found in wines and other grape-derived foods. *P. verrucosum* grows well in cooler climates, so Northern European and North American grains, especially wheat, experience ochratoxin contamination mainly from this source [7]. Ochratoxin A (OTA) is the main ochratoxin important to human health, and is associated with nephritic syndrome, but only in regions with very high exposure to OTA, such as in parts of Egypt and Sierra Leone [6].

A recent casual survey of scientific literature through Pubmed indicates significant research activity, especially focused on mechanisms and mitigation of toxicity of aflatoxins and deoxynivalenol, fungal biology associated with fumonisin production, and novel detection methods for ochratoxins (Table 1). How this pattern of research activity aligns with public health needs associated with these toxins will be discussed in summarizing key recent studies related to mycotoxin risk assessment, metabolism and mitigation. Mycotoxigenic fungi will continue to evolve, so continual improvement of techniques to identify and assess health risks of emerging mycotoxins is needed, but is seemingly not being addressed systematically at this time.

www.manaraa.com

Table 1. Survey of recent scientific papers published in English on mycotoxins catalogued by PubMed from Jan-May 2016

Mycotoxin	Total papers	Quanti-tation in foods	Novel detection methods	Exposure and risk assessment	Mechanisms of action and mitigation of toxicity	Detoxi-fication in foods	Fungal biology
Aflatoxins	161	26 (15%)	35 (20%)	15 (9%)	49 (28%)	17 (10%)	19 (11%)
Deoxynivalenol	91	11 (12%)	10 (11%)	4 (4%)	35 (37%)	5 (5%)	28 (30%)
Fumonisins	64	7 (11%)	13 (20%)	4 (6%)	16 (25%)	4 (6%)	20 (31%)
Ochratoxin	110	12 (11%)	40 (36%)	7 (6%)	26 (24%)	9 (8%)	16 (15%)

18.2 MYCOTOXIN RISK ASSESSMENT

Connecting human health risks with dietary exposure to mycotoxins poses severe challenges. Outbreaks of acute illness are associated with aflatoxin B1 (aflatoxicosis causing hepatic toxicity), DON (gastroenteritis) and OTA (nephritic syndrome). Verification of mycotoxin outbreaks requires mycotoxin analysis of grain samples verified to be of the same lot or source as ingested immediately prior to the onset of illness. Blood or urinary mycotoxin analysis and assessment of disease symptoms is also required, concomitantly. Although numerous methods are available for mycotoxin analysis, most such methods require expensive instrumentation such as LC/MS. Medical personnel with appropriate diagnostic expertise are also required. Public health systems coordinating such efforts are largely lacking worldwide. To assess cancer risk from aflatoxins and fumonisins, much longer term exposure surveillance is required. For a genotoxic agent such as aflatoxin, exposure in early life causing genetic damage may result in much later development of cancer. For fumonisins, chronic exposure seems to be required for its carcinogenic effects. There is yet an incomplete understanding of human dietary exposure patterns for mycotoxins in regions where mycotoxin-related health concerns exist. It may be that OTA causes kidney impairment at lower doses than seen in nephritic syndrome, but establishing

www.manaraa.com

this as a solid connection requires multivariate analysis coordinated across human populations. Likewise, DON may impair immune and intestinal function in important but relatively subtle ways that are difficult to discern. Increased global scientific cooperation and coordination are crucial to address these needs. It is unfortunate that disease presence rather than disease prevention seems to drive investment in such endeavors. Mycotoxin prevention systems that are sustainable will need to include permanent investment in agricultural practices, health surveillance, and basic and translational research. Mitigation of human health risks from mycotoxins is ethically and practically important. Global burden from mycotoxin-associated diseases was estimated recently at ~200,000 excess liver cancer cases per year attributable to aflatoxin. Disease burdens from fumonisin, DON and OTA remain uncertain, however likely, especially for fumonisins [6]. Effects of ingestion of combinations of mycotoxins also needs greater attention.

Recent studies of dietary exposure to aflatoxin modeling intake of 3 maize foods based on aflatoxin analysis of these foods in regions of Kenya. Eating whole kernel maize would result in a 5- to 10-fold greater exposure to aflatoxin than eating maize meal or muthokoi (dehulled and processed maize), about 300 ng aflatoxin/kg body weight. This exposure is 1000-fold greater than noted in the US [8].

In a study in Lebanon, mean aflatoxin B1 exposure was 0.63 ng/kg/d, extrapolating to an increased risk of cancer of ~ 0.05 cases/100,000 individuals[9], a relatively low additional risk. In a survey of aflatoxin intake from foods in Malaysia, mean aflatoxin intake was much greater, about 30 ng/kg/d, contributing ~0.7 liver cancer cases/100,000 individuals. With the current maximum limit for aflatoxin of 15 ppb in Malaysia, this finding indicates some need for continued vigilance in limiting intake of foods contaminated with aflatoxin above that maximum[10].

From the most recent French Total Diet Study, only DON exposure and not exposure to aflatoxin, fumonisin or OTA exceeded the health-based guidance value (HBGV) of estimated intake of 1000 ng DON/kg/d. Only 0.5% of adults and 5% of children exceeded this estimated DON intake. Mean DON exposures were estimated at ~400 ng/kg/d for adults and ~550 ng/kg/d for children from this study [11]. This study should be seen as a model for other countries to better assess health risks from mycotoxins.

A total diet study of urban Lebanese showed that mean DON intake exceeded the European Food Safety Authority's (EFSA) HBGV (1000 ng/kg/d), at 1560 ng/kg/d, whereas mean OTA intake of 4.3 ng/kg/d was 80% of EFSA's HBGV[9]. When exposure to DON was combined with exposures

www.manaraa.com

to 3- and 15-Acetyl DON in a case study of 1269 individuals in Shanghai, China, mean DON exposure from these 3 forms slightly exceeded the HBGV at 1085 ng/kg/d [12]. More work on public health effects of such findings related to DON are needed.

A Tunisian case control study of 69 women with breast cancer and 41 controls showed significantly greater urinary α-zearalenol in women with breast cancer, with mean concentration of 4.6 ng/mL, 3-fold greater than in controls [13]. This estrogenic metabolite of zearalenone might enhance growth of estrogen-responsive breast cancer cells. This study suggests that it would be worth studying the extent to which urinary α-zearalenol might predict breast cancer risk. However, a recent study biomonitoring mycotoxins in Belgium showed that only one adult out of 239 studied had any urinary content of α-zearalenol, and this metabolite was not detected in children (n = 155)[14]. The study in Belgium implies that in countries with more highly developed food safety systems, zearalenone would not pose a human breast cancer risk. A study associating zearalenone exposure with reproductive development in 163 9-10 year old girls in New Jersey showed mean urinary α-zearalenol ten-fold less than seen in Tunisian women, and lesser breast development in girls with greater zearalenone exposure [15], suggesting an anti-estrogenic effect of the mycotoxin at these exposure levels. It is intriguing to consider further work to investigate possible breast cancer protective effects of zearalenone at exposures similar to those noted above in Belgium or the US.

18.3 MYCOTOXIN METABOLISM

The metabolism of mycotoxins, by animals, bacteria associated with the gut, and by plants, may be a significant factor in mitigating health risks of these compounds, but this aspect of mycotoxins has not been incorporated directly into risk assessment or mitigation strategies. It may be that dietary and other health habits of populations either enhance or inhibit mycotoxin detoxification. Such possibilities will be explored in this chapter section.

Among the 4 major mycotoxins, aflatoxin is known to undergo significant mammalian metabolism, both in activation to its proximate carcinogenic (mutagenic) form, aflatoxin 8,9-epoxide, by cytochromes P-450 (P450) [16], and its detoxification, especially by glutathione S-transferases (GSTs) to transform the epoxide site's to a hydroxyl and a glutathione adduct [17]. P450s are inducible by dietary components including flavonoids [18] and cruciferous vegetables such as broccoli and cabbage [19]. Chronic food restriction also may induce P450s [20], suggesting enhanced susceptibility to AFB1 toxicity in regions where food shortages and undernutrition are more common. Paradoxically, P450s may also be inhibited by flavonoids [21]. Some flavonoids

www.manaraa.com

such as apigenin, a flavonoid in parsley, inhibited AFB1 mutagenicity *in vitro* mediated by the human P450 enzyme thought to be important for AFB1 activation, hCYP1A2 [22]. The significance of this finding for prevention of AFB1-associated human cancers remains to be determined. Several studies have shown in animal models the possible mitigation of aflatoxin toxicity and carcinogenesis by dietary alterations of its metabolism. Marked inhibition of AFB1 carcinogenesis in rainbow trout, the most sensitive species to AFB1, was shown for beta-naphthoflavone (BNF) and indole-3-carbinole (a component of cruciferous vegetables) but only BNF induced P450 in this model [23]. This early study illustrated the complexity of attempting to prevent AFB1 carcinogenicity by dietary components, as mediated by modulation of P450. Chickens fed 100 ppb AFB1 showed induction of P450, which was prevented by supplementation with 0.5 mg selenium (Se)/kg diet compared with 0.2 mg Se/kg, suggesting that diets containing this moderately greater amount of Se might mitigate the activation of AFB1. This approach may be feasible to investigate as a human intervention in regions where AFB1 contamination is common. Dietary induction of GSTs as a strategy to mitigate AFB1 carcinogenicity has been shown using a model antioxidant, oltipraz, in rats [24]. Oltipraz increased production of AFB-glutathione metabolites in a human clinical trial, demonstrating the feasibility of this approach [25]. The identification of effective dietary inducers of GSTs that can mitigation AFB1 toxicity in humans remains to be accomplished. It has been recently proposed that strategies not involving AFB1 metabolism, such as increasing dietary chlorophyllin content, which binds to and inhibits absorption of AFB1, may be more useful to consider because altering P450s and GSTs is likely to alter metabolism of many drugs, thus making public policy recommendations about such dietary constituents highly problematic [26].

DON is also metabolized by inducible biotransformation in animals. In particular, the hydroxyls of DON are sites for addition of sulfate (by sulfotransferases, STs) or glucuronide. Glucuronidation by UDP-glucuronosyltransferases (UGTs) is favored in species possessing both types of biotransformation enzymes, based on limited data [27]. Human UGTs have less capability to form DON glucuronides than do rat UGTs *in vitro*, but such metabolites are the predominant urinary excretion products across species [28]. DON-3-glucuronide was shown to have negligible toxicity compared with DON in human K562 cells, consistent with the general idea in toxicology that such metabolites are detoxification products [29]. Because UGTs are highly inducible by some dietary constituents, such induction may mitigate DON toxicity in humans. Neither the extent of UGT induction nor the effect of this phenomenon on DON toxicity has been established yet in humans.

www.manaraa.com

The biotransformation of DON in plants to DON glucosides, especially DON-3-glucoside (D3G) has been observed [30]. Many hydroxylated secondary plant metabolites are also stored in plants in glucoside form. This conversion of DON initially was shown to "mask" DON to its detection. Since then, D3G has been recognized as a minor but not insignificant form of DON in DON-contaminated grains, constituting as much as 25% of total DON in wheat and maize [31]. D3G can be readily converted back to DON by bacterial β-glucosidases in the mammalian gut. D3G per se is practically unabsorbed, so the absorption of DON from dietary D3G would occur mainly in the ileum and colon which contain most of the bacteria in the intestine. Enhanced presence of D3G in the diet could alter the site of intestinal toxicity. The development of grains that have increased ability to convert DON to D3G would not be advisable unless DON de-epoxidation capacity, and hence DON detoxification were also commonly occurring. This has been demonstrated in rats, in which the urinary excretion of D3G was 5-fold less than that seen for DON; most D3G was excreted as DON or de-epoxy DON (DOM-1) in rat feces [32]. When DON was fed to pigs as D3G, its apparent bioavailability was about two-fold less [33]. DON de-epoxidation in the rumen is the main fate of DON in cattle [34], which seems to be why ruminants are relatively protected from DON toxicity. De-epoxidation in the lower intestine of pigs is also common, but this has no protective benefit from DON toxicity because DON seems to be absorbed in the small intestine before the DON de-epoxidating bacteria can be effective [35]. Likewise, in one study of French farmers, about 30% of the humans tested had DON de-epoxidating activity in fecal bacteria [36]. A lesser extent of this metabolism was observed in individuals from the UK [37]. De-epoxidation of DON in humans would not be expected to mitigate DON toxicity appreciably unless DON were present mainly as D3G which is not currently the case. If we presume that DON can be rapidly and extensively converted to DON glucuronides, the DON glucuronides would be expected to be eliminated mainly in bile. These metabolites would not be reabsorbed until they were converted back to DON by bacterial glucuronidases in the lower intestines. At that point in DON metabolism DON might be detoxified by gut bacterial DON de-epoxidases. It may be worth exploring the feasibility of modifying the human gut microbiome to include DON de-epoxidating bacteria in individuals who do not naturally carry such bacterial species. Some such species have been identified and might be seen as a new class of probiotics, potentially beneficial bacteria that might be introduced into the food supply. The need for such alteration of human gut bacteria remains to be established, and would not be a trivial process. But if such a need were confirmed (in humans who do not

www.manaraa.com

already have this metabolic capability in their gut microbiomes), standards exist for assuring the efficacy and safety of probiotic bacteria [38].

Ochratoxin A (OTA) is the main ochratoxin of concern to human health. It can be hydrolyzed by proteases to form an apparently non-toxic form, ochratoxin-alpha, and phenylalanine. The lack of toxicity of OTA-alpha has been demonstrated in zebrafish recently [39]. The percentage of ochratoxin absorbed in humans has not been directly determined, presumably due to ethical concerns about deliberately exposing humans to this presumed carcinogen, but across several species, uptake has been estimated at ~50% of ingested dose [40]. In limited human studies, OTA-alpha seemed to be the predominant urinary form of OTA. In one study, human urinary contents of OTA and OTA-alpha were about equal [41]. Pregnant women showed about 10-fold greater urinary OTA-alpha than OTA [42], indicating seemingly greater OTA detoxification ability of pregnant women than of non-pregnant women. Hydrolysis of OTA by microbial enzymes may be a strategy for mitigation of the mycotoxin [43], but the capability of enhancing such hydrolysis *in vivo* in humans remains to be determined.

The metabolism of fumonisins has been shown to be virtually nil *in vivo*, as might be expected for these highly water-soluble, relatively large and therefore, poorly absorbable toxins. Seemingly their water-solubility facilitates their rapid excretion and poor retention in body tissues, as has been demonstrated by studies of the fate of radio-labeled FB1 in a rodent model [44]. These compounds may be altered during some food processing reactions (e.g., addition of reducing sugars to the primary amine of FB1) and by microbial enzymes (e.g., carboxylesterase FumD) that are potentially useful in mitigating the toxins [45].

In summary, it may be worth considering incorporating alteration of human/gut microbial metabolism of some mycotoxins in future mitigation strategies. Insofar as the future may hold the ability for genetic characterization of individual biotransformation enzyme genetics and polymorphisms, and thus the prospect of tailoring diet to contain the right mix of biotransformation enzyme inducers or inhibitors depending on dietary circumstances, metabolism modification may need to be part of the defense arsenal against these toxins.

18.4 MYCOTOXIN MITIGATION

Mitigating the presence of mycotoxins in the human food supply is mostly about reducing mycotoxin burden in grain crops used for human food. Significant attention is also directed toward reducing mycotoxins in the feed of livestock, for example, in the case of aflatoxin, due to

www.manaraa.com

carry over of the aflatoxin metabolite AFM1 into dairy milk. Mitigation strategies involve improving mycotoxin detection and regulation, which currently means removing from the food supply foods that exceed action, advisory or guidance levels developed by the United States (US) Food and Drug Administration (FDA). Analogous standards that may be somewhat more or less stringent exist in many countries, including the European Union (EU). An action level is mandated by FDA only for aflatoxins in the US, currently set at 20 ppb for foods for human consumption. FDA advisory levels are set at 1 ppm for deoxynivalenol in foods for human consumption, and FDA has also provide guidance levels for fumonisins of 2-4 ppm for foods for human consumption [46].

A strong research publication focus has been on innovative detection methods, but this research does not seem to be well-aligned with the needs, especially in low income countries, for rapid, accurate and inexpensive mycotoxin detection. Mycotoxin analytical methods have been recently reviewed [47] and major constraints in this field were noted, including the varied chemistries of the mycotoxins, the need to assess multiple mycotoxins in food samples and to assure that samples are appropriately representative of the scope of possible contamination, and the need for speed and economy. QuEChERs (quick, easy, cheap, effective, rugged and safe) technologies were also noted to be especially important in the realm of mycotoxin analysis. Portability of analytical methods is improving, with a number of promising advances coming from the realm of nanotechnology coupled with alternatives to antibody-based mycotoxin detection. Such alternatives include aptamers (RNA-binding) and molecular imprint polymers (MIPs). Nanomaterial sensors for mycotoxins including AFB1, DON, FB1 and OTA have been developed [48]. Because many nanomaterials do not occur in nature, particular caution in assessing safety related to disposal, environmental persistence, and potential health effects on humans and ecosystems is warranted. Spectroscopic detection coupled with chromatographic separation methods of varying types and expense remain the state-of-the-art in terms of reliability, but portability of spectroscopy is also improving [47]. A few recent studies on mycotoxin detection show promise. An aptamer-based dipstick for AFB1 was shown to have comparable detectability compared with a standard ELISA method in the ppb range, as needed for food samples. The method took 30 min to complete, with simple solvent extraction (20% methanol) of grain samples including maize [49]. An antibody-based microarray system for simultaneous detection of AFB1 and FB1 was shown to be feasible and comparable to standard ELISAs in detection levels. This method will require further validation for food samples [50]. A portable evanescent wave optical aptasensor with a reversible ligand-grafted biosensing surface was demonstrated for OTA, with

www.manaraa.com

detection limit of 0.4 ppb, and OTA recoveries from powdered wheat of 89—106%, with ~15% CV. This detection limit is sufficient to meet current regulatory policies [51], but this seemingly relatively cost-effective and reusable method will need further validation across food sources of OTA. DON-specific nanobodies (single domain antibodies) that can mimic DON have been recently discovered and might be useful in further optimizing DON detection [52]. The adoption of the Food Safety Modernization Act (FSMA) in the US in 2011 emphasizes prevention of food contamination. It remains to be seen how FSMA will affect mycotoxin detection, but rapid, reliable and inexpensive methods available to farmers are likely to be needed, thus promising emerging technologies such as these will be crucial.

Preventing mycotoxins in the field is a burden for grain producers that currently relies on their ability to identify fungal contamination and insofar as feasible and permissible to apply appropriate fungicides. Fungicide resistance is an ongoing concern, as well as general environmental and human health concern about use of synthetic chemical fungicides, so potentially toxigenic fungi-inhibiting plants and their extracts are under investigation as alternatives [53]. Commercialization remains to be achieved; significant technical and economic barriers exist in this field of "green chemicals".

Identification and development of mycotoxin-resistant crop varieties has shown particular promise in maize, a species for which at least a few naturally occurring variants are resistant to AFB1 [54]. AFB1 Resistance associated proteins have been identified, and current genomic technologies may permit engineering of such proteins into other crop species. But no commercially available AFB1-resistant maize lines are yet available [54]. Several cross bred maize lines were recently identified as resisting both AFB1 and FB1 contamination in field trials in South Africa, in which at least a few crosses were developed that did not accumulate AFB1 above 5 ppb or FB1 above 4 ppm (current regulatory levels) [55]. For DON in wheat, the quantitative trait locus Fhb1 permitted conjugation of DON with glucose and several glucose derivatives as well as glutathione conjugates, significantly increasing D3G/DON ratio [56]. As noted in the above section on DON metabolism, this conversion would not be expected to significantly detoxify DON unless DON-de-epoxidating capability was also present in individuals ingesting this grain. It might be presumed that any DON conjugate, whether with glucose, glutathione or other glucose derivatives would likely be deconjugated by gut bacteria, but that remains to be proven. Barley is another major source of DON; it has been discovered recently that black barley showed about half the DON contamination of yellow barley, so switching to this barley type might be a feasible mitigation approach [57]. A yeast species, *Kluyveromyces thermotolerans* was capable of decreasing OTA in grapes [58], which may be a

www.manaraa.com

significant source of this toxin, so some types of biocontrol may be feasible, but will certainly need to be developed on a crop-specific basis. No work on OTA resistance in grain crop species was uncovered for this review. But progress is being made, seemingly especially for AFB1 and FB1 resistance in maize.

A number of potential strategies to decrease mycotoxins during food processing have been demonstrated in the literature. Current US regulatory policies do not permit blending of a crop contaminated above key limits with non-contaminated crop; exceptions may be made when a severe mycotoxin contamination epidemic occurs. Diversion of mycotoxin contaminated crops into animal feeds may occur where regulatory levels permit[46]. Regulators, scientists and citizens should engage in effective global discourse about the problem of mycotoxin contamination of crops used to feed humans. It is important to determine a rational future for feeding a world in which mycotoxin contamination is likely to be a problem of increasing severity due to increasingly extreme weather and climate conditions that have been occurring and are predicted. More attention to development of low cost and effective means of decreasing mycotoxins in human foods as a part of food processing is warranted.

Aflatoxin decontamination methods have been developed. Screening grain kernels under UV light which can recognize grain grossly contaminated with aflatoxins and mechanical sorting to cull contaminated kernels is permitted in the US to achieve grain batches compliant with the action level for aflatoxin. Ammoniation of cottonseed is permitted by FDA. Although this method has been established to effectively detoxify maize containing aflatoxins[59], with several trials across livestock and laboratory animals showing a reduction in aflatoxin content to 1% or less than in the starting contaminated grain[59], this method is not approved for grains in the US. As summarized in a recent review focused on an African perspective on mycotoxin remediation [60], sorting and cleaning before storage, and keeping stored grain dry may be quite effective in reducing aflatoxin contamination of grains and peanuts. In a study using visibly moldy maize in Malawi, hand sorting to remove obviously damaged or shriveled seeds and seed fragments removed ~95% of AFB1 or FB1. Floating the kernels in water before sorting only removed about 60% of either type of contamination; adding flotation to hand sorting showed no additional benefit[61]. Thus, simple but labor intensive methods may be beneficial where farmers and consumers are educated about the health benefits of removing aflatoxins from foods. A novel method of treating hazelnuts with cold atmospheric plasma in a controlled pressure chamber using power of 1000 W decreased AFB1 content of the nuts by two-thirds after 12 min[62]. This technique should not interfere with food quality and might be useful for many other AFB-

www.manaraa.com

containing foods. The wider feasibility, mainly cost-effectiveness, of such technologies remains for future work.

For DON, as might be expected from its hydrophilicity, processing foods in water such that the water is removed from the final product can remove significant amounts of DON. This is pertinent but probably not practical for pasta. Boiling of 310 g pasta from 0-10 min showed progressive loss of DON from 0.62 ppm to 0.16 ppm (75% loss of DON)[63], but as this was "fresh" pasta, eating quality would not be acceptable to many consumers after the longer boiling times that were more effective. Wheat flour bread making and baking did not diminish DON concentrations[63]. Treatment of DON-contaminated dried distillers grain solids for nursery swine feed with 5% sodium metabisulfite,(SMB) autoclaving and drying decreased DON concentration in this feed by more than 80%. Heating DON with SMB causes formation of a DON-10-sulfonate, which was non-toxic to the pigs. Average daily gain was restored to control levels by this treatment [64]. Practically, such treatments of grain flours for human intake might be feasible, but prevention of toxic effects to workers from sulfur dioxide gas release during processing would be important. Also, some individuals may have allergic-like reactions to sulfites as food additives, and warning labels would be needed. Heat processing per se, such as during extrusion of corn flour[65] may remove DON by as much as 98%, but results from another lab with wheat flour did not show this ability of heat processing [66]. It seems prudent to conduct additional studies on SMB using human foods because this may be a cost-effective approach that could be necessary depending on the extent of DON contamination that may emerge in some regions. Additional investigations as to the potential of SMB treatment of DON contaminated grain flours to adversely affect sulfite sensitive individuals, and appropriate additional food labeling may be needed as well.

Regulatory limits for ochratoxins in foods range from 2-10 ppb in the EU. Pre-harvest control by good agricultural practices, careful use of fungicides and biocontrol agents (e.g., yeasts, natamycin) are thought to be most effective against OTA [67], as well as low-moisture storage. Adsorption of OTA from beverages may be feasible but must be evaluated carefully for effects on nutritional quality and taste; modified zeolites may be particularly useful[67]. Quaternary ammonium beta-cyclodextrin was shown *in vitro* to have 200-fold stronger affinity for OTA than beta-cyclodextrin, as measured by fluorescent spectroscopic changes; this cyclodextrin derivative may be a good candidate for pass-through adsorption of OTA from beverages[68]. More practical conditions will need to be investigated for such an adsorbent, as well as determination of any significant adverse effects on beverage quality from use of the adsorbent.

www.manaraa.com

The prospect that human metabolic capabilities may also mitigate health risks from mycotoxins also deserves greater attention, based on the theoretical framework developed above (see section on mycotoxin metabolism).

18.5 RECOMMENDATIONS

Human risk assessment of mycotoxins that includes better recognition of disease and cost burdens of these food borne toxins is a primary need. Such risk assessment should move toward incorporating the assessment of dietary and other health habits in addition to mycotoxin exposure assessment. A number of dietary constituents, as discussed previously, might mitigate adverse effects of mycotoxins. Exercise is increasingly recognized as a strong factor in mitigation of cancer risk[69], but taking a global perspective, does intensive physical activity in the case of subsistence farmers confer benefits or add health stress?

Discovery and development of mycotoxin resistant crop species is progressing. This work will need to continue permanently as it is reasonable to consider that mycotoxigenic species will continue to evolve. Integrated pest management systems that employ "green" technologies of biocontrol against mycotoxins must become feasible and affordable in the future.

The recognition of the potential of microbes to degrade and detoxify mycotoxins may extend from the field to the fork, in that anti-mycotoxin microbes might be developed into a new generation of probiotics that could be incorporated into an array of ready-to-eat food products. Such a recommendation should be approached with great caution and respect for the many unknowns that need careful testing as fundamental discoveries move into product development. Engineering or manipulation of the human gut microbiome to contain microbes beyond what are naturally present across diverse human populations seems unwise without a great deal more understanding of gut microbial populations and interactions between these microbes and complex food constituents.

A focus on extending adequate resources for mycotoxin management and mitigation to low income world regions must be the greatest priority. Advances in the ability of human populations to effectively govern themselves and abide by fair rules of law will be needed to accomplish the needed eradication of excess liver cancer due to aflatoxin. Humanity deserves better assurance of food safety; mycotoxins remain an important global consideration in that regard.

Key words

www.manaraa.com

399 aflatoxin, deoxynivalenol, fumonisin, ochratoxin, remediation, risk assessment

400 **References**

401 1. Olarte, R. A.; Worthington, C. J.; Horn, B. W.; Moore, G. G.; Singh, R.; Monacell, J. T.;
402 Dorner, J. W.; Stone, E. A.; Xie, D. Y.; Carbone, I., Enhanced diversity and aflatoxigenicity in
403 interspecific hybrids of Aspergillus flavus and Aspergillus parasiticus. *Mol Ecol* **2015,** *24* (8),
404 1889-909.
405 2. In *Mycotoxin control in low- and middle-income countries*, Wild, C. P.; Miller, J. D.;
406 Groopman, J. D., Eds. International Agency for Research on Cancer

407 (c) International Agency for Research on Cancer, 2015. For more information contact
408 publications@iarc.fr.: Lyon (FR), 2015.
409 3. Alberts, J. F.; van Zyl, W. H.; Gelderblom, W. C., Biologically Based Methods for Control
410 of Fumonisin-Producing Fusarium Species and Reduction of the Fumonisins. *Front Microbiol*
411 **2016,** *7*, 548.
412 4. Escriva, L.; Font, G.; Manyes, L., *In vivo* toxicity studies of fusarium mycotoxins in the last
413 decade: a review. *Food Chem Toxicol* **2015,** *78*, 185-206.
414 5. Hellin, P.; Dedeurwaerder, G.; Duvivier, M.; Scauflaire, J.; Huybrechts, B.; Callebaut, A.;
415 Munaut, F.; Legreve, A., Relationship between Fusarium spp. diversity and mycotoxin contents
416 of mature grains in southern Belgium. *Food Addit Contam Part A Chem Anal Control Expo Risk*
417 *Assess* **2016**, 1-13.
418 6. Wu, F.; Groopman, J. D.; Pestka, J. J., Public health impacts of foodborne mycotoxins.
419 *Annu Rev Food Sci Technol* **2014,** *5*, 351-72.
420 7. Ostry, V.; Malir, F.; Ruprich, J., Producers and important dietary sources of ochratoxin A
421 and citrinin. *Toxins (Basel)* **2013,** *5* (9), 1574-86.
422 8. Kilonzo, R. M.; Imungi, J. K.; Muiru, W. M.; Lamuka, P. O.; Njage, P. M., Household
423 dietary exposure to aflatoxins from maize and maize products in Kenya. *Food Addit Contam Part*
424 *A Chem Anal Control Expo Risk Assess* **2014,** *31* (12), 2055-62.
425 9. Raad, F.; Nasreddine, L.; Hilan, C.; Bartosik, M.; Parent-Massin, D., Dietary exposure to
426 aflatoxins, ochratoxin A and deoxynivalenol from a total diet study in an adult urban Lebanese
427 population. *Food Chem Toxicol* **2014,** *73*, 35-43.
428 10. Chin, C. K.; Abdullah, A.; Sugita-Konishi, Y., Dietary intake of aflatoxins in the adult
429 Malaysian population - an assessment of risk. *Food Addit Contam Part B Surveill* **2012,** *5* (4), 286-
430 94.
431 11. Sirot, V.; Fremy, J. M.; Leblanc, J. C., Dietary exposure to mycotoxins and health risk
432 assessment in the second French total diet study. *Food Chem Toxicol* **2013,** *52*, 1-11.
433 12. Han, Z.; Nie, D.; Ediage, E. N.; Yang, X.; Wang, J.; Chen, B.; Li, S.; On, S. L.; De Saeger, S.;
434 Wu, A., Cumulative health risk assessment of co-occurring mycotoxins of deoxynivalenol and its
435 acetyl derivatives in wheat and maize: case study, Shanghai, China. *Food Chem Toxicol* **2014,** *74*,
436 334-42.
437 13. Belhassen, H.; Jimenez-Diaz, I.; Arrebola, J. P.; Ghali, R.; Ghorbel, H.; Olea, N.; Hedili, A.,
438 Zearalenone and its metabolites in urine and breast cancer risk: a case-control study in Tunisia.
439 *Chemosphere* **2015,** *128*, 1-6.
440 14. Heyndrickx, E.; Sioen, I.; Huybrechts, B.; Callebaut, A.; De Henauw, S.; De Saeger, S.,
441 Human biomonitoring of multiple mycotoxins in the Belgian population: Results of the BIOMYCO
442 study. *Environ Int* **2015,** *84*, 82-9.

www.manaraa.com

15. Bandera, E. V.; Chandran, U.; Buckley, B.; Lin, Y.; Isukapalli, S.; Marshall, I.; King, M.; Zarbl, H., Urinary mycoestrogens, body size and breast development in New Jersey girls. *Sci Total Environ* **2011,** *409* (24), 5221-7.
16. Croy, R. G.; Essigmann, J. M.; Reinhold, V. N.; Wogan, G. N., Identification of the principal aflatoxin B1-DNA adduct formed *in vivo* in rat liver. *Proc Natl Acad Sci U S A* **1978,** *75* (4), 1745-9.
17. Degen, G. H.; Neumann, H. G., The major metabolite of aflatoxin B1 in the rat is a glutathione conjugate. *Chem Biol Interact* **1978,** *22* (2-3), 239-55.
18. Siess, M. H.; Guillermic, M.; Le Bon, A. M.; Suschetet, M., Induction of monooxygenase and transferase activities in rat by dietary administration of flavonoids. *Xenobiotica* **1989,** *19* (12), 1379-86.
19. Prochaska, H. J.; Santamaria, A. B.; Talalay, P., Rapid detection of inducers of enzymes that protect against carcinogens. *Proc Natl Acad Sci U S A* **1992,** *89* (6), 2394-8.
20. Sohn, H. O.; Lim, H. B.; Lee, Y. G.; Lee, D. W.; Lee, K. B., Modulation of cytochrome P-450 induction by long-term food restriction in male rats. *Biochem Mol Biol Int* **1994,** *32* (5), 889-96.
21. Moon, Y. J.; Wang, X.; Morris, M. E., Dietary flavonoids: effects on xenobiotic and carcinogen metabolism. *Toxicol In Vitro* **2006,** *20* (2), 187-210.
22. Peterson, S.; Lampe, J. W.; Bammler, T. K.; Gross-Steinmeyer, K.; Eaton, D. L., Apiaceous vegetable constituents inhibit human cytochrome P-450 1A2 (hCYP1A2) activity and hCYP1A2-mediated mutagenicity of aflatoxin B1. *Food Chem Toxicol* **2006,** *44* (9), 1474-84.
23. Nixon, J. E.; Hendricks, J. D.; Pawlowski, N. E.; Pereira, C. B.; Sinnhuber, R. O.; Bailey, G. S., Inhibition of aflatoxin B1 carcinogenesis in rainbow trout by flavone and indole compounds. *Carcinogenesis* **1984,** *5* (5), 615-9.
24. Kensler, T. W.; Egner, P. A.; Dolan, P. M.; Groopman, J. D.; Roebuck, B. D., Mechanism of protection against aflatoxin tumorigenicity in rats fed 5-(2-pyrazinyl)-4-methyl-1,2-dithiol-3-thione (oltipraz) and related 1,2-dithiol-3-thiones and 1,2-dithiol-3-ones. *Cancer Res* **1987,** *47* (16), 4271-7.
25. Kensler, T. W.; Curphey, T. J.; Maxiutenko, Y.; Roebuck, B. D., Chemoprotection by organosulfur inducers of phase 2 enzymes: dithiolethiones and dithiins. *Drug Metabol Drug Interact* **2000,** *17* (1-4), 3-22.
26. Gross-Steinmeyer, K.; Eaton, D. L., Dietary modulation of the biotransformation and genotoxicity of aflatoxin B(1). *Toxicology* **2012,** *299* (2-3), 69-79.
27. Chen, L.; Yu, M.; Wu, Q.; Peng, Z.; Wang, D.; Kuca, K.; Yao, P.; Yan, H.; Nussler, A. K.; Liu, L.; Yang, W., Gender and geographical variability in the exposure pattern and metabolism of deoxynivalenol in humans: a review. *J Appl Toxicol* **2016**.
28. Maul, R.; Warth, B.; Schebb, N. H.; Krska, R.; Koch, M.; Sulyok, M., In vitro glucuronidation kinetics of deoxynivalenol by human and animal microsomes and recombinant human UGT enzymes. *Arch Toxicol* **2015,** *89* (6), 949-60.
29. Wu, X.; Murphy, P.; Cunnick, J.; Hendrich, S., Synthesis and characterization of deoxynivalenol glucuronide: its comparative immunotoxicity with deoxynivalenol. *Food Chem Toxicol* **2007,** *45* (10), 1846-55.
30. Berthiller, F.; Dall'Asta, C.; Schuhmacher, R.; Lemmens, M.; Adam, G.; Krska, R., Masked mycotoxins: determination of a deoxynivalenol glucoside in artificially and naturally contaminated wheat by liquid chromatography-tandem mass spectrometry. *J Agric Food Chem* **2005,** *53* (9), 3421-5.
31. Berthiller, F.; Dall'asta, C.; Corradini, R.; Marchelli, R.; Sulyok, M.; Krska, R.; Adam, G.; Schuhmacher, R., Occurrence of deoxynivalenol and its 3-beta-D-glucoside in wheat and maize. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess* **2009,** *26* (4), 507-11.

www.manaraa.com

491 32. Nagl, V.; Schwartz, H.; Krska, R.; Moll, W. D.; Knasmuller, S.; Ritzmann, M.; Adam, G.;
492 Berthiller, F., Metabolism of the masked mycotoxin deoxynivalenol-3-glucoside in rats. *Toxicol*
493 *Lett* **2012,** *213* (3), 367-73.
494 33. Nagl, V.; Woechtl, B.; Schwartz-Zimmermann, H. E.; Hennig-Pauka, I.; Moll, W. D.; Adam,
495 G.; Berthiller, F., Metabolism of the masked mycotoxin deoxynivalenol-3-glucoside in pigs.
496 *Toxicol Lett* **2014,** *229* (1), 190-7.
497 34. Seeling, K.; Danicke, S.; Valenta, H.; Van Egmond, H. P.; Schothorst, R. C.; Jekel, A. A.;
498 Lebzien, P.; Schollenberger, M.; Razzazi-Fazeli, E.; Flachowsky, G., Effects of Fusarium toxin-
499 contaminated wheat and feed intake level on the biotransformation and carry-over of
500 deoxynivalenol in dairy cows. *Food Addit Contam* **2006,** *23* (10), 1008-20.
501 35. Danicke, S.; Valenta, H.; Doll, S., On the toxicokinetics and the metabolism of
502 deoxynivalenol (DON) in the pig. *Arch Anim Nutr* **2004,** *58* (2), 169-80.
503 36. Turner, P. C.; Hopton, R. P.; Lecluse, Y.; White, K. L.; Fisher, J.; Lebailly, P., Determinants
504 of urinary deoxynivalenol and de-epoxy deoxynivalenol in male farmers from Normandy, France.
505 *J Agric Food Chem* **2010,** *58* (8), 5206-12.
506 37. Turner, P. C.; Hopton, R. P.; White, K. L.; Fisher, J.; Cade, J. E.; Wild, C. P., Assessment of
507 deoxynivalenol metabolite profiles in UK adults. *Food Chem Toxicol* **2011,** *49* (1), 132-5.
508 38. Tuomola, E.; Crittenden, R.; Playne, M.; Isolauri, E.; Salminen, S., Quality assurance
509 criteria for probiotic bacteria. *Am J Clin Nutr* **2001,** *73* (2 Suppl), 393s-398s.
510 39. Haq, M.; Gonzalez, N.; Mintz, K.; Jaja-Chimedza, A.; De Jesus, C. L.; Lydon, C.; Welch, A.;
511 Berry, J. P., Teratogenicity of Ochratoxin A and the Degradation Product, Ochratoxin alpha, in
512 the Zebrafish (Danio rerio) Embryo Model of Vertebrate Development. *Toxins (Basel)* **2016,** *8*
513 (2), 40.
514 40. Galtier, P.; Alvinerie, M.; Charpenteau, J. L., The pharmacokinetic profiles of ochratoxin
515 A in pigs, rabbits and chickens. *Food Cosmet Toxicol* **1981,** *19* (6), 735-8.
516 41. Coronel, M. B.; Marin, S.; Tarrago, M.; Cano-Sancho, G.; Ramos, A. J.; Sanchis, V.,
517 Ochratoxin A and its metabolite ochratoxin alpha in urine and assessment of the exposure of
518 inhabitants of Lleida, Spain. *Food Chem Toxicol* **2011,** *49* (6), 1436-42.
519 42. Klapec, T.; Sarkanj, B.; Banjari, I.; Strelec, I., Urinary ochratoxin A and ochratoxin alpha in
520 pregnant women. *Food Chem Toxicol* **2012,** *50* (12), 4487-92.
521 43. Dobritzsch, D.; Wang, H.; Schneider, G.; Yu, S., Structural and functional characterization
522 of ochratoxinase, a novel mycotoxin-degrading enzyme. *Biochem J* **2014,** *462* (3), 441-52.
523 44. Dantzer, W. R.; Hopper, J.; Mullin, K.; Hendrich, S.; Murphy, P. A., Excretion of (14)C-
524 fumonisin B(1), (14)C-hydrolyzed fumonisin B(1), and (14)C-fumonisin B(1)-fructose in rats. *J*
525 *Agric Food Chem* **1999,** *47* (10), 4291-6.
526 45. Masching, S.; Naehrer, K.; Schwartz-Zimmermann, H. E.; Sarandan, M.; Schaumberger,
527 S.; Dohnal, I.; Nagl, V.; Schatzmayr, D., Gastrointestinal Degradation of Fumonisin B(1) by
528 Carboxylesterase FumD Prevents Fumonisin Induced Alteration of Sphingolipid Metabolism in
529 Turkey and Swine. *Toxins (Basel)* **2016,** *8* (3).
530 46. Association, N. G. a. F. FDA Mycotoxin Regulatory Guidance. https://www.ngfa.org/wp-
531 content/uploads/NGFAComplianceGuide-FDARegulatoryGuidanceforMycotoxins8-2011.pdf.
532 47. Turner, N. W.; Bramhmbhatt, H.; Szabo-Vezse, M.; Poma, A.; Coker, R.; Piletsky, S. A.,
533 Analytical methods for determination of mycotoxins: An update (2009-2014). *Anal Chim Acta*
534 **2015,** *901*, 12-33.
535 48. Rai, M.; Jogee, P. S.; Ingle, A. P., Emerging nanotechnology for detection of mycotoxins
536 in food and feed. *Int J Food Sci Nutr* **2015,** *66* (4), 363-70.
537 49. Shim, W. B.; Kim, M. J.; Mun, H.; Kim, M. G., An aptamer-based dipstick assay for the
538 rapid and simple detection of aflatoxin B1. *Biosens Bioelectron* **2014,** *62*, 288-94.

www.manaraa.com

539 50. Lamberti, I.; Tanzarella, C.; Solinas, I.; Padula, C.; Mosiello, L., An antibody-based
540 microarray assay for the simultaneous detection of aflatoxin B1 and fumonisin B 1. *Mycotoxin*
541 *Res* **2009,** *25* (4), 193-200.
542 51. Liu, L. H.; Zhou, X. H.; Shi, H. C., Portable optical aptasensor for rapid detection of
543 mycotoxin with a reversible ligand-grafted biosensing surface. *Biosens Bioelectron* **2015,** *72*,
544 300-5.
545 52. Qiu, Y. L.; He, Q. H.; Xu, Y.; Bhunia, A. K.; Tu, Z.; Chen, B.; Liu, Y. Y., Deoxynivalenol-mimic
546 nanobody isolated from a naive phage display nanobody library and its application in
547 immunoassay. *Anal Chim Acta* **2015,** *887*, 201-8.
548 53. Santino, A.; Poltronieri, P.; Mita, G., Advances on plant products with potential to
549 control toxigenic fungi: A review. *Food Additives & Contaminants* **2005,** *22* (4), 389-395.
550 54. Brown, R. L.; Menkir, A.; Chen, Z.-Y.; Bhatnagar, D.; Yu, J.; Yao, H.; Cleveland, T. E.,
551 Breeding aflatoxin-resistant maize lines using recent advances in technologies – a review. *Food*
552 *Additives & Contaminants. Part A: Chemistry, Analysis, Control, Exposure & Risk Assessment*
553 **2013,** *30* (8), 1382-1391.
554 55. Chiuraise, N.; Derera, J.; Yobo, K.; Magorokosho, C.; Nunkumar, A.; Qwabe, N., Progress
555 in stacking aflatoxin and fumonisin contamination resistance genes in maize hybrids. *Euphytica*
556 **2016,** *207* (1), 49-67.
557 56. Kluger, B.; Bueschl, C.; Lemmens, M.; Michlmayr, H.; Malachova, A.; Koutnik, A.; Maloku,
558 I.; Berthiller, F.; Adam, G.; Krska, R.; Schuhmacher, R., Biotransformation of the Mycotoxin
559 Deoxynivalenol in Fusarium Resistant and Susceptible Near Isogenic Wheat Lines. *PLoS ONE*
560 **2015,** *10* (3), 1-19.
561 57. Choo, T. M.; Vigier, B.; Savard, M. E.; Blackwell, B.; Martin, R.; Junmei, W.; Jianming, Y.;
562 Abdel-Aal, E.-S. M., Black Barley as a Means of Mitigating Deoxynivalenol Contamination. *Crop*
563 *Science* **2015,** *55* (3), 1096-1103.
564 58. Chulze, S. N.; Palazzini, J. M.; Torres, A. M.; Barros, G.; Ponsone, M. L.; Geisen, R.;
565 Schmidt-Heydt, M.; Köhl, J., Biological control as a strategy to reduce the impact of mycotoxins
566 in peanuts, grapes and cereals in Argentina. *Food Additives & Contaminants. Part A: Chemistry,*
567 *Analysis, Control, Exposure & Risk Assessment* **2015,** *32* (4), 471-479.
568 59. Park, D. L., Perspectives on mycotoxin decontamination procedures. *Food Addit Contam*
569 **1993,** *10* (1), 49-60.
570 60. Gnonlonfin, G. J. B.; Hell, K.; Adjovi, Y.; Fandohan, P.; Koudande, D. O.; Mensah, G. A.;
571 Sanni, A.; Brimer, L., A Review on Aflatoxin Contamination and Its Implications in the Developing
572 World: A Sub-Saharan African Perspective. *Critical Reviews in Food Science & Nutrition* **2013,** *53*
573 (4), 349-365.
574 61. Matumba, L.; Van Poucke, C.; Njumbe Ediage, E.; Jacobs, B.; De Saeger, S., Effectiveness
575 of hand sorting, flotation/washing, dehulling and combinations thereof on the decontamination
576 of mycotoxin-contaminated white maize. *Food Additives & Contaminants. Part A: Chemistry,*
577 *Analysis, Control, Exposure & Risk Assessment* **2015,** *32* (6), 960-969.
578 62. Siciliano, I.; Spadaro, D.; Prelle, A.; Vallauri, D.; Cavallero, M. C.; Garibaldi, A.; Gullino, M.
579 L., Use of Cold Atmospheric Plasma to Detoxify Hazelnuts from Aflatoxins. *Toxins (Basel)* **2016,** *8*
580 (5).
581 63. Cano-Sancho, G.; Sanchis, V.; Ramos, A. J.; Marín, S., Effect of food processing on
582 exposure assessment studies with mycotoxins. *Food Additives & Contaminants. Part A:*
583 *Chemistry, Analysis, Control, Exposure & Risk Assessment* **2013,** *30* (5), 867-875.
584 64. Frobose, H. L.; Fruge, E. D.; Tokach, M. D.; Hansen, E. L.; DeRouchey, J. M.; Dritz, S. S.;
585 Goodband, R. D.; Nelssen, J. L., The influence of pelleting and supplementing sodium

www.manaraa.com

586 metabisulfite (Na2S2O5) on nursery pigs fed diets contaminated with deoxynivalenol. *Animal*
587 *Feed Science & Technology* **2015,** *210*, 152-164.
588 65. Cazzaniga, D.; Basilico, J. C.; Gonzalez, R. J.; Torres, R. L.; de Greef, D. M., Mycotoxins
589 inactivation by extrusion cooking of corn flour. *Lett Appl Microbiol* **2001,** *33* (2), 144-7.
590 66. Dänicke, S.; Valenta, H.; Gareis, M.; Lucht, H. W.; Reichenbach, H. v., On the effects of a
591 hydrothermal treatment of deoxynivalenol (DON)-contaminated wheat in the presence of
592 sodium metabisulphite (Na2S2O5) on DON reduction and on piglet performance. *Animal Feed*
593 *Science & Technology* **2005,** *118* (1/2), 93-108.
594 67. Amézqueta, S.; González-Peñas, E.; Murillo-Arbizu, M.; López de Cerain, A., Ochratoxin A
595 decontamination: A review. *Food Control* **2009,** *20* (4), 326-333.
596 68. Poór, M.; Kunsági-Máté, S.; Szente, L.; Matisz, G.; Secenji, G.; Czibulya, Z.; Kőszegi, T.,
597 Interaction of ochratoxin A with quaternary ammonium beta-cyclodextrin. *Food Chemistry* **2015,**
598 *172*, 143-149.
599 69. Printz, C., A 'field in motion'. *Cancer (0008543X)* **2013,** *119* (6), 1117-1118.

600

www.manaraa.com