



Systematic review of clinician awareness of mycotoxin impact in neural tube defects and best practices for pediatric neurosurgeons: implications for public health and policy

Rebecca Y. Du¹ · Melissa A. LoPresti¹ · Caroline C. Hadley¹ · Sandi Lam¹

Received: 15 November 2018 / Accepted: 4 December 2018 / Published online: 14 December 2018
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Abstract

Purpose In lower-income populations, high rates of neural tube defects (NTDs) are a concern. Nutritional folate deficiencies and mycotoxins in contaminated food supplies increase risk of NTDs. As physicians in public health and involved in the care of children with NTDs, pediatric neurosurgeons have an interest in the treatment and prevention of NTDs. We aimed to evaluate the literature to assess the awareness and the existence of best practices/educational materials on this issue to better guide management.

Methods A systematic review using the National Library of Medicine PubMed database was conducted to find articles related to mycotoxins in foods causing neural tube defects. Additional citation searches of key publications and personal collections were used. Two reviewers evaluated the resulting studies for subject area analysis. Best practice recommendations were drawn from articles selected for full-text review.

Results Seventy-three articles were identified. Most articles were found in “nutritional sciences” (18), “teratology” (14), and “toxicology” (13). No articles were found in neurosurgery. Thirty-two additional articles were identified through other sources to screen best practice recommendations. Of the 105 articles, 34 journal articles were included in best practice recommendation guidelines. Key recommendations included education of proper food storage, hygienic agricultural practices, decontamination techniques, diet diversification, folate supplementation, risk assessment, and food safety policy and public health initiatives.

Conclusion There is an absence of neurosurgical literature–related mycotoxins and NTDs. We suggest a set of best practices/educational materials on this topic and advocate pediatric neurosurgery engagement in public health initiatives targeted towards populations most affected by mycotoxins.

Keywords Neural tube defect · Spina bifida · Mycotoxin · Fumonisin · Folate · Public health · Global neurosurgery · Public policy

Abbreviations and acronyms

CAC Codex Alimentarius Commission
EFSA European Food Consumption Database
EU European Union
FDA Food and Drug Administration
FOA Food and Agriculture Organization

NLM National Library of Medicine
NTD Neural tube defects
USA United States
WHO World Health Organization

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00381-018-4023-3>) contains supplementary material, which is available to authorized users.

✉ Rebecca Y. Du
rebecca.du@bcm.edu

¹ Department of Neurosurgery, Baylor College of Medicine; Division of Pediatric Neurosurgery, Texas Children’s Hospital, 6701 Fannin St., Ste. 1230, Houston, TX 77030, USA

Background

Due to public health initiatives aimed at prevention, the incidence of neural tube defects (NTDs) such as spina bifida has decreased in the USA and other developed countries over time. Thanks to folate supplementation, increased prenatal screening, and heightened awareness, developmental dysraphisms such as spina bifida, encephaloceles, and other NTDs can be better prevented and assessed for prenatally [7]. However, in some parts of the world, where resources and

access to such initiatives may be limited, including sub-Saharan Africa, high rates of NTDs remain a concern [49].

Mycotoxins in contaminated food supplies are a systemic risk factor for NTDs. Mycotoxins are metabolic by-products of fungi that contaminate food and animal feed supplies [22]. The most common mycotoxin-producing fungi are *Fusarium*, *Aspergillus*, and *Penicillium*. These fungi generate numerous mycotoxins, which have been linked to a plethora of negative human and animal health consequences, including but not limited to hepatotoxicity [48], teratogenicity [43], carcinogenicity [25], neurotoxicity [13], and childhood growth retardation [21].

Fumonisin, produced by *Fusarium verticilloides*, the most common food contaminant of maize worldwide [10, 48], is associated with an increased risk for NTDs if consumed during early pregnancy [14, 15, 26, 28, 34, 48]. Fumonisin is thought to inhibit the enzyme ceramide synthase, thereby disrupting sphingolipid biosynthesis, modulating cell cycle regulators [6, 9, 30], and stimulating tumor necrosis factor alpha production [41]. The exact link between fumonisin and NTDs is not well understood; however, studies have found a correlation between high consumption of maize contaminated by fumonisins and NTDs [18, 26].

Mycotoxin exposure is widespread. In 1994, the Food and Agriculture Organization (FAO) of the United Nations estimated that one fourth of the world's food crops were contaminated by mycotoxins [50], with food security threats due to mycotoxins most significant in low-income countries. Surveillance data from sub-Saharan Africa have reported the prevalence of fumonisins in food supplies to be nearly 100% [4]. The burden of mycotoxins in sub-Saharan Africa is thought to be due to the region's growing census. As the population grows, demand for food also increases, leading to increased food production, storage, transportation, and processing, all of which increases risk of contamination and facilitates fungal growth and mycotoxin contamination of food supplies [47].

As physicians interested in public health, and pediatric neurosurgeons involved in the treatment of NTDs, we have firsthand knowledge of the deleterious implications of mycotoxin exposure in neonatal and pediatric health and are in a unique position to counsel families with children who have NTDs to try to decrease occurrence of NTDs in subsequent pregnancies. In this study, we aimed to conduct a systematic review of the literature to assess clinician awareness of mycotoxins and the existence of best practices or educational materials on this issue.

Methods

A systematic review was conducted using the online National Library of Medicine PubMed database for relevant articles related to mycotoxins in food supplies causing NTDs. No date of publication restriction was placed on search results. Key

words searched in the database review were “mycotoxin” or “fumonisin” and “neural tube defect,” including related pairs “mycotoxin” and “spina bifida,” “mycotoxin” and “encephalocele,” “fumonisin” and “spina bifida,” and “fumonisin” and “encephalocele.” Resulting articles were sorted by subject area using the keywords assigned to the journal article by the National Library of Medicine (NLM). Due to the limited number of articles resulting from the search, no articles were excluded from subject area evaluation.

To review recommendations for best practices, an additional citation search of key publications was performed using Google Scholar to identify additional articles. All additional articles were included. The abstracts of all articles from key word searches and other sources written in English were read in full to screen for inclusion of best practice recommendations. Any articles with abstracts indicating inclusion of best practice recommendations were read in their entirety. Only articles regarding recommendations for *Fusarium* mycotoxins were included in best practice recommendations. We excluded studies exclusively regarding recommendations for mycotoxins caused by other species of fungi, such as *Aspergillus* or *Penicillium*. We included studies regardless of recommended interventions or geographic location. However, specific focus was given to individual- or community-level interventions over state- or country-wide interventions as well as interventions targeting low- or middle-income countries over high-income countries. Articles of all types were included in the review.

To collect data on best practice recommendations, two reviewers screened the titles and abstracts and read full-text reports of all potentially relevant articles. Discordant decisions were then discussed until a consensus was reached, and recommendations were extracted from selected articles.

Results

A total of 73 articles were identified in our key word search (Supplementary Table S1). No duplicates were found. Due to the low yield, no articles were excluded in our evaluation of subject area. Several articles were assigned more than one broad subject term by NLM. For articles with more than one broad subject term, subject areas were assigned redundantly.

Most articles were found in journals pertaining to “nutritional sciences” (18), “teratology” (14), and “toxicology” (13). The remaining articles were found in “embryology” (5), “microbiology” (5), “medicine” (4), “pharmacology” (4), “anatomy” (3), “biology” (3), “environmental health” (3), “genetics” (3), “chemistry” (2), “molecular biology” (2), “neoplasms” (2), “neurology” (2), “pathology” (2), “science” (2), “biochemistry” (1), “biotechnology” (1), “chemistry techniques” (1), “epidemiology” (1), “health services” (1), “jurisprudence” (1), “obstetrics/gynecology” (1), “occupational

medicine” (1), “pediatrics” (1), and “physiology” (1) journals (Fig. 1). No articles were found in neurosurgical journals.

Following initial collection of articles using keyword search, an additional 32 articles were identified through other sources for best practice recommendations. From a total of 105 articles, three were excluded as articles not written in English. One hundred and two abstracts were screened, and 49 journal articles were read in full. Twelve were excluded for overall lack of best practice recommendations, and three were excluded for lack of *Fusarium*-specific recommendations. Thirty-four journal articles were identified for best practice recommendations (Fig. 2). Recommendations were organized into five domains: prevention, decontamination, decreasing toxicity, surveillance of exposure and risk, and policy.

Prevention

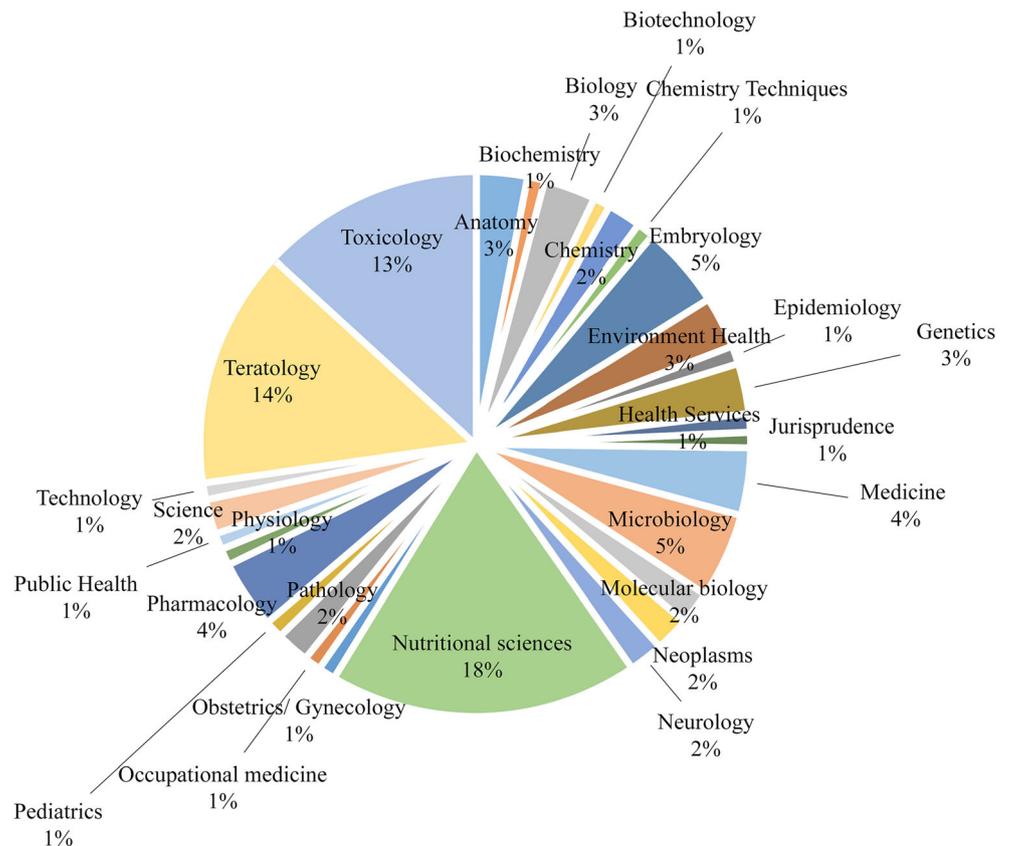
The goal of prevention is to prevent contamination of crops with mycotoxins. Key interventions found in this domain included hygienic agricultural practices, proper storage of crops, and the use of conventional or transgenic breeding to resist insect pest damage or fungal infection. Below are the highlighted recommendations for prevention of mycotoxin contamination during cultivation, harvest, storage, and transport of crops and food sources.

- Hygienic agricultural practice should involve crop rotation, soil cultivation, irrigation, fertilization, and early harvesting of maize crops [11, 14].
- During harvest, avoid physical damage or contact with soil [11].
- Crop planting and harvesting should be timed to avoid high temperatures and humid climates, which increase susceptibility to mycotoxins [11].
- Store properly to less than 10% moisture with adequate protection from insects [10, 11, 37].
- Store in cooler temperatures to reduce the risk of mycotoxin contamination [11].
- Seeds can be bred for increased resistance to fungal contamination based on geographic region [11].
- Transgenic breeds of maize with enhanced ability to degrade fumonisin have been produced to prevent contamination [11].

Decontamination

The goal of decontamination is to remove mycotoxins from already contaminated food supplies. Key interventions of this domain included physical and chemical methods for decontamination. Below are the highlighted

Fig. 1 Chart showing subject areas of journal articles



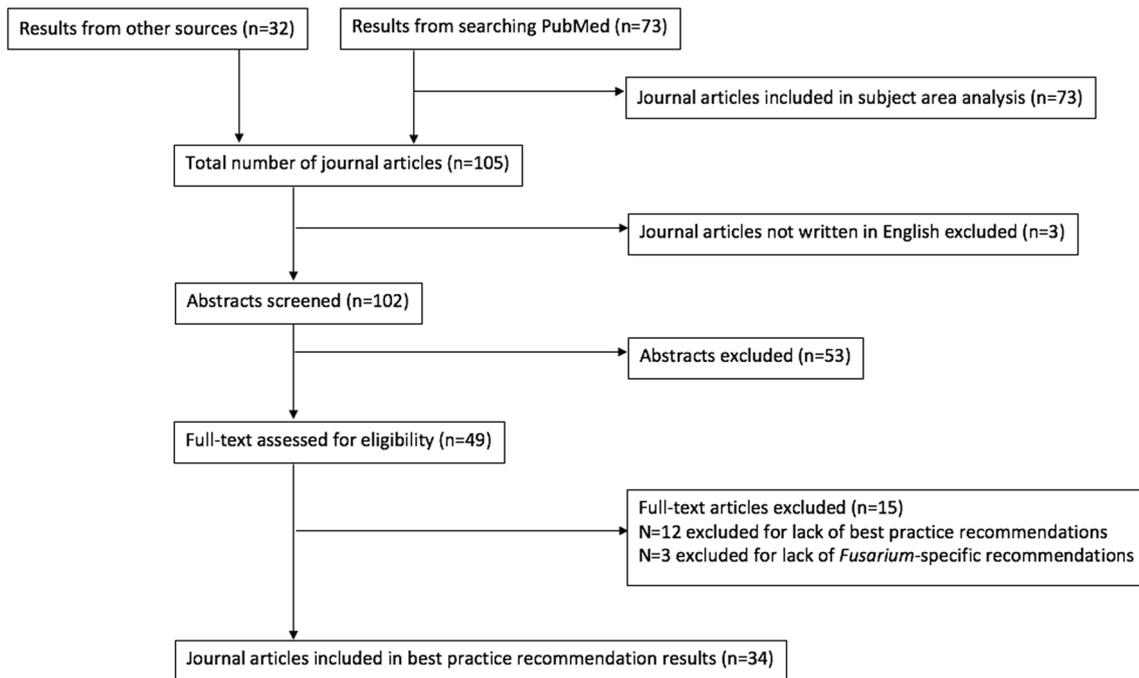


Fig. 2 Journal articles identified for best practice recommendations

recommendations for decontamination physically, thermally, and chemically.

- An initial three-step process of washing, dehulling, and removing visibly moldy and/or floating maize kernels is effective in removing mycotoxins by removing dust and broken kernels, susceptible to fungal infections [10, 19, 27, 35, 36, 46].
- Milling of contaminated wheat can reduce mycotoxin concentrations [23, 24].
- Although mycotoxins are heat stable and generally not destroyed in the cooking process [8], thermal treatment with temperatures ranging from 120 to 220 °C can reduce mycotoxin contamination [20, 31, 33, 46].
- The process of nixtamalization or alkali cooking can lead to partial degradation of fumonisin toxins in maize-based foods [20, 42]. Chemical reduction of mycotoxin concentrations can be achieved through the use of fungicides, such as tebuconazole [11, 17], antagonistic bacteria and yeasts [11], or through allyl, benzyl, and phenyl isothiocyanate [2].
- There is conflicting evidence supporting fermentation to reduce mycotoxin concentrations [5, 12, 32, 39].

Decreasing toxicity

The goal of decreasing toxicity is to decrease both short- and long-term toxic effects of mycotoxins after ingestion of contaminated food supply. Key interventions included

administration of adsorption agents to decrease gastrointestinal absorption of mycotoxin-contaminated food or targeted interventions for specific health concerns [48]. Below are the recommendations regarding toxicity reduction interventions.

- Adsorptive agents, including clay minerals (Novasil), selected calcium montmorillonites, or essential oils [29, 45], are not recommended due to possible negative side effects, namely malnutrition due to decreased absorption of micronutrients, in addition to mycotoxins.
- Nutritional supplementation and diet diversification to increase folate can prevent toxic effects of mycotoxin, including NTDs [14, 34, 48].
- Nonnutritive sorbents can sequester mycotoxins and reduce toxin transfer to humans from animal products [50].

Surveillance of exposure and risk

Surveillance practices aim to identify those at risk of mycotoxin exposure. Key surveillance interventions include screening for contaminations and identifying those most susceptible via risk assessment. Below are recommendations regarding surveillance of exposure and risk.

- There is no established biomarker identification to assess fumonisin exposure [14, 38, 40, 46].
- Screening for exposure must target food sources and be aimed at those populations most at risk, namely low- or middle-income regions with limited health infrastructure.

- Food sources most at risk of mycotoxin exposure include insect-damaged maize [1, 44], home-grown or home-stored crops [3], and those stored in places ill-equipped for storage or decontamination methods.
- Recommend the establishment of country or regional reference testing laboratories and clinics for accurate testing and reporting of mycotoxin exposure [10].
- The European Food Consumption Database (EFSA) supports the use of total diet studies (TDS) to provide estimates for average mycotoxin contamination in food consumed [50].
- The US Food and Drug Administration (FDA) recommends evaluation of the dietary intake of corn products by specific groups in a community [28].

Policy

Policy aims to standardize the interventions in order to control and reduce mycotoxin contamination. The goal of policy interventions is to increase country and continent regulation of mycotoxin concentrations in food supplies; this can be done on a community, regional, or nationwide level. Below are policy recommendations.

- The European Union (EU) and joint FAO-World Health Organization (WHO) Expert Committee for Food Additives have set maximum tolerable intake of mycotoxins at 2 µg/kg body weight/day. In lower-income countries, there are less resources and often weaker regulatory bodies to form and enforce similar restrictions [46].
- Sub-Saharan Africa, where mycotoxin contamination is highest, lacks functional food control administrative and regulatory agencies [10].
- Currently, sub-Saharan Africa is using guidelines from the EU, FDA, and the Codex Alimentarius Commission (CAC) on *Fusarium* mycotoxins, which lack consideration of region-specific feeding habits, food security status, occurrence levels in the region, and genetic and environmental interactions [10, 46].
- There should be established regulatory policies and guidelines for the cultural and demographic characteristics of low- and middle-income countries in different regions of the world to better address their specific needs.

Discussion

The aim of this review was to identify all the data in the literature relevant to neurosurgeons and public health workers regarding mycotoxin contamination and its relation to NTDs. Of the 105 articles identified, and 34 articles involving best

practice recommendations, none were published in neurosurgery journals. Additionally, no specific recommendations, best practice guidelines, or educational materials for neurosurgeons were found. Moreover, the literature on mycotoxins as risk factors for NTDs is overall sparse in the realm of clinical practice for any specialty. Therefore, we sought to review the literature to develop a series of recommendations and best practices for those healthcare providers in the apt position to help motivate change and reduce mycotoxin contamination, exposure, and related deleterious effects. When adapting the existing literature to neurosurgical practice, we considered the feasibility and safety of each initiative. Below, we have identified the recommended best practices for neurosurgeons, or any provider aiming to help address this public health concern, when encountering patients at risk for NTDs due to mycotoxins (Table 1).

The most overarching theme found in the literature is the role of patient education. While many prevention measures can be targeted at industry-wide agricultural practices or on more broad scale regional levels, patient education of proper food storage techniques, on an individual level, can be applied when counseling patients—confirming that patients store food prone to contamination in cool, dry, and protected from insects. Additionally, education of hygienic agricultural practices, such as the early harvesting of crops, may be appropriate when practicing in areas dependent on subsistence farming. Similarly, counseling patients on the process of washing, dehulling, and removing visibly moldy and/or floating maize kernels prone to contamination can help educate the public and prone to mycotoxin exposure on decontamination.

While education and patient engagement in prevention is key, the most important practice for physicians to decrease the toxic effects of mycotoxins is folate supplementation and diet diversification, especially in mothers or women of child-bearing age prior to conception and during early pregnancy. Important considerations, when counseling patients on diet diversification, include the role of maize as a primary food group in most regions with high rates of mycotoxin contamination. While reality may limit the ability to diversify diets, education may encourage incorporation of other foods that

Table 1 Summary of best practice recommendations for neurosurgeons

Mycotoxin practice recommendations for neurosurgeons

- Education of patients on proper food storage
- Education of patients on simple hygienic agricultural practices
- Education of patients on simple decontamination techniques
- Encouragement of diet diversification for patients
- Folate supplementation for patients
- Individual patient risk assessment and comprehensive dietary history
- Engagement with food safety policy legislation and guidelines
- Advocate for public health and public education initiatives

may be accessible and affordable in the area, such as sweet potatoes, rice, vegetables, fruits, and/or lentils.

One barrier to education includes reaching the target population. Infants and prenatal mothers or women of childbearing age are best suited to benefit from interventions aimed to reduce mycotoxin contamination and prevent NTDs. While patient education is a means of counseling this target population on many interventions and solutions, many pregnant women in regions of limited resources may receive little or no prenatal care and deliver at home, putting this population out of reach from many of those willing and capable of helping. While many may not know about the benefits of folic acid supplementation in pregnancy, others who know may not have the means to purchase folic acid. To promote access, local government and public health initiatives are vital for education and providing the avenue for the distribution of affordable folic acid supplementation and mycotoxin prevention and decontamination methods at healthcare and government facilities. On a larger scheme, a more comprehensive alternative to fortify the general food supply with important supplements is required. Legislation and policy enforcing clean production, storage, and decontamination methods are important for a broader reaching impact [16].

Policy may not be in the scope of most healthcare providers, however, for those interested in public health, there is an emphasis on widening the impact for the care of the public and humanity. Larger organizational, community initiatives, or governmental agencies may hold the key in providing long-lasting change. Neurosurgeons, and most healthcare workers, are uniquely positioned to advocate on behalf of their patients for more food safety regulations tailored specifically to the cultural, economic, and demographic characteristics of specific regions in which they are practicing. By advocating for and enforcing better prevention, storage, and decontamination methods, as well as healthcare initiatives to redress the deleterious effects, mycotoxin-contaminated food supplies across low-income countries, as seen in sub-Saharan Africa, for example, can be contained and eventually eliminated, helping prevent subsequent neurological disorders, like NTDs.

As a survey of the literature, this study is limited and cannot assess awareness and practices of neurosurgeons on an individual level. It is possible that there are already local examples of best practices in patient and community education on mycotoxin awareness. If so, we hope that this manuscript may start the conversation on collaboration and establishment of more widespread education and advocacy efforts. We recognize that clinical correlation between fumonisin consumption and incidence of neural tube defects is currently only supported in epidemiologic and animal model studies. Data elucidating the effects of fumonisin consumption on patients is limited and must be a focus of further study by clinicians as well as basic science and public health researchers. Areas of further study include not only data linking fumonisin to neural tube

defects but also diagnostic techniques to screen patients for exposure to high levels of fumonisin mycotoxins. However, those areas of research are not in the scope of this literature review. This study aims to raise attention to the research that has already been done, evaluate awareness among clinicians of mycotoxins, and provide recommendations which can be easily implemented by individual practitioners who help patients exposed fumonisin mycotoxins.

Conclusion

There is a need for increased awareness of mycotoxins contaminating food supplies as a risk factor for NTDs. As the world population continues to grow and climate change increases the number of tropical regions susceptible to fungal growth, the public health threat of mycotoxins will most likely only increase. Using these outlined best practices, as physicians and healthcare workers, we can provide patient education to arm populations with the knowledge to prevent, decontaminate, and reduce the toxicity of mycotoxins. As public health workers and caretakers of patients in low- and middle-income countries impacted by mycotoxin contamination of food supplies, we must act beyond our own capacities as individual neurosurgeons and advocate on behalf of our patients for broader public health and policy interventions that will address the root causes of this widespread public health issue.

Acknowledgements We thank Dr. Leland Albright for his insights in the preparation of this manuscript and guidance on his important work done in Kijabe, Kenya.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

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