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ORIGINAL PAPER

Assessing the Mycotoxin-related Health Impact of Shifting from Meat-based Diets to Soy-based Meat Analogues in a Model Scenario Based on Italian Consumption Data

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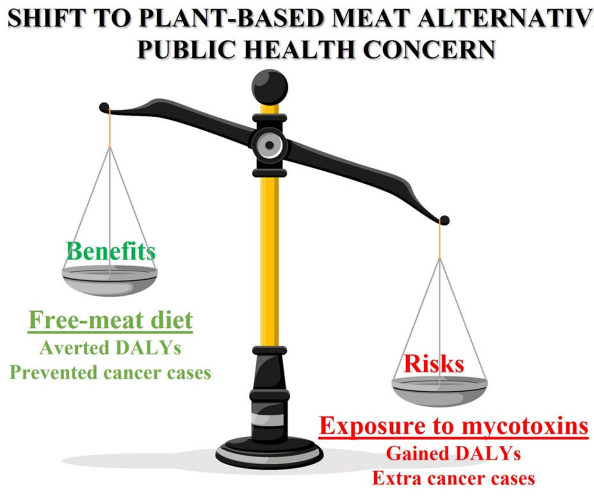
Abstract

The aim of this study was to assess the risk of replacing meat with plant-based analogues with respect to mycotoxin exposure, as a proof of concept to demonstrate the need for a proper regulatory framework for mycotoxins in meat imitates. Hence, we considered a full replacement of meat consumption with soy-based meat analogues and we evaluated the exposure to AFB_1 and OTA, based on the Italian National Food Consumption Survey INRAN-SCAI 2005–2006 and the European Food Safety Authority occurrence data. The overall health impact from soy-based food consumption and a meat-free diet was quantified in terms of Disability-Adjusted Life Years (DALYs) in three different contamination and consumption scenarios. The substitution of meat products with soy-based imitates would prevent up to 406.2 colorectal cancer cases/year/country associated with 532 healthy years of life. However, we also determined an increased risk of liver cancer and loss of healthy life-years due to AFB_1 exposure and a potential risk of renal cancer as due to an increased intake of OTA, leading up to 1208 extra cancer cases associated with the loss of 12,080 healthy life-years/country. Shifting to a plant-based diet actually eliminates a cancer risk factor such as processed meat, however, higher and unexpected risks could arise if mycotoxins are not properly regulated in plant-based meat alternatives. Taking into account the ubiquitous occurrence of mycotoxins, also in the light of climate change, and the growing trend toward plant-based meat analogues, greater importance should be given to actual food consumption trends and correlated with updated natural toxins regulations and risk assessments.

Graphical abstract



Keywords Risk assessment · Plant-based meat alternative · Risk of cancer · Mycotoxin · Soybean · DALY

Extended author information available on the last page of the article

Introduction

Over the past few years reducing the consumption of animal-based foods has been considered a key element for healthy and sustainable diets (Springmann et al. 2018; McMichael et al. 2007; Willett et al. 2019). For this reason, plant-based alternatives, such as dairy and meat substitutes have been developed and are continuously expanding in the food market (Boukid 2021; Curtain and Grafenauer, 2019). The European market of plant-based meat alternatives (PBMA) was valued at €4.4 billion in 2019 and is expected to grow by 70% in the next 6 years up to €7.5 billion by 2025 (Geijer and Gammoudy 2020). A recent survey showed that 42% of European consumers purchase plant-based sausages, burgers, and mince at least once per month and 24% at least once per week (Gebhardt et al. 2020). PBMA, also known as meat analogues are usually produced with wheat gluten, or legumes such as chickpea, pea, or soybeans (Boukid 2021; Kumar et al. 2017). Among them, soy proteins are of high interest for meat analogues especially because of their high protein quality (Kumar et al. 2017), although the content of certain essential amino acids like L-methionine is lower compared to animal proteins (Friedman and Brandon 2001).

Although the urgency to decrease meat consumption has been largely debated in the literature discussing the impact in terms of sustainability and health (Ekmekcioglu et al. 2018; Stanton et al. 2022; Willett et al. 2019), little to nothing has been done so far to assess the risk related to an extensive consumption of plant-based meat analogues (Kołodziejczak et al., 2022; Mayer et al. 2022).

As a matter of fact, it must be noticed that shifting toward meat imitates can lead to a substantial change of exposure to certain food contaminants compared to an omnivore diet, as reported by several authors (LeBlanc et al. 2005; Penczynski et al. 2022). In particular, Penczynski et al. (2022) pointed out a significantly higher exposure to OTA in vegans compared to omnivores based on human biomonitoring (both in urine and blood). Starting from the dietary recall data, the authors discussed the potential association of this increased exposure to the higher consumption of bean-based food in the vegan population.

As recently reviewed (Mihalache et al. 2022), mycotoxins such as aflatoxin B1 and ochratoxin A may occur in soy and legumes at significant concentrations and without a regulatory ceiling (EFSA 2020a, 2020b).

The most common health metric used for quantifying the health impact of contaminants is the Disability-Adjusted Life Year (DALY), where one DALY is equal to 1 year of healthy life lost (Membré et al. 2021). This metric is also used by the World Health Organization (WHO) for the estimates of the global burden of diseases (Hay et al., 2017) and of foodborne diseases (Devleesschauwer et al. 2015).

The lack of proper consideration of an increased consumption in current risk assessment may indeed expose the vegetarian and vegan population to a higher risk of exposure to these contaminants compared to the omnivores, mainly considering that consumption collection in use for risk assessment is often more than a decade old and therefore does not reflect the current consumption pattern.

This study, therefore, aims to be a proof of concept to demonstrate the need of a proper regulatory framework for mycotoxins in meat imitates. For this purpose, a full replacement of meat consumption with soy-based products was considered, using consumption data retrieved from the Italian National Food Consumption Survey INRAN-SCAI 2005–2006, which is the latest Italian consumption report currently available. Soy was selected among other plant-based proteins based on the availability of evidence-based data (i.e., low numbers of samples provided for other legumes such as peas and chickpeas with 100% left-censored data) (EFSA 2020a, 2020b). However, the consumption and contamination data from this study are retrieved from official EFSA reports and may therefore well represent the current occurrence pattern (EFSA 2020a, 2020b). Uncertainties and knowledge gaps are therefore discussed in a proper section.

Overall, to our best knowledge, this is the first attempt to evaluate under a risk assessment (RA) approach the potential health concern deriving from an increased mycotoxin exposure in alternative diets.

Materials and Methods

To assess the health impact in an extreme scenario with a full replacement of meat with soy-based meat analogues we first collected contamination data of aflatoxin B1 (AFB_1) and ochratoxin A (OTA) in soy from the most recent EFSA reports (EFSA 2020a, 2020b) and consumption data for meat from the latest Italian National Food Consumption Survey INRAN-SCAI 2005–06. After identifying the most relevant adverse health effects of AFB_1 and OTA, we assessed Italian consumers' dietary exposure in the full substitution scenario and performed a risk characterization. Afterward, the number of extra liver cancer cases due to exposure to AFB_1 were calculated based on data from literature, consumption scenarios, and contamination scenarios. The burden of disease was quantified in gained DALYs/year/country. In order to provide a more comprehensive overview of the health impact of fully replacing meat with soy-based meat analogues, we also took into consideration the burden of disease associated with the consumption of processed meat. Processed meat is classified by the International Agency for Research on

Cancer (IARC) as a Group 1, carcinogenic agent to humans, while red meat is in Group 2A, probably carcinogenic for humans, based on their associations with colorectal cancer (CRC) (IARC 2019). Hence, for the estimation of prevented CRC cases and associated DALYs, only data for processed meat was used.

Identification of the Most Relevant Adverse Health Effects

Recent reports from EFSA with results from several European countries found that soy was contaminated with mycotoxins such as aflatoxins and OTA (EFSA 2020a, 2020b). IARC classified AFB_1 as a group I carcinogen and established the following order for the toxicity of the aflatoxins: $AFB_1 > AFG_1 > AFB_2 > AFG_2$ (IARC 2019). High exposure to AFB_1 can cause acute aflatoxicosis which has a high mortality rate and high risk of liver cancer while low chronic exposure is associated with cirrhosis and liver dysfunction (EFSA 2020a). The global cancer statistics show that the main risk factors of hepatocellular carcinoma (HCC) are chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), and ingestion of food contaminated with aflatoxins (Bray et al. 2018). Besides liver cancer, AFB_1 exposure is known to cause other adverse health effects like stunting (Rasheed et al. 2021) and immune suppression (Turner et al. 2007). However, we estimated the burden related to liver cancer as this outcome is the only endpoint that has a reliable etiology mechanism (WHO 2020).

OTA is a genotoxic, nephrotoxic, neurotoxic, and hepatotoxic mycotoxin (EFSA 2020b) and has been classified by the IARC in the group 2B as a possibly carcinogenic agent to humans (IARC 2019). OTA is absorbed fast in the body but is poorly metabolized and eliminated slowly, which leads to accumulation in the body (EFSA 2020b). In vitro studies show that exposure to OTA induces gene mutations and chromosome damage in mammalian cells, while in vivo research indicates genetic damage and gene mutations in rats and mice with the cancer target site being the kidney (EFSA 2020b). The genotoxicity of OTA manifests through microscopic kidney lesions in female pigs and kidney tumors in male rats (EFSA 2020b).

Hence, the main risk that can come with soy consumption considered for this study is the risk of liver cancer due to aflatoxins. For OTA, risk characterization was based on the Margin of Exposure (MOE) approach regarding renal cancer.

Soy/Soy-Based Food Consumption

The consumption data was retrieved from the Italian National Food Consumption Survey INRAN-SCAI 2005–06. Soy-based food was not among the questionnaire's items, hence we simulated that each meat item would be made with soy, as many meat analogues are nowadays, and used the consumption data from those items. The cross-sectional survey was conducted between October 2005 and December 2006 using consecutive 3-day food records. The number of respondents was 3323 out of which 1822 were females and 1501 males. The age varied between 0.1 months and 97.7 years and were grouped according to EFSA Comprehensive European Food Consumption Database in Exposure Assessment (EFSA 2011) like this: infants ($N=16$; up to and including 11 months old); toddlers ($N=36$; 12–35 months old); other children ($N=193$; 3–9 years old); adolescents ($N=247$; 10–17 years old); adults ($N=2313$; 18–64 years old); elderly ($N=290$; 65–74 years old); very elderly ($N=228$; 75 > years old).

Consumption Scenarios

The FoodEx2 hierarchical system for classifying and describing food was used for collecting the consumption data. FoodEx2 contains descriptions of a large number of food items aggregated into boarder food groups and different levels of food categories (EFSA 2011). The level of each food item from this study is presented in Supplementary file S1. Consumption data are from the INRAN-SCAI survey conducted in 2005–06, where plant- and soy-protein based products were not included. Therefore, a full replacement of meat consumption to simulate vegetarian and vegan diets was preferred over a partial replacement. The foods that were simulated to be replaced with meat analogues included mammals meat, poultry meat, processed whole meats, and sausages. The processed whole meats include raw and cooked cured/seasoned pork/bovine/poultry meat (i.e., pork ham, beef ham, and pancetta) and the sausages include fresh sausages (i.e., Italian-style sausage, fresh spiced sausages in casing, and fresh bratwurst) and preserved/partially preserved sausages (i.e., cured unripened/ripened sausages and cooked sausages). For processed meats consumption the category "total processed meats" (i.e., pork ham and preserved sausages) was taken into consideration. The intake of each food per consumer category can be seen in Supplementary file S1.

It must be noticed that data consumption from the INRAN-SCAI survey indicated a maximum meat consumption of 70 g/day, while the current FAO data reported a consumption of meat of 82 kg/capita/year in Italy (FAO 2018) which is 224 g/day. This discrepancy can be explained based on the changes in lifestyle over the past two decades. Besides the baseline (BS) scenario based on the consumption frequency from the INRAN-SCAI survey, two alternative scenarios (AS) were considered to reflect an increased consumption of meat, which was then fully replaced by soy-based meat imitates. Thus, the AS consisted of:

- AS_1 considering an increased consumption of meat alternatives with soy of 50%,
- AS_2 considering an increased consumption of meat alternatives with soy of 100%,

Problem Formulation and EFSA Exposure Scenarios

The purpose of this assessment was to model the potential chronic dietary exposure to AFB_1 and OTA and the potential health impact in the Italian population in the case of a full substitution of meat with soy-based meat analogues.

The exposure scenarios were based on data summarized in EFSA reports (EFSA 2020a, 2020b). Three types of scenarios were considered using contamination data from EFSA (EFSA 2020a, 2020b): (i) the optimistic scenario (OS) where the contamination values used were for the mean Lower Bound (LB) ($AFB_1 = 170$ ng/kg; OTA = 950 ng/kg), (ii) the pessimistic scenario (PS) (conservative) where the contamination values used were for the mean Upper Bound (UB) ($AFB_1 = 780$ ng/kg; OTA = 2260 ng/kg), and (iii) the worst-case scenario (WCS) where the contamination values used were for the 95th percentile (P95) UB ($AFB_1 = 1300$ ng/kg; OTA = 5300 ng/kg). For each scenario, the mean and P95 of the chronic dietary exposure were estimated using the Dietary Exposure (DietEx) tool from EFSA while the risk characterization was performed using the Rapid Assessment of Contaminant Exposure (RACE) tool from EFSA.

Exposure Assessment and Risk Characterization

The estimated daily intake (EDI) of AFB_1 and OTA was calculated according to Eq. (1):

$$\text{EDI }(\mu\text{g/kg bw/day}) = \frac{\text{Cmycotoxin } \times \text{ CONsoy}}{bw} \qquad (1)$$

where Cmycotoxin = the concentration of the mycotoxins found in soy (μg/kg), CONsoy = soy consumption in g/day, and bw = bodyweight.

For substances that are both genotoxic and carcinogenic EFSA stated that no level of exposure is considered safe and no health-based guidance values (HBGV) are appropriate (EFSA 2012). Instead, the MOE approach is recommended. The MOE is the ratio of the benchmark dose lower confidence limit ($BMDL_{10}$) and the consumers' exposure to the contaminant as shown in Eq. (2):

$$MOE = \frac{BMDL10}{EDI} \qquad (2)$$

The values of $BMDL_{10}$ were 0.4 μg/kg bw/day for AFB_1 for the incidence of hepatocellular carcinoma in rats (EFSA 2020a) and 14.5 μg/kg bw/day for OTA considering its neoplastic effects (EFSA 2020b). The magnitude of the MOE is related to the risk level and EFSA concluded that an MOE of 10,000 or higher is of low concern, while an MOE lower than 10,000 raises a health concern from a public health point of view (EFSA 2012).

For the cumulative risk assessment of AFB_1 and OTA, we used the total margin of exposure (MOE_T). The MOE_T was calculated as the sum of the MOEs (Eq. (3)) and it was considered to indicate risk if it was lower than 10,000.

$$MOE_T = 1/\left(1/MOE_{AFB1} + 1/MOE_{OTA}\right) \qquad (3)$$

Estimation of the Relative Risk of Colorectal Cancer from Processed Meat Intake, Hepatocellular Carcinoma (HCC) from AFB_1 Exposure, and the Potential Impact Fraction in Dietary Change

The relative risk (RR) describes the probability of an outcome in an exposed population group compared with an unexposed population group. In our study, the RR was based on amount of food ingestion (processed meats for the RR of CRC) or exposure to contaminants (AFB_1).

For the RR of CRC due to processed meat consumption we used data from a recent study conducted by the Cancer Epidemiology Unit from Oxford, UK on 474,996 men and women (Knuppel et al 2020). The results indicate a RR of 1.18 for consumers who eat 20 g/day of processed meat.

The research regarding the carcinogenicity of aflatoxins shows that there is sufficient evidence for AFB_1, AFG_1, and AFM_1 for induced liver tumors (IARC 2019). Ming et al. (2002) determined a RR of 3.5 when the level of AFM_1 in participants with HCC was > 3.6 ng/l. Hence, we used these data as a starting point to model the RR depending on the processed meat intake and exposure to AFB_1 and report it as a decreased/increased risk of CRC and HCC following Eqs. (4) and (5):

$$\beta = \frac{\ln RRliterature}{Dose} \qquad (4)$$

$$RRi = \exp\left(\beta \times \text{exposure}_i\right) \qquad (5)$$

where RRliterature is the RR from the literature for a specific dose reported in the literature and RRi and exposure_i are the RR and exposure to mycotoxins/intake of processed meat for the baseline and alternative scenarios.

The potential impact fraction (PIF) is a measure used to calculate the proportional change in a disease incidence, prevalence, burden, or mortality (Barendregt and Veerman 2010).

For the number of prevented CRC cases due to elimination of processed meats from the diet the PIF formula was the following (Eq. 6):

$$\mathrm{PIF} = \frac{\left(P - P'\right)(RR - 1)}{P(RR - 1) + 1} \tag{6}$$

where P is the prevalence of the risk factor (consumption of processed meat) which we retrieved from the Global Burden of Disease (GBD) database (0.00031), P' is the counterfactual, and RR is the relative risk of CRC.

We calculated the prevented CRC cases and averted DALYs by multiplying the PIF with the incidence of CRC/capita associated with processed meat consumption using data from GBD 2006 in order to align the CRC data with our consumption survey data (GBD 2019).

At the same time, the PIF was analyzed to investigate the impact of each scenario on the risk of HCC due to the change in soy/soy-based food consumption. The PIFs were compared between the baseline scenario and all of the alternative scenarios. The estimated change in the health outcome due to exposure to AFB_1 was calculated as shown in Eq. (7):

$$PIF = \frac{RR\,alternative\,scenario - RR\,base\,scenario}{RR\,base\,scenario} \tag{7}$$

where RRbase scenario is the relative risk of HCC (due to exposure to AFB_1) in the current consumption data from the INRAN-SCAI survey and RRalternative scenario is the relative risk of HCC calculated in the alternative scenarios with increased soy-based food consumption.

Estimation of Population Risk for AFB_1-Induced Liver Cancer

The risk of hepatocellular carcinoma (HCC) for Italian consumers due to ingestion of soy-based food contaminated with AFB_1 was calculated per 100,000 individuals with the following Eq. (8):

$$\begin{aligned}&\text{Population risk (per 100,000 individuals)} = \\ &\text{EDI} \times \text{Average HCC potency}\end{aligned} \tag{8}$$

The average HCC potency for AFB_1 was adopted from the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (WHO 2017). JECFA established an HCC potency of 0.3 cancer cases per 100,000 persons/year/ng AFB_1/kg bw/day for HBV-positive individuals and a potency of 0.01 cancer cases per 100,000 persons/year/ng AFB_1/kg bw/day for HBV negative individuals. For the calculation of the average HCC potency for Italian consumers, we used data from the GBD (GBD 2019) and found that the prevalence of the burden for HBV^+ individuals is 0.76%, meaning that 99.24% are HBV^- individuals. Hence, the average HCC potency was calculated as shown below:

$$\begin{aligned}&\text{Average HCC potency} = \left(\text{HBV}^{+}\text{prevalence} \times\right. \\ &\text{HCC potency}) + (\text{HBV}^{-} \times \text{HCC potency})\end{aligned} \tag{9}$$

Estimating Health Burden by Calculating DALY

The DALY is the sum of years of healthy life lost due to premature mortality (YLL) and years of healthy life lost due to disability (YLD).

The DALYs due to AFB_1-induced liver cancer in Italy based on contaminated soy food consumption were calculated by multiplying the mean annual incidence of AFB_1-induced liver cancer with the DALY/one case of AFB_1 liver cancer cases. Based on the data from GBD (2019) we calculated the DALY/case related to liver cancer causes. The prevalence of all causes of liver cancer in Italy in 2019 was 12,643 and the DALY 131,542. By dividing the former by the latter, we obtained the DALYs per capita (10). The prevalence of CRC in Italy due to intake of processed meats was 18,419 associated with 24,129 DALYs. By following the same steps mentioned previously we obtained the DALYs per capita due to CRC caused by intake of processed meat (1.31).

The overall health impact that comes with the dietary pattern change in each AS was calculated as the DALY difference between AS and BS as shown in Eq. (10):

$$\Delta \mathrm{DALY}_{AS} = \mathrm{DALY}_{AS} - \mathrm{DALY}_{BS} \tag{10}$$

When $\Delta\mathrm{DALY} > 0$ = health loss and when $\Delta\mathrm{DALY} < 0$ = health gain due to the dietary pattern change.

Statistical Analysis

The data from this study were analyzed using Microsoft Excel 19 (Microsoft, Redmond, Washington) and SPSS Statistics 26 (IBM Software Group, Chicago, IL). Dietary Exposure (DietEx) and the Rapid Assessment of Contaminant Exposure (RACE) tools were used for the estimation of dietary exposure and risk characterization (https://www.efsa.europa.eu/en/science/tools-and-resources).

The MOEs and PIFs were displayed as scatter plots while the number of extra/prevented HCC cases/CRC cases and gained/averted DALYs were depicted through bar charts using Tableau Software 2020.1 (Salesforce, Seattle, WA).

Results

Data from the European Commission show that Italy is the main soya beans producer in the EU with 1,001,200 tonnes being produced annually. The consumption of meat and dairy alternatives increased by 84% in the last 5 years (EC 2020) and the plant-based food industry grew by 49% in the last 2 years (EC 2021). All of these data support the on-growing demand and consumption of meat alternatives and led to the authors' decision to use the INRAN-SCAI 2005–06 report as a reference for consumption data.

Exposure Assessment and Risk Characterization for the Baseline Scenario (BS), Alternative Scenario 1 (AS1), and Alternative Scenario 2 (AS2)

The mean estimated daily intake (EDI) of AFB_1 ranged from 0.05 ng/kg bw/day to 6.50 ng/kg bw/day, while the mean EDI for OTA was between 0.29 and 26.5 ng/kg bw/day. For high consumers, the P95 EDI ranged from 0.12 to 7.03 AFB_1 ng/kg bw/day and from 0.66 up to 28.67 OTA ng/kg bw/day. Figure 1 shows the MOEs for the optimistic, pessimistic, and worst-case scenarios. To see the EDI and MOE estimated in all the scenarios and for each consumer group check Supplementary file S1.

The mean MOEs for AFB_1 ranged from 61.54 to 7716, while the mean MOES for OTA ranged from 547.17 to 50,056. The P95 AFB_1 MOEs ranged from 65.47 to 3038 while for OTA the P95 MOEs were between 582.12 and 21,887. Most of the MOEs for OTA in the optimistic and pessimistic scenarios are > 10,000. However, AFB_1 MOEs in all the scenarios and OTA MOEs for the worst-case scenario were < 10,000. This is of high concern as EFSA stated that MOEs < 10,000 may pose a threat to consumers' health, in this case related to liver and renal cancer.

If AFB_1 and OTA were to co-occur for the cumulative risk assessment we would use the total margin of exposure (MOE_T). In this case, the mean MOE_T would be between 55.32 and 6685 and the P95 MOE_T between 51.95 and 2929, indicating once again the potential risk consumers expose themselves to by the consumption of soy-based food.

In AS1 and AS2 the mean EDI of AFB_1 was between 0.08 and 13 ng/kg bw/day, while for OTA it was between 0.29 and 53 ng/kg bw/day. The P95 AFB_1 values ranged from 0.18 to 14.06 ng/kg bw/day, and for OTA from 0.66 to 57.34 ng/kg bw/day. Figure 2 displays the mean and P95 MOEs values in the alternative scenarios (AS1 and AS2) for AFB_1 and OTA exposure based on three contamination scenarios: optimistic scenario (OS), pessimistic scenario (PS), and worst-case scenarios (WCS).

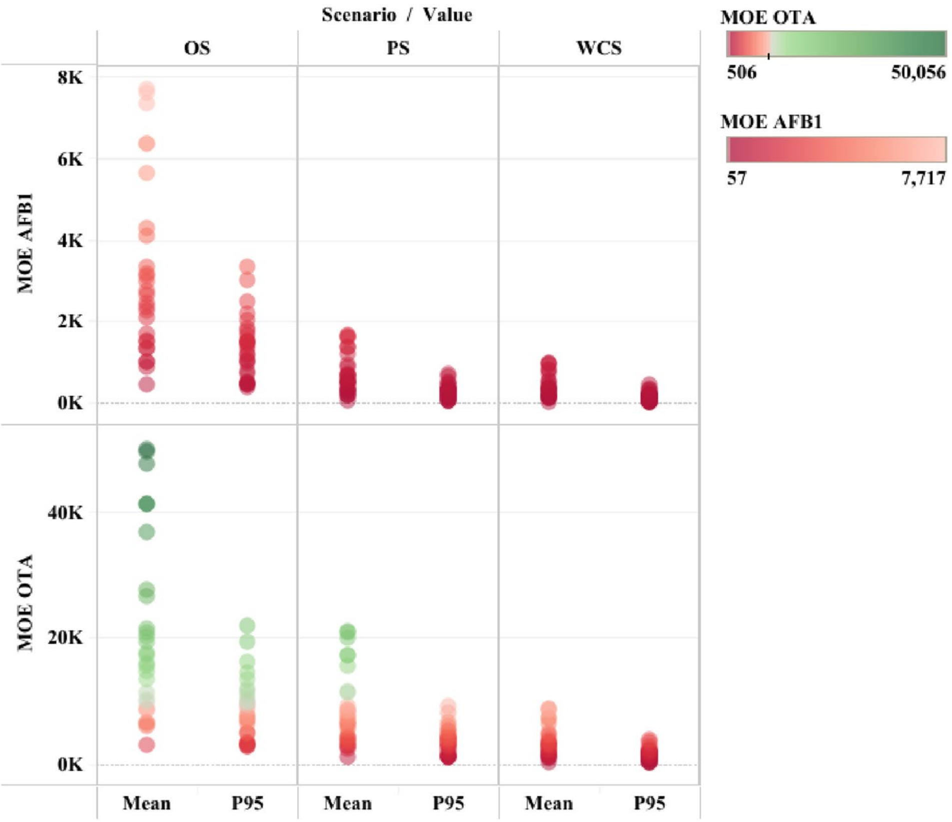


Fig. 1 Mean and P95 MOEs values in the baseline scenario (BS) for AFB_1 and OTA exposure based on three contamination scenarios: optimistic scenario (OS), pessimistic scenario (PS), and worst-case scenarios (WCS); values > 10,000 indicate a low health concern (colored green), while values < 10,000 indicate a high health concern (colored red)

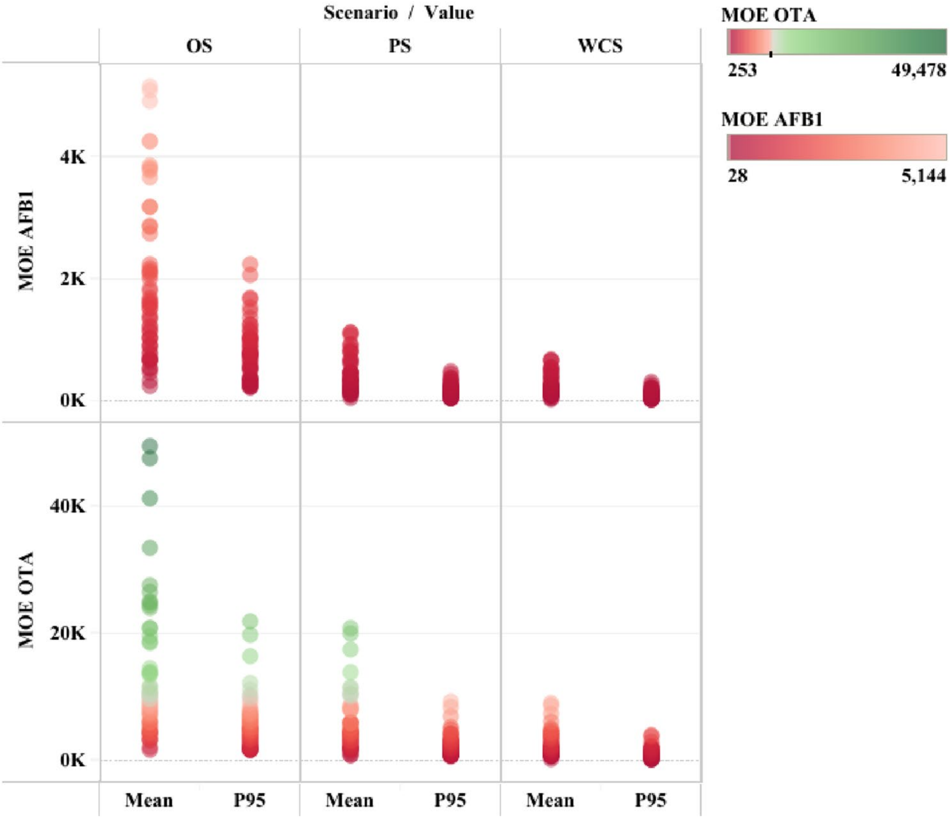


Fig. 2 Mean and P95 MOEs values in the alternative scenarios (AS1 and AS2) for AFB_1 and OTA exposure based on three contamination scenarios: optimistic scenario (OS), pessimistic scenario (PS), and worst-case scenarios (WCS); values > 10,000 indicate a low health concern (colored green), while values < 10,000 indicate a high health concern (colored red)

The mean AFB_1 MOEs were between 235 and 5144, while for OTA the mean MOEs values were between 1526 and 49,477. The MOEs values for the P95 were extremely low for AFB_1 ranging from 32.72 to 2252, while for OTA the values were in the interval of 32.72–21,887. The co-occurrence of AFB_1 and OTA would lead to a mean MOE_T between 82.98 and 13,371, while the P95 MOE_T would be between 76.70 and 5847. Except for a few cases in the AS1 OS where there were a few instances when the OTA MOE was > 10,000 in the other contamination scenarios and AS2, all the MOEs were < 10,000.

Few studies have assessed consumers' dietary exposure to aflatoxins and OTA due to intake of soy-based food. Lee et al. (2022) reported that the dietary exposure of South Koreans to total aflatoxins (AFs) in soybean paste in different exposure scenarios is 0.1012–0.1080 ng/kg bw/day with MOEs between 730 and 22,642, while Lee et al. (2009) reported even lower exposure scenarios between 0.0033 and 0.01 ng/kg bw/day. Both studies, likely in consideration of the different approach adopted, reported a lower exposure to AFs following consumption of soy than the one estimated for Italian consumers in this study.

Brazilian consumers' exposure to AFs due to beans intake is 0.007 µg/kg bw/day (7 ng/kg bw/day) which is in the range of our mean EDI in the BS, but still lower than in the AS1 and AS2 (Franco et al. 2019). Based on tofu, beans, and products consumption, the mean EDI of AFB_1 for Vietnamese consumers is between 0.1 and 0.8 ng/kg bw/day with an MOE of 2909 (Huong et al. 2016) indicating a lower level of exposure than in our study no matter the consumption scenario.

The EDI of OTA for Czech consumers due to intake of spices, seasoning, and legumes varied between 0.11 and 22.6 ng/kg bw/day which is similar to our mean EDI in the BS and lower than in our alternative scenarios (Ostry et al. 2015). The mean dietary exposure to OTA of pregnant women from Bangladesh who had pulses in their diet was between 400 and 8070 ng/kg bw/day and a positive correlation was found between pulses and OTA exposure. However, the high exposure might be due to other contaminated food items such as nuts, seeds, and vegetables (Kyei et al. 2022). Vietnamese consumers' dietary exposure to OTA based on tofu, beans, and products consumption is between 0.2 and 0.7 ng/kg bw/day with MOEs > 10,000 (Huong et al. 2016), depicting a lower exposure than the one reported herein in all our scenarios.

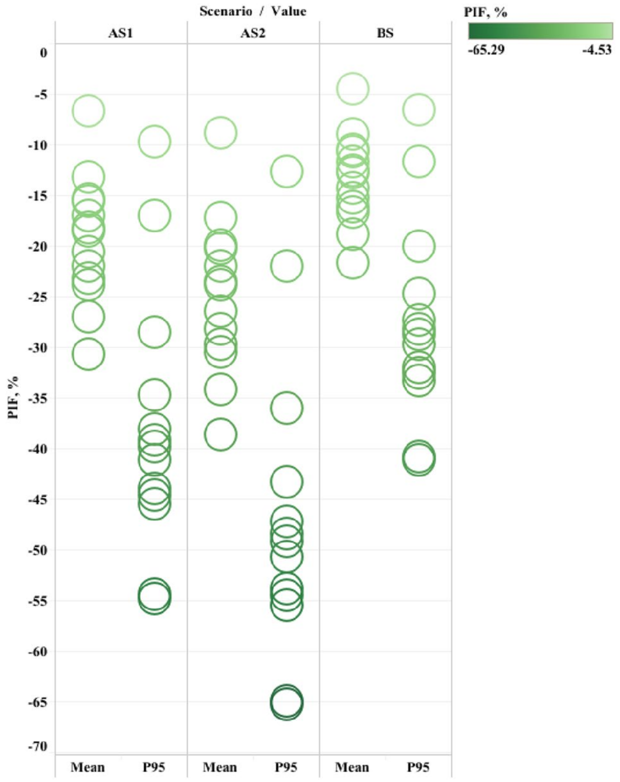


Fig. 3 The potential impact fraction (PIF) for the mean and P95 intake (g/day) of processed meat in the baseline scenario (BS), alternative scenario 1 (AS1), and alternative scenario 2 (AS2)

Relative Risk (RR) of CRC Due to Eliminating Processed Meat and HCC from AFB$_1$ Exposure in BS, AS1, and AS2

The relative risk of CRC in the BS, AS1, and AS2 was compared with a free-meat diet model. Hence, the RR of CRC due to processed meat intake in meat-based diets varied between 1.04 and 1.7 in the BS, indicating an increased risk of CRC by up to 1.7 times higher when compared with no consumption of processed meats.

Based on the intake of processed meat in the AS1 and AS2, the RRs of CRC varied between 1.07 and 2.9, implying that the risk of CRC can potentially be 2.9 times higher in AS2 due to the increased consumption of processed meat. The PIF showing the decreased risk of CRC due to processed meat consumption is presented in Fig. 3.

Consumers that adopt a free-meat diet are at 28% less risk of CRC compared with consumers from BS. The risk of CRC in a free-meat diet decreases even more when compared with processed meat consumption from AS1 with 6–54% lower risk, while for AS2 a free-meat diet could reduce the risk of CRC by up to 65%.

The relative risk (RR) of HCC in the baseline scenario was compared with a model where no contamination would take place. Thus, the RR values based on the mean EDI ranged from 1.01 in the optimistic scenario to 9.6 in the worst-case scenario indicating that based on the consumption and contamination data, the risk of liver cancer can

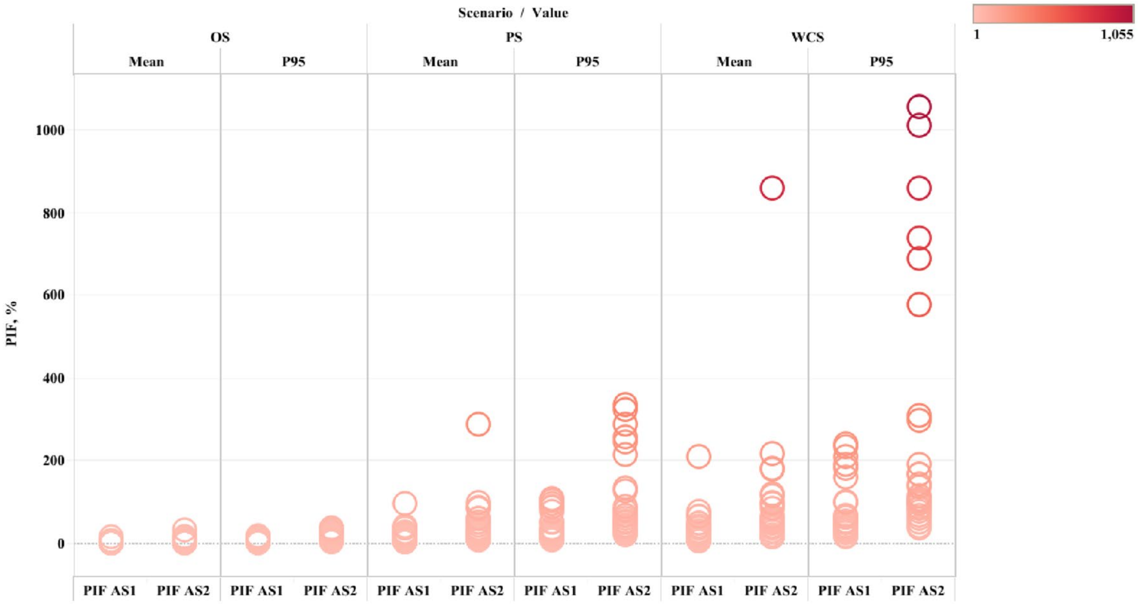


Fig. 4 The potential impact fraction (PIF) for the mean and P95 EDI of AFB$_1$ in the alternative scenario 1 (AS1) and alternative scenario 2 (AS2) in three types of contamination scenarios: optimistic scenario (OS), pessimistic scenario (PS), and worst-case scenarios (WCS)

Fig. 5 Number of extra liver cancer cases due to exposure to AFB_1 (colored red) and number of prevented CRC cases (colored green) due to replacing processed meats with soy-based meat analogues for the mean and P95 values in BS, AS1, and AS2 based on three contamination scenarios: optimistic scenario (OS), pessimistic scenario (PS), and worst-case scenarios (WCS); CC—cancer cases

be up to nine times higher for consumers exposed to AFB_1 than those with no exposure levels. The RRs for P95 were between 1.37 and 11.55 indicating that high consumers in the worst-case scenario are up to 11 times more likely to be burdened by AFB_1 than those with no exposure. To see the RRs in all of the scenarios and for each consumer group check Supplementary file S1.

Based on the mean EDI of AFB_1 in AS1 and AS2 the RRs of HCC were between 1.02 and 92.19, while for the P95 exposure the RRs were between 1.23 and 123.62, indicating a higher risk of HCC when compared with the exposure from the baseline scenario. Figure 4 displays the PIF for the mean and P95 EDI of AFB_1 in the alternative scenario 1 (AS1) and alternative scenario 2 (AS2) in three types of contamination scenarios: optimistic scenario (OS), pessimistic scenario (PS), and worst-case scenarios (WCS).

By increasing the consumption frequency by 50% (AS1) we can see that the mean PIF was between 0.9% and 77% and the P95 PIF was between 2 and 239% indicating that increasing the consumption of AFB_1-contaminated soy-based food by 50% the risk of HCC increases by up to 239%. The risk of HCC is even higher when the consumption is increased by 100% (AS2) with the mean PIF ranging between 1 and 860% and the P95 PIF between 14 and 1055%. Thus, compared with the baseline scenario which reflects an older consumption pattern, the alternative scenarios, which reflect a more accurate dietary pattern, indicate that the risk of HCC can be up to ten times higher.

Estimation of the Prevented CRC Cases in a Free-Meat Diet, the Population Risk for AFB_1-Induced Liver Cancer, and Health Burden Using DALYs

By completely replacing processed meats with soy-based meat analogues, a decrease in number of CRC cases is expected. Hence, we compared the prevented CRC cases in a free-meat diet with the extra liver cancer cases by consumption of AFB1-contaminated soy-based meat analogues.

Figure 5 shows the number of extra HCC cases due to AFB_1 exposure and prevented CRC cases due to the elimination of meat from the diet in the BS, AS1, and AS2 based on three contamination scenarios optimistic scenario (OS), pessimistic scenario (PS), and worst-case scenarios (WCS).

The mean numbers of prevented CRC cases in the BS were between 11.6 and 23.7 (0.02–0.04/100,000 individuals) while for high consumers (P95) up to 223.66 CRC cases/year/country (0.37/100,000 individuals) could be prevented by completely eliminating processed meat from the diet. In AS1 and AS2 the mean value was as low as 82.7 CRC cases/year/country (0.13/100,000 individuals) while for high consumers the value was up to 406.2 prevented CRC cases/year/country (0.7/100,000 individuals).

Based on the contamination scenarios, in the BS the mean numbers of AFB_1-induced liver cancer were as low as 4.69 HCC cases/year/country (OS; substitution of meat sausages with soy sausages) and as high as 131.8 HCC cases/year/country (WCS; substitution of mammals meat with soy) (0.0078–0.22/100,000 individuals). For high consumers (P95), the risk is even higher ranging from 12.9 HCC cases/year/country to 230.3 extra HCC cases/country (0.02–0.38/100,000 individuals) depending on the contamination scenario and the type of meat that was substituted with soy.

The total number of extra HCC cases for the mean and P95 exposure in the WCS was between 301 and 604 HCC cases/country (0.5–1.01/100,000 individuals). In the AS1 and AS2, the lowest mean number of AFB_1-induced liver cancer cases was 7.04/year/country, while the highest was 263.76 HCC cases/year/country (0.01–0.44/100,000 individuals). The P95 exposure revealed extra HCC cases between 19.3 and 460.6/country (0.03–0.77/100,000 individuals). In the WCS at P95, the total number of extra cancer cases in AS1 was 906 HCC cases/year/country (1.51/100,000 individuals), and in AS2 1208 HCC cases/year/country (2.02/100,000 individuals). To see the cancer cases in all of the scenarios and for each consumer group check Supplementary file S1.

For the burden of HCC and CRC, we calculated the DALYs that would be gained/averted due to exposure to AFB_1/full replacement of meat with soy-based meat analogues in the BS, AS1, and AS2 based on three contamination scenarios: optimistic scenario (OS), pessimistic scenario (PS), and worst-case scenarios (WCS) (Fig. 6). To see the DALYs gained/averted in all of the scenarios and for each consumer group check Supplementary file S1.

The mean number of DALYs that would be averted by substituting processed meat in the BS was between 15.14 and 31 DALYs/year/country (0.02–0.05/100,000 individuals) while for P95 it was up to 76 DALYs/year/country (0.12/100,000 individuals). In the AS1 and AS2 the lowest mean value was 108.4 DALYs/year/country (0.18/100,000 individuals), while the highest P95 value was 532 DALYs/year/country (0.64/100,000 individuals) indicating that up to 532 healthy years of life would be gained by eliminating processed meat from the diet.

Based on the mean value exposure in the BS the gained DALYs per country due to liver cancer varied from 46.93 (OS; substitution of meat sausages with soy sausages) to 1318.8 DALYs/year/country (WCS; substitution of mammals meat with soy) (0.07–2.21/100,000 individuals), while for the P95 exposure the gained DALYs/year/country were between 129.1 (OS; substitution of meat sausages with soy sausages) and 2303.2 DALYs/country (WCS; substitution of mammals meat with soy) (0.21–3.86/100,000 individuals) which translates to the loss of 2303 healthy years of life/year/country. In the WCS P95, the total number of gained DALYs was as high as 6040 DALYs/year/country (10.14/100,000 individuals). The gained DALYs based on the mean value exposure varied from 70.4 in the AS1 (OS; substitution of meat sausages with soy sausages) to 2637 DALYs/year/country in the AS2 (WCS; substitution of mammals meat with soy) (0.11–4.42/100,000 individuals) while for the P95 exposure the gained DALYs/country were between 193.6 in the AS1 and 4606 DALYs/year/country in the

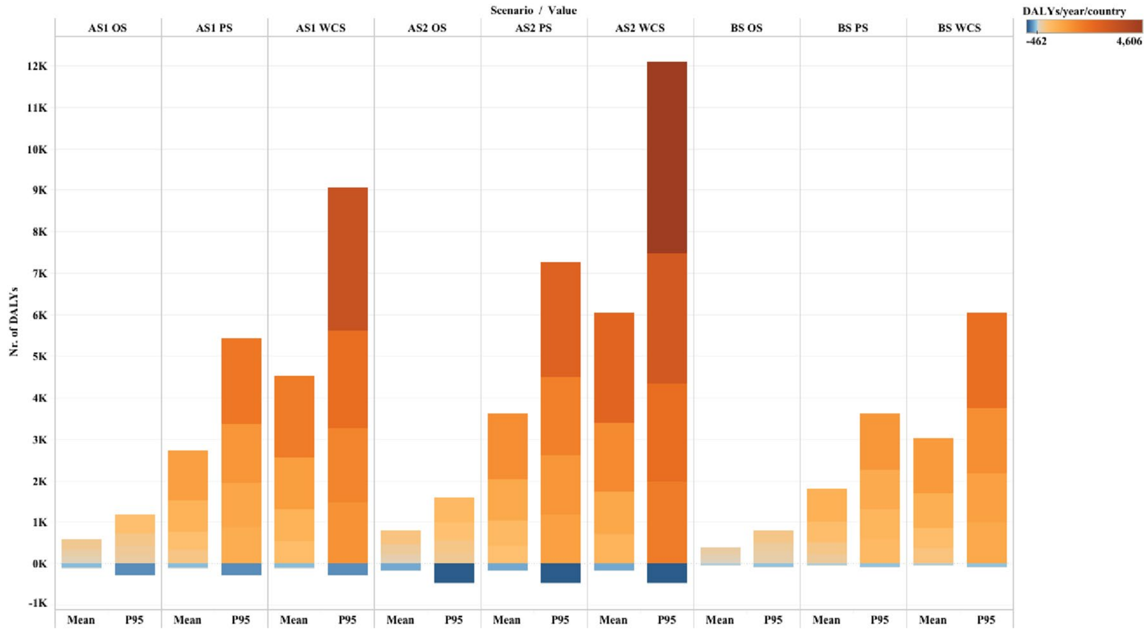


Fig. 6 The number of DALYs gained (colored orange) due to AFB_1 burden and DALYs averted (colored blue) due to replacing processed meat with soy-based meat analogues for the mean and P95 values in BS, AS1, and AS2 based on three contamination scenarios: optimistic scenario (OS), pessimistic scenario (PS), and worst-case scenarios (WCS)

AS2 (0.32–7.73/100,000), revealing that a 100% consumption increase of contaminated soy-based food could lead to the loss of up to 4606 healthy years of life/year/country. In the WCS P95, the total number of gained DALYs in AS1 was 9060 and in the AS2 it was 12,081/year/country (15.21–20.28/100,000 individuals).

While the number of extra HCC cases was three times higher than the number of prevented CRC cases, the number of gained DALYs was 22 times higher than the number of averted DALYs depending on the contamination and consumption scenarios. That is also because the relative survival rate for liver cancer is 31% when it is localized (https://www.cancer.org/cancer/liver-cancer/detection-diagnosis-staging/survival-rates.html), while for colon and rectal cancer it is 90–91% when it is localized (https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/survival-rates.html), indicating a higher burden of disease for liver cancer. This is also supported by the DALYs/capita for liver cancer (10) versus CRC (1.31).

Our results, based on the assumption of a full meat replacement and following calculation based on available AFB_1 occurrence data, reveal an increased risk of cancer and a high number of extra liver cancer cases due to increased consumption of soy-based meat imitates contaminated with AFB_1. The population at risk includes consumers from the vulnerable groups (i.e., pregnant women, and the elderly) which is of high importance as these consumers are more susceptible to diseases than other consumers.

Previous studies have assessed the risk of AFB_1-induced cancer liver due to intake of contaminated cereals, peanuts, rice, tofu, and beans. A few studies reported higher risks of cancer than our study. Kortei et al. (2021) reported between 1.62 and 37.15 extra cancer cases/100,000 individuals through AFB_1-contaminated maize intake. Kimanya et al. (2021) estimated 2.95 AFB_1-induced liver cancer cases/100,000 individuals, respectively, 1480 cases/country in Tanzania mainly based on maize consumption. An even higher number of estimated cancer cases was reported by Nugraha et al. (2018) where the values ranged between 1.5 and 6668 cancer cases/100,000 individuals due to maize consumption and between 0.1 and 35 liver cancer cases/100,000 individuals due to peanuts consumption in Indonesia. Biomonitoring in Portugal showed that the risk of liver cancer due to aflatoxins exposure based on the deterministic approach is 0.167 extra cancer cases/100,000 individuals (Martins et al. 2020), in China the number of extra HCC cases/100,000 individuals is 0.125 (Chen et al., 2022), and 0.011/100,000 individuals based on a total diet study in France (Sirot et al. 2013) which is in the range of the number of cancer cases in our scenarios (0.007–0.77 cancer cases/100,000 individuals) (Supplementary file S1). In Vietnam, the number of extra HCC cases based on tofu and beans consumption is between 0 and 0.1/100,00 individuals (Huong et al. 2016), while due to consumption of maize, rice, and peanuts the number of HCC cases is between 0.21 and 55.45/100,000 individuals (Do et al. 2020) suggesting a higher number of HCC cases than in Italy.

Based on Eq. (10) ($\Delta DALY_{AS} = DALY_{AS} - DALY_{BS}$) the difference in DALYs is > 0 indicating a health loss and the burden of disease associated with the consumption of AFB_1-contaminated soy-based meat analogues due to the shift in dietary patterns.

Martins et al. (2020) reported the gain of 1.7 DALYs/100,000 individuals, respectively, 171.5 DALYs/country due to consumers' exposure to aflatoxins in Portugal. These results are comparable with the gained DALYs in our scenarios (0.07–7.7 gained DALYs/100,000 individuals). In China the number of DALYs gained due to exposure to aflatoxins is extremely higher than in our study with reported gained DALYs of 21,625/100,000 individuals (Chen et al. 2020), while in Tanzania the number of gained DALYs due to the burden of AFB_1 is 56,247/country (Kimanya et al. 2021).

Eneroth et al. (2017) assessed the risk–benefit assessment of nut consumption accounting for cardiovascular health benefits and the carcinogenic effects due to exposure to AFB_1. In their study, an increased nut consumption would prevent > 7000 cardiovascular diseases and save 55,000 DALYs/country for stroke and 22,000 DALYs/country for myocardial infarction, while the AFB_1 exposure would lead to the gain of 159 DALYs/country.

A survey conducted in six European countries (Denmark, France, Germany, Italy, Poland, and Spain) showed that the preferred PBMAs are burger patties, slices, shredded meat, steaks, sausages, nuggets, and tofu (Gebhardt et al. 2020). As plant-based meat and plant-based milk are the leading categories of all plant-based food consumed by flexitarians in Europe (Smart Protein Project 2021) the exposure to plant toxins is expected to continue growing over the next years if no proper regulation will be set in place, further increasing the risks that come with the shift in dietary patterns.

Critical Discussion of the Study Outcome

Sources of Uncertainty and Limitations

This study has unquantified uncertainties such as under/over-reported consumption data and a large proportion of left-censored data (93%). It must be noted, however, that consumption and occurrence data used in our study are obtained from official reports (EFSA 2020a, 2020b), and therefore such uncertainty also affects—and are a limitation of—the current risk assessment. Our substitution model was based on a deterministic approach, speculating that all of the consumers would substitute the meat products with soy-based meat imitates in the same manner and in all scenarios. Hence, variability in the substitution was not taken into account. This has clearly led to a potential overestimation of the overall exposure, risk and benefit. Although the consumption data used are relatively old, the BS fits with previous consumption patterns while AS1 and AS2 reflect actual meat consumption patterns which we replaced with soy-based meat analogues.

Moreover, due to recent findings that indicate a higher exposure to OTA for vegans than omnivores (Penczynski et al. 2022), the RA took into consideration only vegetarians and vegans by completely replacing mammals and poultry meat with soy. Due to the difficulties in performing a partial replacement of meat consumption and the lack of inclusion of soy-based products in the INRAN-SCAI 2005–2006 dietary survey, omnivore and flexitarian exposure was not included in this study. Considering that the growth of plant-based imitates market is also due to the large uptake of these products in the omnivore and flexitarian diets, this is a clear limitation in our approach.

Potential Impact of the Study on Policy Making

The health metric DALY was used to adequately present to policymakers the health burden related to mycotoxin exposure that comes with the shift toward PBMAs. Worth of notice, that although it is known that soy and legumes may be contaminated with mycotoxins, large surveys targeting meat- and milk alternatives are still lacking and no proper regulations are in place at the moment (Mihalache et al. 2022).

The authors are fully aware that a full replacement scenario is unlikely to be adopted because consumers have different eating behaviors with some individuals being small legume eaters while the others are high eaters. In addition, not only soy but a large variety of legumes are used so far for the production of meat imitates currently marketed in Europe, and not all of them are prone the mycotoxins contamination as soybeans are. However, our approach clearly showed the increased risk of cancer based on the consumption of AFB_1-contaminated soy meat analogues, making it easy to correlate it with contamination and consumption data and communicate “what if all individuals ate the same given amount?”.

The authors also acknowledge the importance of alternative protein sources to ensure sustainable dietary patterns in the United Nations Sustainable Goals (UN SDGs) policy framework (https://www.un.org/sustainabledevelopment/). However, in order to support a real shift toward healthier and more sustainable dietary habits, the policymakers should also consider adapting the current regulatory framework to include new products and patterns. Unfortunately, the current turnover in dietary and occurrence surveys used for risk assessment do not reflect the quick uptake of new dietary styles, especially among the younger population. Hence, efforts are required both from the scientific and regulatory bodies to carefully assess the current consumption trends, collect proper and not left-censored occurrence data and increase the monitoring and analysis studies of mycotoxins in PBMAs. The data could be used by the EU for implementing maximum limits of mycotoxins in meat alternatives as such is the case for other food items like wheat and maize.

The RA presented here is of interest from a public health perspective because it presents the toxicological risk that might arise from soybeans used as meat replacers in different contamination and consumption scenarios. As mycotoxin contamination is a ubiquitous problem (De Ruyck et al. 2020) with AFB_1 being responsible for 25,000–155,000 worldwide HCC cases per year (Liu and Wu 2010) and the consumption of meat analogues is continuously growing, greater importance should be given to actual food consumption trends and correlated with updated natural toxins regulations and risk assessments.

Conclusion

This study represents a first attempt to evaluate the risk assessment of a full replacement of meat with soy-based analogues with regards to mycotoxin exposure. Although it must be regarded as a proof of concept with large limitations mainly due to gaps in knowledge and subsequent assumptions, it clearly shows that the change in dietary habits should come with a proper change in the food safety regulatory framework.

By eliminating processed meat from the diet, up to 406.2 CRC cases/year/country could be prevented, indicating the gain of 532 healthy years of life/year/country.

Nonetheless, the alternative scenarios that reflect a more accurate consumption pattern with recent contamination data from EFSA revealed that the consumption of contaminated soy-based meat analogues could lead up to 1208 extra liver cancer cases associated with the loss of 12,080 healthy life-years/country. Hence, shifting to PBMAs has a clear advantage at least due to the elimination of a cancer risk factor such as processed meat. However, if mycotoxins occurrence is not regulated in PBMAs, we could end up with a higher and unexpected risk for consumers.

Future studies focusing on natural toxins exposure can be conducted in a similar manner emphasizing on other common PBMAs such as peas, chickpeas, and seitan, and different types of diets such as omnivore and flexitarian. To get reliable RAs and reduce the associated uncertainties, data gaps in mycotoxin occurrence and food consumption should be solved. This clearly requires efforts from the scientific community and the regulators to keep up with the quick shift toward plant-based dietary patterns.

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Data Availability The datasets generated during and/or analyzed during the current study are available in the Zenodo repository (Supplementary file S1). https://zenodo.org/record/7097793#.YyoApHZByUk.

Declarations

Conflict of Interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical Approval This study does not require ethical approval.

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