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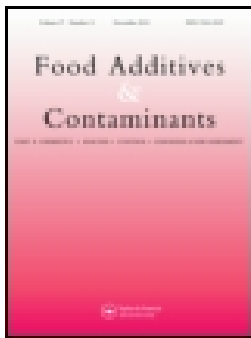
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Climate change and the health impact of aflatoxins exposure in Portugal – an overview

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Abstract

Climate change has been indicated as a driver for food safety issues worldwide, mainly due to the impact on the occurrence of food safety hazards at various stages of food chain. Mycotoxins, natural contaminants produced by fungi, are among the most important of such hazards. Aflatoxins, which have the highest acute and chronic toxicity of all mycotoxins, assume particular importance. A recent study predicted aflatoxin contamination in maize and wheat crops in Europe within the next 100 years and aflatoxin B1 is predicted to become a food safety issue in Europe, especially in the most probable scenario of climate change (+2 °C). This review discusses the potential influence of climate change on the health risk associated to aflatoxins dietary exposure of Portuguese population. We estimated the burden of disease associated to the current aflatoxin exposure for Portuguese population in terms of Disability Adjusted Life Years (DALYs). It is expected that in the future the number of DALYs and the associated cases of

hepatocellular carcinoma due to aflatoxins exposure will increase due to climate change. The topics highlighted through this review, including the potential impact on health of the Portuguese population through the dietary exposure to aflatoxins, should represent an alert for the potential consequences of an incompletely explored perspective of climate change. Politics and decision-makers should be involved and committed to implement effective measures to deal with climate change issues and to reduce its possible consequences. This review constitutes a contribution for the prioritisation of strategies to face the unequal burden of effects of weather-related hazards in Portugal and across Europe.

Keywords: climate change, aflatoxins, risk assessment, health-impact, Portugal

Introduction

The Fifth Assessment Report of the Intergovernmental Panel on Climate Change (IPCC) states that “warming of the climate system is unequivocal, and since the 1950s, many of the observed changes are unprecedented over decades to millennia. The atmosphere and ocean have warmed, the amounts of snow and ice have diminished, and sea level has risen” (IPCC 2014). According to this report, in recent decades, changes in climate have caused impacts on natural and human systems on all continents and across the oceans (IPCC 2014). Climate change has become one of the most critical issues for the sustainable development of human societies and the functioning of ecosystems on earth (van der Fels-Klerx et al. 2012). Given the potential of climate change to reverse the health gains from economic development, and the health co-benefits that accrue from actions for a sustainable economy, climate change constitutes one of the biggest global threats to human health of the 21st century (Watts et al. 2015). At the Conference of Parties in Paris (COP21), in December 2015, negotiators from 195 countries agreed to “pursue efforts to limit the (global average) temperature increase to 1.5 °C above pre-

industrial levels”, recognizing that this would significantly reduce the risks and impacts of climate change (UNFCCC 2015). Nevertheless, projected climate change effects will undoubtedly influence primary agricultural systems, including animal and plant production, and thus food availability (Van der Fels-Klerx et al. 2016). These projected climate change effects include a global air temperature increase, variation in precipitation, drought and the atmospheric carbon dioxide accumulation. These effects constitute some of the main concerns for agriculture and food safety connected to the climate change (Van der Fels-Klerx et al. 2016). The potential impact of climate change on food security is a widely debated and investigated issue. Nonetheless, the specific impact on safety of food and feed has remained a less studied topic (Miraglia et al. 2009; Tirado et al. 2010). Climate change is also likely to increase the risk of food contaminants through the tendency to increase the use of agrochemicals to balance the effects of more frequent extreme weather events and water scarcity in some regions (Santos 2017). Portugal is highly vulnerable to climate change impacts due to its geographical situation at the extreme southwestern part of Europe (Carvalho et al. 2014; Campos et al. 2017). Climate change impacts in Portugal result from a decreasing annual precipitation, more intense extreme weather and climate events (e.g. heat waves and droughts). Traditionally, the Portuguese climate is considered as Mediterranean, characterized by warm and dry summers and cool and wet winters. The mean annual air temperature varies between 7 °C in the inner highlands of central Portugal and 18 °C in the southern coast. The mean annual precipitation is around 900 mm with a strong north–south gradient, reaching values of 3000 mm in the northwest mountains and values below 500 mm in the south-eastern part of the country (Carvalho et al. 2014). In Portugal, studies have been revealing periods of warming similar to global temperature behaviour. Ramos et al. (2011) studied the evolution of extreme temperatures over

Portugal, and in the period of 1976 – 2006, the authors verified that the annual mean temperature in the country increased by 0.52 °C per decade, which is more than double the rate of mean annual global temperature increase. Fonseca et al. (2016) described the recent trends of extreme temperature indices for the Iberian Peninsula and reported an increase in the number of warm days and warm nights, especially during summer. Eight of the ten warmest years occurred in the last 20 years and heat waves have becoming more frequent since the beginning of this century (Ramos et al. 2011). All these observations are consistent with a tendency of more intense and frequent extreme weather and climate events. The observed trends are very similar to those projected by the future climate scenarios as regards both temperature and precipitation (Carvalho et al. 2014). In fact the Mediterranean region, including mainland Portugal, was considered a climate change hotspot (Giorgi 2006).

Climate change may have an impact on the occurrence of food safety hazards at various stages of the food chain, from primary production through to consumption (Tirado et al. 2010). Both chemical and microbiological risks are foreseen to impair food and feed safety as a consequence of climate change: in particular mycotoxins, marine biotoxins (phycotoxins), pesticide residues, trace metals, among others (Miraglia et al. 2009). The expected impact of climate change on the presence of mycotoxins in food and feed is of great concern (Paterson & Lima 2010; Paterson & Lima 2011; Battilani et al. 2016). Due to the public health and economic implications, the legislated mycotoxins are aflatoxins, ochratoxin A (OTA), deoxynivalenol (DON), fumonisins, zearalenone and patulin (European Commission 2006). Some of the main health toxic effects of mycotoxins include liver cancer or hepatocellular carcinoma (HCC) (aflatoxins), oesophageal cancer and neural tube defects (fumonisins), immunotoxicity and gastroenteritis (DON and other trichothecenes), and renal diseases (OTA) (Wu et al.

2014). Economic implications of mycotoxin contamination include trade disruptions due to recall or rejection of products; this food safety hazard accounted for 489 notifications on mycotoxins in food, most related to the presence of aflatoxins in 2016 (European Commission 2017).

The most toxic mycotoxins are aflatoxins, which can occur in host crops infected by some species of *Aspergillus* spp. (Wu et al. 2014). Aflatoxins are genotoxic, carcinogenic and immunosuppressive substances, and cause both acute and chronic toxicity. HCC is the third leading cause of cancer deaths worldwide (WHO 2008). Due to its carcinogenic and genotoxic effects, mixes of aflatoxins have been classified as Group 1 (carcinogenic to humans) by the International Agency for Research on Cancer (IARC 2012). The four major aflatoxins are known as B₁, B₂, G₁, and G₂. Aflatoxin B₁ (AFB₁) is the most potent (in some species) naturally occurring chemical liver carcinogen known. Maize contamination is of very high concern since this crop plays a main role both in food and feed supply worldwide. Additionally, when animals that are intended for dairy production consume aflatoxin-contaminated feed, a metabolite, aflatoxin M₁, is excreted in the milk (Strosnider et al. 2006). Aflatoxins are reported in several agricultural crops, mainly maize, peanuts, pistachio nuts and cottonseeds (CAST 2003). The possible change in patterns of aflatoxin occurrence in food and feed crops due to climate change is a matter of concern that may require anticipatory actions (Battilani et al. 2016). Until a few years ago, aflatoxins had not been signalled as a matter of concern for primary production in Europe (Logrieco & Moretti 2008). However, in 2003, 2012 and 2015 several reports from Southern-eastern Europe countries identified an alarming contamination in maize (Piva et al. 2006; Tabuc et al. 2009; Levic et al. 2013; Dobolyi et al. 2013; Kos et al. 2013; Pleadin et al. 2014; Dimitrieska-Stojković et al. 2016; Janić Hajnal et al. 2017).

In Portugal, previous studies have demonstrated the occurrence of aflatoxins in food products consumed by the Portuguese population (Alvito et al. 2010; Rodrigues et al. 2012; Martins et al. 2018) and exposure to aflatoxins through food (Assunção et al. 2015) and occupational exposure in different occupational environments (Viegas et al. 2012; Viegas et al. 2013a; S. Viegas et al. 2014; S. Viegas et al. 2016). Few published studies describe changes in the burden of climate-sensitive diseases in Portugal in response to changes in weather and climate, as assessed by Casimiro et al. (2006). According to the National Assessment of Human Health Effects of Climate Change in Portugal (Casimiro et al. 2006), the annual heat-related death rates in Lisbon may increase from between 5.4 and 6 per 100,000 in 1980–1998 to between 8.5 and 12.1 by the 2020s and to a maximum of 29.5 by the 2050s, if no adaptations occur. Recent catastrophes resulting from summer high temperatures and reduced air humidity in Portugal that took the form of severe and dramatic forest fires with significant consequences including loss of human lives (Jones 2017). The impact of climate change on these events remains unknown. Considering the potential consequences of climate change on food safety, particularly in mycotoxin contamination of food products available in Portugal, this review discusses the potential influence of climate change in the health risk associated to aflatoxins dietary exposure of Portuguese population.

Environmental conditions modulating mycotoxin exposure

Although there are many factors involved in mycotoxins production by fungi, the climate is the most important (Magan et al. 2011; Milani 2013). Climate changes and their consequences on fungal dissemination are critical aspects of human exposure to mycotoxins (Magan et al. 2011; Milani 2013; Battilani et al. 2016). Effects of climate change on fungal species distribution and activity are difficult to predict because they are influenced in many different ways, such as: fungal characteristics, host features and

availability, and competitive interactions between microbiota. In addition, environmental variables such as temperature, water availability and atmospheric CO₂ and the interaction of these variables make it difficult to predict their influence on fungal distribution (Boddy 1984) and, consequently, mycotoxins presence in food and feed (IPCC 2007).

Mycotoxins are profoundly dependent on climate, plant and storage-associated problems, and also influenced by non-infectivity factors (e. g. bioavailability of (micro)nutrients, insect damage, and other pests attack), that are also driven by climatic conditions. Therefore, climate represents the crucial factor for agro-ecosystem powering fungal colonization and mycotoxin production (Magan et al. 2011).

Increasing temperatures are known to benefit the proliferation of several fungal species with toxigenic potential, namely: *Fusarium graminearum* complex (Miller 2008; Miraglia et al. 2009; Tirado et al. 2010), *Fusarium verticilloides* complex (Munkvold & Desjardins 1997; Tirado et al. 2010; Paterson & Lima 2011) and *Aspergillus* genus (Robens & Cardwell 2003). Among *Aspergillus* genus, *Aspergillus section Flavi* is also facilitated by this climate scenario (Payne 1998; Bunyavanich et al. 2003; Paterson & Lima 2010; Baranyi et al. 2015).

It has already been reported that European countries with temperate climates have a higher risk of exposure to fungal burden comprising fungi and mycotoxins (Paterson & Lima 2011). The climate of these countries will most likely become warmer reaching temperatures of 33 °C, which is very close to the optimum for aflatoxins production, among other mycotoxins (Paterson & Lima 2011).

Lately, a wide incidence prevalence of aflatoxins contamination was reported in several crops from Southern-eastern European countries and can be associated with climate change (dry conditions and increased ambient temperatures) in those countries

(Blaney et al. 2008; Tabuc et al. 2009; Levic et al. 2013; Dobolyi et al. 2013; Kos et al. 2013; Pleadin et al. 2014; Leggieri et al. 2015; Dimitrieska-Stojković et al. 2016; Janić Hajnal et al. 2017). *Aspergillus* section *Flavi*, the key fungus for aflatoxin production, is well adapted to warm and dry weather conditions (Payne 1998; Paterson & Lima 2010; Baranyi et al. 2015). Although crops from tropical and/or sub-tropical areas are affected more commonly and severely by aflatoxin contamination, this can be changed due to climate change, and temperate areas like Southern-eastern European countries could also be affected (Battilani et al. 2016). Therefore, and due to the predicted temperature increase, *Aspergillus* section *Flavi* growth and consequently aflatoxin B₁ production, will be boosted (Paterson & Lima 2010; Baranyi et al. 2015; Battilani et al. 2016). In Portugal, previous papers have already reported AFB₁ and AFM₁ in flours and dairy products, respectively (Alvito et al. 2010; Abrunhosa et al. 2016). Other aflatoxins have also been reported in wide variety of food products such as spices, honey, almonds, peanuts, hazelnuts, dry figs, pistachio nuts, raisins, pig liver and corn (Abrunhosa et al. 2016). In 2008, a published overview regarding Portuguese feed contamination (Martins et al. 2008) reported that 13% of the 513 raw materials samples analysed between the periods of 2000 to 2007 presented AFB₁ contamination. The same authors described that 28% of the 1534 feed samples collected in the same period showed AFB₁ contamination, being the most reported mycotoxin despite other mycotoxins were also measured (Martins et al. 2008).

The higher prevalence of this *Aspergillus* section already observed in different Portuguese occupational environments, such as animal production (Sabino et al. 2012), waste sorting plant (C. Viegas et al. 2014) and feed industry (C. Viegas, Faria, et al. 2016) is of note. Moreover, occupational exposure to Aflatoxin B₁ in poultry, swine and in waste treatment plants has been reported (Viegas et al. 2012; Viegas et al. 2013b;

Viegas et al. 2013a; Viegas et al. 2015). This can imply, besides an increasing problem of food safety, a growing problem in specific occupational settings due to climate change (C. Viegas, Meneses, et al. 2016).

Dietary exposure levels of Portuguese population to mycotoxins

Considering that aflatoxins are recognized as carcinogenic mycotoxins (International Agency for Research on Cancer 2002), the continuous monitoring of the population exposure is of utmost importance, permitting the identification of groups potentially more exposed and consequently more vulnerable. Due to the constraints of exposure assessment through the human biomonitoring studies and with the indirect approach where occurrence data in food is combined with consumption data (Choi et al. 2015; Heyndrickx et al. 2015; de Nijs et al. 2016; Assunção et al. 2016), the main efforts should be focused on the development of studies that gather the biomonitoring evaluation with validated biomarkers with food consumption and occurrence in food data, as recommended by EFSA (EFSA 2010).

Studies published in the last ten years (2007-2017) on the Portuguese dietary exposure to aflatoxins and their occurrence in food are presented in

Table 1 and revealed that the population is exposed through food consumption. Despite the importance of aflatoxins as carcinogenic compounds, there are not many available and reported studies in Portugal concerning the exposure of the Portuguese population. There were no reports available for the assessment of exposure to aflatoxins using human biomonitoring regarding the Portuguese population. In addition, there is a lack of data regarding the weather conditions and their effects on the frequency of aflatoxins contamination.

(Table 1)

The reports presented in

Table 1 assessed the presence of aflatoxins in a wide variety of food products (e.g. dairy products, baby foods, breakfast cereals) and confirm that the occurrence of these mycotoxins is a reality in food products marketed in Portugal (Martins et al. 2007; Alvito et al. 2010; Duarte et al. 2013; Martins et al. 2018). Alvito et al. (2010) and Martins et al. (2018) highlighted the co-occurrence of mycotoxins, including aflatoxins. Duarte et al. (2013) also reported two milk samples above the legislative limits (50 µg/L) (European Commission 2006; Duarte et al. 2013).

Cereals are raw materials that are very prone to mycotoxins contamination, including maize that was identified previously as a matrix susceptible to be contaminated in a climate change scenario (Battilani et al. 2016). Breakfast cereals analysed in Portugal included maize in their composition revealing the potential of being affected by the climate change. Interestingly, some studies reported AFM₁ in cereal-based products; it is possible to hypothesize that the origin of this contamination is the presence of small amounts of milk in the final product, indicating that feed grown locally is contaminated with AFB₁. In spite of some food products referred in Table 1 are originated from regions of the world where the climatic conditions are already optimal for fungal growth, it is expected that in the future, samples originated from Portugal could represent a higher risk with increased temperatures.

The exposure assessment estimates presented in

Table 1 referred to studies that applied the indirect approach, gathering occurrence in food and consumption data. In the performed studies, different scenarios

were considered regarding the statistical treatment of non-detects (<LOD) in accordance with the EFSA recommendations (European Food Safety Authority 2010), and deterministic and probabilistic methodologies were used. In general, these studies confirmed that the Portuguese population is exposed to aflatoxins and since there is no TDI (Tolerable Daily Intake) for aflatoxins (the ALARA principle, As Low As Reasonably Achievable, is applied as proposed by EFSA), it is not possible to evaluate the closeness to any reference value. However, when comparing to the French PDI (Probable Daily Intake) estimated by Leblanc et al. (2005), the Portuguese PDI for aflatoxins estimated by Abrunhosa et al. (2016) was about five times higher (Leblanc et al. 2005; Abrunhosa et al. 2016). Assunção et al. (2015) also characterized the risk associated with this exposure; AFB₁ revealed a margin of exposure (MoE) below 10,000 suggesting potential health concern for the high percentiles of intake (P90, P95 and P99) (European Food Safety Authority 2013, Assunção et al 2015).

These presented studies highlighted the lack of data on the occurrence of aflatoxins in foodstuffs and the consequent exposure of the Portuguese population. Our review also identified the absence of human biomonitoring studies regarding these mycotoxins and metabolites. In Portugal, and despite that the levels of occurrence of mycotoxins are low, it is expected that climate change will potentially increase its production, raising the risk of exposure, similarly to the situation of other Southern-eastern European countries. Future efforts should be put in motion for a continuous surveillance, allowing for the identification of more susceptible population groups and for the prediction of the possible effects of climate and contamination patterns changes.

Burden of disease caused by dietary exposure to aflatoxins in Portugal

Burden of disease measures the impact that a disease represents on society in terms of mortality, morbidity and disability. Several measures can be applied to estimate the

burden of disease, one of the most-used being Disability Adjusted Life Years (DALY). DALY provides a metric to compare the health impact of various diseases, injuries and risk factors, by integrating in a single measure the quantification of the burden of diseases (Murray & Lopez 2013; Murray & Lopez 2017). One DALY is equivalent to one year of healthy life lost. DALYs are calculated by adding the adjusted number of years lived with disability (YLDs) and the number of years of life lost due to premature mortality (YLLs), through $YLD = \text{Number of incident cases} \times \text{Duration until remission or death} \times \text{Disability Weight}$ and $YLL = \text{Number of deaths} \times \text{Residual life expectancy at the age of death}$ (Devleesschauwer et al. 2015).

Food contaminants, including mycotoxins, among which particularly aflatoxins, are considered a worldwide health concern (Gibb et al. 2015). Dietary aflatoxin exposure is considered a significant risk factor for hepatocellular carcinoma (HCC) or liver cancer (Wild & Gong 2010). Liver cancer is the fifth most common cancer in men and the ninth most common cancer in women and is the second most common cause of death from cancer worldwide, estimated to have been responsible for nearly 746,000 deaths in 2012 (9.1% of all cancer deaths that year) (IARC/WHO 2016). In Portugal, the last available statistics revealed 1,133 deaths due to liver cancer in 2015 (INE 2016). The prognosis for liver cancer is very poor (with an overall ratio of mortality to incidence of 0.95), so the geographical patterns in incidence and mortality are very similar (IARC/WHO 2016).

A model was developed to estimate the health impact of dietary aflatoxins exposure of the Portuguese population, estimated number of cases of HCC and DALYs attributed to aflatoxins exposure (Table 2). The details of the model are described in the supplemental material.

(Table 2)

Because different levels of aflatoxin intake could characterize the dietary exposure of the Portuguese population (i.e. the national exposure levels reported by Abrunhosa et al. (2016) and the European levels suggested by EFSA (2007)), the corresponding number of annual extra cases of HCC ranged from 0.52 and 2.00 was estimated (Table 2). Similarly, DALYs were derived for the same levels of aflatoxins exposure and for the Portuguese population an annual DALY could range between 8.0 and 30.9 (Table 2). Depending on the level of exposure, a range between 0.08 and 0.30 DALY/100,000 could be due to Portuguese dietary exposure to aflatoxins (Table 2). Little previous work has estimated the burden of disease associated to aflatoxin exposure using DALYs and none was previously reported in Portugal. Liu and Wu (2010) determined the global burden of HCC attributable to aflatoxin exposure. The authors reported that of the 550,000–600,000 new cases worldwide each year, about 25,200–155,000 may be attributable to aflatoxin exposure, and the most cases occur in sub-Saharan Africa, Southeast Asia and China. This study did not derive the associated DALYs. More recently, a WHO report by the Foodborne Disease Burden Epidemiology Reference Group (FERG) estimated the global burden of foodborne diseases using DALYs, including for aflatoxins exposure (World Health Organization 2015). In their report, FERG estimated a global number of foodborne illnesses, deaths and DALYs for aflatoxins of: 21,757; 19,455; and 636,869, respectively (WHO 2015; Havelaar et al. 2015). This study also estimated the burden of disease for each of 14 subregions, including Portugal in the group named EUR A (with other countries from Europe, such as Spain, France, Greece and Italy). The study reported a median rate of 0.3 DALYs/100,000 population for the EUR A subregion. This is similar to our estimates of a maximum of 0.3 DALYs/100,000. Our model has several limitations, mainly due to uncertainties in the data used (e.g. aflatoxins exposure levels). Our estimates are

probably conservative, i.e., underestimates rather than overestimates. For example, simultaneous health outcomes that could co-occur and consequently affect the associated DALYs or other than cancer outcome as a consequence of aflatoxins exposure, were not taken into account. Despite the data gaps and limitations, this study presents the first estimates of the burden of disease of Portuguese dietary aflatoxins exposure and should serve as an important starting point to evaluate the health impact of this type of exposure and also to infer about potential consequences of some factors that could interfere with Portuguese dietary exposure to aflatoxins, as climate change.

Climate change and the associated health risk of Portuguese dietary aflatoxins exposure

In terms of food safety, and by means of climate prediction models and scenario studies, scientists attempt to predict the consequence of the observed changes in order to advise policy-makers of the best strategy to circumvent the anticipated problems (Miraglia et al. 2009). In addition to the impact on the agriculture, food safety consequences namely the impact on the livestock production, the occurrence of certain microalgae in seas and oceans and consequently their phycotoxins, the occurrence of residues of pesticides, persistent contaminants and pathogenic microorganisms, and the production of mycotoxins by moulds growing on crops have aroused the interest of worldwide scientific community (Miraglia et al. 2009). Paterson and Lima (2011) in their review concerning the further mycotoxin effects from climate change referred increased levels of aflatoxin, ochratoxin A from *Aspergillus* spp., and fumonisins in sub Mediterranean countries (e.g. North Portugal) as the temperature increases. In Southern and South-Eastern Europe (i.e. Portugal, Spain, Southern France, Italy, Slovenia, Greece, Malta, Cyprus, Bulgaria, and Southern Romania) as a consequence of temperature increase (in

the order of 4 – 5 °C) and reduced water availability in summer, some effects are expected, namely a decrease in the agricultural yields (in the range of 10–30% in many regions), drought, heat waves, degradation of soil and ecosystems, and desertification (Paterson & Lima 2011). Directly or indirectly, it is expected that these factors could interfere with fungi growth and mycotoxins production. In Europe, a pioneer research project has addressed quantitatively the potential impact on aflatoxin contamination of cereal grains (Van der Fels-Klerx et al. 2016). MODMAP-AFLA, a research project addressing a model approach to predict the future aflatoxin contamination of maize produced in Europe, considered three different climate scenarios (the present, +2 °C and +5 °C) (Battilani et al. 2012). MODMAP-AFLA revealed an estimated increase of aflatoxin contamination of maize, mainly in the +2 °C scenario, with an increase of AFB₁ contamination in the southern European countries. More recently, Battilani et al. (2016) studied the estimated aflatoxin contamination in maize and wheat crops, within the next 100 years, under +2 °C and +5 °C climate change scenarios. The authors reported that AFB₁ is predicted to become a food safety issue in maize in Europe, especially in the +2 °C scenario, which is the most probable scenario of climate change for the next years. Based on the results obtained by these authors, the most concerned areas with an increase of aflatoxin contamination were: Eastern Europe, Balkan Peninsula and the Mediterranean regions including Portugal. Based on their results, Battilani et al. (2016) also referred that aflatoxin contamination above the legal limit are expected to become more frequent in the future. The potential ways that the health of the Portuguese population could be affected should be taken into account. As estimated by MODMAP-AFLA, climate change will affect Southern Europe, including Portugal. Aflatoxins could represent a significant issue in the future (Battilani et al. 2016). Considering the results on the aflatoxins estimated exposure levels in Portugal (

Table 1) and the consequent disease burden in terms of DALYs derived (Table 2), it is expected that in the future the number of DALYs and the associated HCC due to aflatoxins exposure should increase. A quantification of the health impact of this exposure is crucial to better raise awareness among policy makers for the need to establish preventive measures that could protect populations. Predictions concerning the risks to society connected to weather-driven hazards were recently reported. Forzieri et al. (2017) estimated that about 350 million Europeans could be exposed to harmful climate extremes on an annual basis by the end of this century, with a 50-times increase in fatalities compared with now, unless global warming is curbed as a matter of urgency and appropriate adaptation measures are taken. The same authors considered climate change as the dominant driver for the projected trends, accounting for more than 90% of the rise in the risk to human beings and they justified this considering that Europe is expected to face major changes in the frequency of multiple climate extremes during the coming decades and will be exposed to a progressive and strong increase in overall weather-related hazards (Forzieri et al. 2017). In this context, it is of utmost importance to refer that although possible and plausible scenarios, all these estimates and results should be interpreted with caution and as predictions based on modelling approaches.

Considering all the scenarios and predictions, it is possible that we are ready to predict and estimate the potential risks and health impact of human exposure to aflatoxins in a climate change perspective. In Portugal there is knowledge and mechanisms to characterize the potential impact of climate change on human exposure to aflatoxins, namely there are analytical methodologies to determine toxins in different food products, to assess the human exposure and to derive the potential health risks.

However, other aspects should be addressed in the future, namely, i) the inclusion of

mycotoxins other than aflatoxins in the predictive models, producing outputs that could be used in the risk assessment of different health outcomes; ii) the development of tools that anticipate the contamination levels of food products, since the present models just estimate the risk of crop contamination by some mycotoxins; iii) the consideration of other mycotoxin-cereal grains combinations, that could reflect the combinations mostly occurring in some countries, as for example in Portugal. Another important perspective is the need for political commitment. At global and national level, policy-makers should recognize, understand and prepare actions that reduce the impact of climate change, including those effects highlighted through this article. Actions that contribute to i) prevent mycotoxin levels that could represent risk for consumers, ii) survey and monitor the exposure levels of population (e.g. through biomonitoring), and iii) support research studies that could contribute to characterize the associated risks, develop new approaches for dealing with them and prevent some of the potential outcomes, are critical and urgent in a global and national levels, considering climate change and its health impact as an eminent, unequivocal and real risk.

Conclusion

An integrated approach is advisable to adequately tackle the food safety risks associated with climate change, including perspectives from different disciplines such as natural and social sciences. In addition, and due to the high impact driver of this topic, politicians and decision-makers should be involved and committed to implement effective measures to reduce the possible consequences and to protect lives. This review article should represent an alert of the potential consequences of one incompletely-explored perspective of climate change: the health impact of human exposure to aflatoxins. The work should aid in prioritisation of strategies to face the unequal burden of effects of weather-related hazards in Portugal and across Europe.

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Table 1. Dietary exposure assessment of Portuguese population to aflatoxins and their occurrence in food products. The presented studies were published between 2007 and 2017.

Table 2. Disease burden estimates for hepatocellular carcinoma (HCC) considering estimated Portuguese dietary exposure to aflatoxins.

Table 3. Dietary exposure assessment of Portuguese population to aflatoxins and their occurrence in food products. The presented studies were published between 2007 and 2017.

Reference	Mycotoxin	Food product	Occurrence in food data				Exposure data	
			LOD ($\mu\text{g}/\text{Kg}$; $\mu\text{g}/\text{L}$)	Positive Samples	Mean Concentration ($\mu\text{g}/\text{Kg}$; $\mu\text{g}/\text{L}$)	Range of Concentration ($\mu\text{g}/\text{Kg}$; $\mu\text{g}/\text{L}$)	Population group	Exposure assessment - PDI (ng/Kg bw/day)
Martins et al. (2007)	AFM ₁	Cheese ^{1,2}	0.005	3/48 (6.3%)	0.010	NK	-	-
EFSA (2007)	Sum of AFB ₁ , AFB ₂ , AFG ₁ , AFG ₂	hazelnuts, almonds, pistachios, other nuts, maize, oilseeds, dried fruits, spices ¹	-	-	-	-	Adults, children, vegetarians	0.838 - 1.934 ⁴
Alvito et al. (2010)	AFM ₁	Infant cereals ^{1,2}	0.004	4/19 (21.0%)	NR	\geq LOD – 0.018	-	-
	AFB ₁	Infant formulae ^{1,2}	0.001	6/7 (85.7%)	NR	< LOD – 0.041	-	-
Duarte et al. (2013)	AFM ₁	Milk ^{1,2}	0.005	11/40 (27.5%)	23.4	< LOD – 0.069	Adults	0.080
	AFB ₁	Breakfast cereals ^{1,2}	-	-	-	-	Children	0.012
AFB ₂	-		-	-	-	1-3 years	0.003	
AFG ₁	-		-	-	-	-	0.005	
Abrunhosa et al. (2016)	Sum of AFB ₁ , AFB ₂ , AFG ₁ , AFG ₂	Pistachio, peanuts, dry figs, spices, almonds, pig liver, other nuts ¹	-	-	-	-	Adults	0.501
	AFM ₁	Milk, powdered milk, yoghurt, cheese ^{1,2}	-	-	-	-	-	0.073
Martins et al. (2018)	AFB ₁	Breakfast cereals ^{1,2}	0.005	18/26 (69%)	0.013	< LOD – 0.130	-	-
	AFB ₂		0.001	7/26 (27%)	0.004	< LOD – 0.011	-	-
	AFG ₁		0.006	1/26 (4%)	0.013	< LOD – 0.013	-	-
	AFG ₂		0.010	0/26 (0%)	NA	NA	-	-
	AFM ₁		0.011	3/26 (12%)	0.013	< LOD – 0.024	-	-

AFB₁ – aflatoxin B₁; AFB₂ – aflatoxin B₂; AFG₁ – aflatoxin G₁; AFG₂ – aflatoxin G₂; AFM₁ – aflatoxin M₁; ¹ Imported foods; ² Food samples produced in Portugal.

Table 4. Disease burden estimates for hepatocellular carcinoma (HCC) considering Portuguese estimated dietary exposure to aflatoxins.

Aflatoxin exposure (reference)	Aflatoxin dietary exposure level (ng kg bw⁻¹ day⁻¹)	Annual Extra case of HCC	Annual Extra case of HCC per 100,000	Annual DALY	Annual DALY per 100,000
Europe lower bound (EFSA 2007)	0.838	0.87	0.008	13.4	0.13
Europe upper bound (EFSA 2007)	1.934	2.00	0.019	30.9	0.30
Portugal (Abrunhosa et al. 2016)	0.501	0.52	0.005	8.0	0.08

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Supplemental material

Estimated Health impact considering aflatoxin exposure and aflatoxin-related hepatocellular carcinoma

A population attributable fraction (PAF) approach was used to estimate the number of cases of aflatoxin-related hepatocellular carcinoma (HCC), following the procedure described by (World Health Organization 2015). Within this context, PAF signifies the contribution of a risk factor to a disease or a death. For the present calculations, HCC was selected as a clinical outcome of the aflatoxin exposure. The excess risk due to aflatoxin exposure was estimated multiplying an aflatoxin cancer potency factor [according to (Liu & Wu 2010)] by the considered estimated levels of Portuguese aflatoxin exposure (according to Table 1).

The burden disease associated to aflatoxin exposure was estimated using Disability-Adjusted Life Years (DALY). DALY summarize the occurrence and impact of morbidity and mortality in a single measure and quantifies the healthy life years lost due to a disease or injury (Devleesschauwer et al. 2015). DALY were calculated by adding the adjusted number of years lived with disability (YLDs) and the number of years of life lost due to premature mortality (YLLs) (Devleesschauwer et al. 2015), calculated by:

$$DALY = (t_f \times dw_f \times p_f) + (t_{nf} \times dw_{nf} \times p_{nf}) + (YLL \times p_f)$$

where t_f is the duration of disease of fatal cancer in years, dw_f is the disability weight of fatal cancer, p_f is the probability of a cancer being fatal, t_{nf} is the duration of disease of non-fatal cancer in years, dw_{nf} is the disability weight non-fatal cancer, p_{nf} is the probability of a cancer being non-fatal and YLL is the life years lost due to premature death to a fatal cancer (Jakobsen et al. 2016). YLD_f and YLD_{nf} were obtained through the first and second terms of the previous equation, respectively. National statistical

data (obtained at Statistics Portugal, <https://www.ine.pt/>), HCC cancer data and WHO disability weights (dw) were used to perform these calculations, according to Table S1.

Table S5. Parameters used to calculate Disability-Adjusted Life Years (DALYs)

through the summation of adjusted number of years lived with disability (YLDs) and the number of years of life lost due to premature mortality (YLLs).

Parameter	Values	Reference
Life expectancy at birth (in years)	80.62	(INE 2016)
Age of onset of HCC – Portuguese data (in years)	63.7	(Silva 2015)
Duration of disease of fatal cancer, t_f (in years)	0.5	(Mathers et al. 1999)
Disability weight of fatal cancer, dw_f	0.508	(World Health Organization 2015)
Probability of a cancer being fatal, p_f	0.92	(Mathers et al. 1999)
Duration of disease of non-fatal cancer, t_{nf} (in years)	5	(Mathers et al. 1999)
Disability weight of non-fatal cancer, dw_{nf}	0.294	(World Health Organization 2015)
Probability of a cancer being non-fatal, p_{nf}	0.08	(Mathers et al. 1999)

HCC = hepatocellular carcinoma

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