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FW0617 Risk Profile Mycotoxin in the New Zealand Food Supply

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Scientific Interpretive Summary

This SIS is prepared by MPI risk assessors to provide context to the following report for MPI risk managers and external readers

The New Zealand Mycotoxin Surveillance Program 06-14 Report Series

FW0617 Risk Profile Mycotoxin in the New Zealand Food Supply

These reports are the outputs of MPIs ongoing mycotoxin surveillance programme. The nine reports form a series detailing the research undertaken over the last eight years to characterise and quantify the risk to the New Zealand public through the presence of mycotoxins in the food supply.

The nine reports are:

- Risk Profile: Mycotoxin in Foods 2006
- Aflatoxins in Maize Products 2008
- Aflatoxins and Ochratoxin A in Dried Fruits and Spices 2009
- Aflatoxins in Nuts and Nut Products 2010
- Dietary Exposure to Aflatoxins 2011
- Ochratoxin A in Cereal Products, Wine, Beer and Coffee 2011
- Trichothecene Mycotoxins in Cereal Products 2014
- Dietary Exposure to Ochratoxin A and Trichothecene Mycotoxins 2014
- Risk Profile: Mycotoxin in Foods 2014

<u>Risk Profile: Mycotoxin in Foods 2014</u>

Maintaining an updated Risk Profile is valuable in ensuring all planned research is prioritised to those mycotoxins deemed to represent a risk in the diet. The scope of this updated profile stated three requirements, these were:

To consolidate the Mycotoxins Risk Profile with the outcome of this survey work completed to date on the top three priority mycotoxin groups in the 2006 risk profile.

To capture any new scientific research on mycotoxins published since the 2006 risk profile to ensure the rankings remain appropriate based on the developing understanding of occurrence and toxicity of the compounds.

To identify and review five emerging mycotoxins to determine if they present any significant risk in the New Zealand diet and to prioritise future research on them.

The report is a very detailed update to the 2006 risk profile and comprehensively compiles all the current understating on mycotoxin occurrence levels in New Zealand and overseas food. The toxicological hazards of each mycotoxin are assessed and the weight of evidence as to the mycotoxin being attributable to human disease is estimated. Where there are data gaps with the New Zealand understanding of occurrence levels these are recorded

Based on this review future priorities for the Mycotoxin surveillance programme have been recommended.

The profile concluded that future priorities to be considered are the generation of occurrence data for Fumonisins, Ergot Alkaloids and Zeralenone
Additionally further occurrence data for Aflatoxin in spices and occurrence data in imported wheat would be valuable in refining the exposure assessment to this mycotoxin group.

No issues of immediate concern were noted with Patulin or with the five emerging mycotoxins, additionally with the completion of surveys and exposure assessments on Ochratoxin A and Trichothecens no additional work was deemed necessary.

RISK PROFILE: MYCOTOXINS IN THE NEW ZEALAND FOOD SUPPLY

Client Report FW14005

by

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RISK PROFILE: MYCOTOXINS IN THE NEW ZEALAND FOOD SUPPLY

Prepared for the Ministry for Primary Industries
under project CFS/13/01, Chemical risk profile for mycotoxins in New Zealand foods,
as part of overall contract for scientific services

Client Report FW14005

by

Peter Cressey

May 2014

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SUMMARY

The purpose of a Risk Profile is to provide contextual and background information relevant to a food/hazard combination so that risk managers can make decisions and, if necessary, take further action. Risk Profiles include elements of a qualitative risk assessment, as well as providing information relevant to risk management. Risk profiling may result in a range of activities, such as immediate risk management action, a decision to conduct a quantitative risk assessment, or a programme to gather more data. Risk Profiles also provide information for ranking of food safety issues.

The current document contains updated individual risk profiles for the fungal toxins (mycotoxins) likely to be of greatest concern in New Zealand: aflatoxins, ochratoxin A (OTA), trichothecenes, fumonisins, zearalenone (ZEA), ergot alkaloids (EAs) and patulin (PAT). Novel risk profiles were also produced for citrinin (CIT), cyclopiazonic acid (CPA), sterigmatocystin (STC), *Alternaria* toxins and penicillic acid (PEN). The information in the risk profiles was also used to provide a qualitative ranking of the risks to the New Zealand consumer due to mycotoxin exposure.

The following general comments can be made:

- There is consistent evidence to support a causal link between chronic aflatoxin exposure and serious human disease (primary liver cancer). Exposure levels in New Zealand are low and represent a very low level of risk. Improved information on aflatoxin contamination of spices and the aflatoxin status of imported wheat would assist further characterisation of the risks associated with aflatoxins in New Zealand.
- There is some evidence to support a link between human kidney disease and exposure to OTA, although little has happened in the last decade to strengthen the evidence base. Further work is required to establish a causal relationship. Dietary exposure to OTA in New Zealand is low.
- While there is good evidence for the trichothecene mycotoxins, T-2/HT-2 toxins, causing human disease, there is little evidence that these toxins occur in New Zealand or Australian cereal crops.
- There is very good evidence that the trichothecene mycotoxins, DON, is able to cause outbreaks of gastrointestinal disease in humans. A recent assessment concluded that New Zealanders' exposure to DON is low.
- While there is a body of information linking fumonisin exposure to serious human diseases, there is virtually no information on the exposure of New Zealanders to these mycotoxins. The fungal species that produce fumonisins have only rarely been reported in New Zealand and New Zealanders only consume relatively small quantities of the food most commonly contaminated (maize). However, the emergence of wheat and fruit products as potential sources of fumonisin exposure means there is previously unrecognised potential for New Zealanders to be exposed to fumonisins. There is a general lack of information on fumonisins in the New Zealand food supply.
- Evidence linking ZEA exposure to human disease states is fragmentary and inconsistent. However, the exposure of New Zealanders to ZEA may be significant when compared to tolerable daily intakes. Further investigation of the role of wheat-based foods in ZEA dietary exposure in New Zealand would help to clarify this issue. The emergence of analytical techniques capable of measuring metabolites of ZEA has

highlighted that earlier exposure assessments may have significantly underestimated dietary ZEA exposure.

- Ergotism, caused by EAs, represents a serious and real human health risk. Recent events have highlighted that ergot may occur in New Zealand cereals at levels high enough to result in shipment rejections. Ergot in cereals is regulated in New Zealand and there is currently a complete lack of information on EAs in our food supply.
- While toxicological experiments have raised concerns about PAT exposure, there is no evidence linking PAT exposure to human disease. However, high levels of PAT contamination are indicative of poor manufacturing practice and a level of ongoing monitoring is probably justified.
- For the remaining mycotoxins considered in this risk profile (CIT, CPA, STC, *Alternaria* toxins, PEN) there is little evidence linking their presence in the food supply to human disease. The co-occurrence of these toxins in foods with better characterised toxins (e.g. CPA and STC co-occurring with aflatoxins) suggests that some level of control on exposure to these toxins will occur through existing mycotoxin control measures. No information on levels of these toxins in the New Zealand food supply is available.

Ranking of risk across different mycotoxins will involve a degree of subjectivity, as there is no absolute measure for the relative seriousness of different health effects. The development of the benchmark dose approach is useful in this regard.

The MPI mycotoxin work programme since the previous version of this risk profile has better characterised risks associated with priority mycotoxin (aflatoxins, OTA, trichothecene mycotoxins) and risks associated with these toxins are currently low in New Zealand. Amongst toxins reviewed for the first time in this risk profile (CIT, CPA, STC, *Alternaria* toxins, PEN), no issues of immediate concern were identified. There is still a lack of New Zealand information on which to assess the potential risks associated with fumonisin and EA exposure. These topics are the most obvious next tier candidates for mycotoxin surveillance projects.

The toxicological impact of combinations of mycotoxins is starting to gain some attention in the scientific literature. While this topic is not addressed in the current Risk Profile, co-occurrence of mycotoxins and resulting toxicological implications are likely to be important topics for future Risk Profiles or other risk analysis studies.

1 INTRODUCTION

The purpose of a Risk Profile is to provide information relevant to a food/hazard combination so that risk managers can make better informed decisions and, if necessary, take further action. Risk Profiles are part of the Risk Management Framework (RMF)[1] approach taken by the Ministry for Primary Industries (MPI) Food Safety. The Framework consists of a 4-step process, as shown in Figure 1.

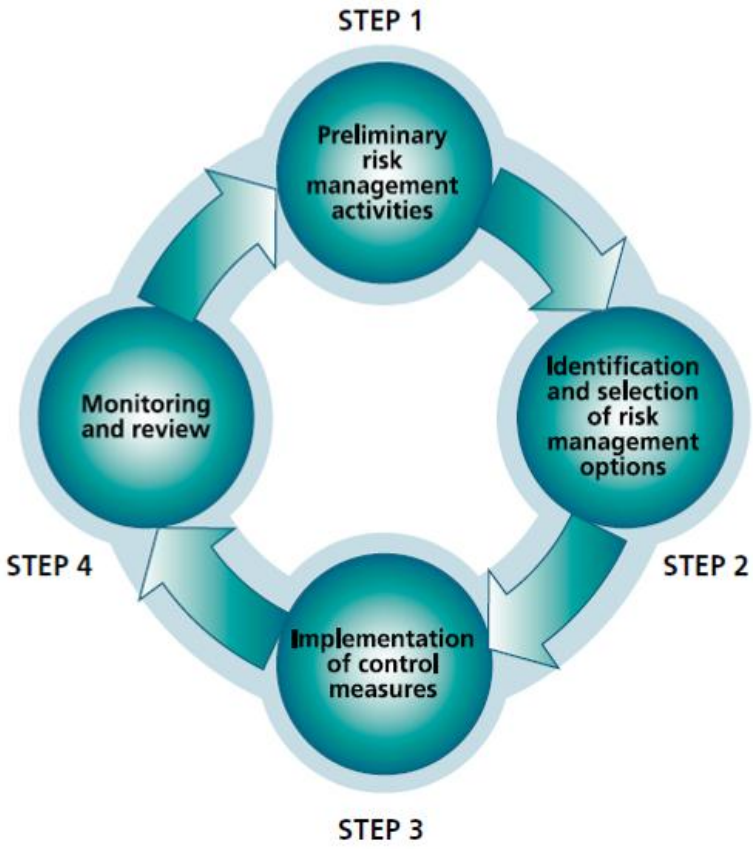


Figure 1: The four steps of the Risk Management Framework

This initial step in the RMF, Preliminary Risk Management Activities, includes a number of tasks:

- Identification of food safety issues
- Risk profiling
- Establishing broad risk management goals
- Deciding on the need for a risk assessment
- If needed, setting risk assessment policy and commissioning of the risk assessment
- Considering the results of the risk assessment

[1] http://www.foodsafety.govt.nz/elibrary/industry/RMF_full_document_-_11604_NZFSA_Risk_Management_Framework_3.1.pdf accessed 2 November 2011

- Ranking and prioritisation of the food safety issue for risk management action.

Risk profiling may be used directly by risk managers to guide identification and selection of risk management options, for example where:

- Rapid action is needed;
- There is sufficient scientific information for action;
- Embarking on a risk assessment is impractical.

1.1 Hazards and Risk Management Questions

This Risk Profile is made up of 2 parts:

- Updates of Risk Profiles for 7 mycotoxins or groups of mycotoxins (aflatoxins, ochratoxin A, trichothecenes, fumonisins, zearalenone, ergot alkaloids and patulin).
- Novel Risk Profiles for an additional 5 mycotoxins or groups of mycotoxins (citrinin, cyclopiazonic acid, sterigmatocystin, *Alternaria* toxins and penicillic acid).

Information on fungal species responsible for the production of each mycotoxin is reviewed in the relevant section, but has also been summarised in Appendix 1, for easy reference. In general, the risk profile does not report studies in which fungal strains are reported to produce mycotoxins in culture, but only studies in which the mycotoxins are produced in food matrices.

The current risk profile does not address issues related to mycotoxin contamination of animal feed or animal health issues, except where these are relevant to human health. The toxicological impact of combinations of mycotoxins is starting to gain some attention in the scientific literature and a meta-analysis of the available information has been published (Grenier and Oswald, 2011). While this topic is not addressed in the current Risk Profile, co-occurrence of mycotoxins and resulting toxicological implications are likely to be important topics for future Risk Profiles or other risk analysis studies.

The sections in this Risk Profile are organised as much as possible as they would be for a conventional qualitative risk assessment.

Hazard identification, including:

- A description of the chemical(s).
- A description of the food group.

Hazard characterisation, including:

- A description of the adverse health effects caused by the chemical.
- Dose-response information for the chemical in humans, where available.

Exposure assessment, including:

- Data on the occurrence of the hazard in the New Zealand food supply.
- Data on the consumption of the food group by New Zealanders.

- Qualitative estimate of exposure to the chemical (if possible).
- Overseas data relevant to dietary exposure to the chemical.

Risk characterisation:

- Information on the number of cases of adverse health effects resulting from exposure to the chemical with particular reference to the identified food (based on surveillance data) or the risk associated with exposure (based on comparison of the estimated exposure with exposure standards).
- Qualitative estimate of risk, including categorisation of the level of risk associated with the chemical in the food.

Risk management information

- A description of relevant food safety controls.
- Information about risk management options.

Conclusions and recommendations for further action

1.2 Main Information Sources

Information on the toxicology of and exposure to mycotoxins has been reviewed or otherwise considered by a number of groups. These assessments were major resources for the current project. Sources included:

- JECFA (the Joint FAO/WHO Expert Committee on Food Additives). Assessment reports were accessed at: http://www.inchem.org/
- EFSA (European Food Safety Authority). Opinions were accessed at: http://www.efsa.europa.eu/
- IARC (the International Agency for Cancer Research). Monographs were accessed from ESR's standing collection. Summaries can be accessed at: http://www.inchem.org/

Reports on surveys carried out by the UK Food Standards Agency (FSA) and, before them, the Ministry of Agriculture, Fisheries and Food were also used and can be accessed at: http://www.foodstandards.gov.uk/

More recent and additional information than that included in these resources was located by general searching of the World Wide Web (internet) and use of specific citation databases, including:

- PubMed. Accessed at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?DB=pubmed
- Scopus. Accessed at: http://www.scopus.com/scopus/home.url

While all abbreviations and acronyms used in this report are defined at their first use, a glossary of these terms has also been included as Appendix 2.

2 AFLATOXINS

2.1 Hazard Identification

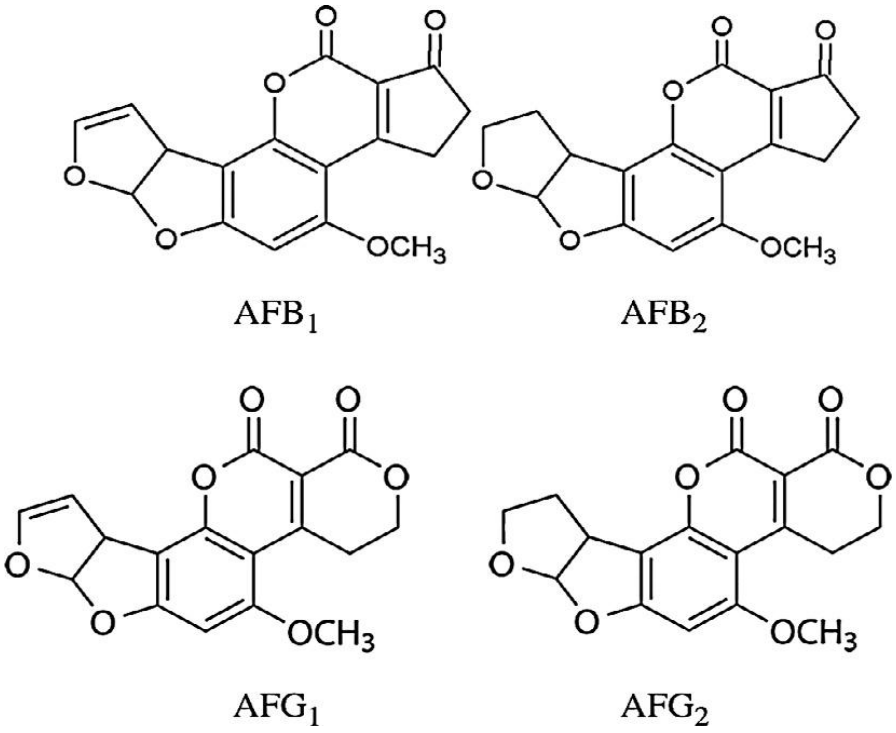
Aflatoxins are secondary metabolites produced by 3 species of *Aspergillus* mould: *A. flavus, A. parasiticus* and *A. nomius* (JECFA, 1998). *A. flavus* occurs in all tropical and subtropical regions and is particularly associated with peanuts and other nuts, maize and other oilseeds. *A. parasiticus* is less widely distributed and is usually only associated with peanuts (Pitt and Tomaska, 2001).

2.1.1 Structure and nomenclature

While the aflatoxins comprise a group of about 20 related compounds, the 4 major naturally-occurring compounds are aflatoxins B_1, B_2, G_1 and G_2 (AFB_1, AFB_2, AFG_1 and AFG_2). The 'B' and 'G' refer to the blue and green fluorescent colours produced by these compounds under ultraviolet light, while the subscripts '1' and '2' refer to major and minor components respectively (Pitt and Tomaska, 2001). The '2' compounds are dihydro derivatives of the major ('1') metabolites. Chemical structures are shown in Figure 2. Aflatoxins M_1 and M_2 (AFM_1 and AFM_2) are hydroxylated metabolites of the respective 'B' aflatoxins produced when ruminant animals consume aflatoxin-contaminated feed. The 'M' aflatoxins may be excreted in milk (Pitt and Tomaska, 2001). Aflatoxins are fat soluble (lipophilic).

Reference to 'aflatoxins' or 'total aflatoxins' can be taken to refer to the sum of B and G aflatoxins.

Figure 2: Structure of aflatoxins



AFB_1 AFB_2

AFG_1 AFG_2

Reproduced from (Marín et al., 2013)

2.1.2 Occurrence

A. flavus produces only 'B' aflatoxins (AFB_1 and AFB_2), with only about 40% of isolates producing toxins. *A. parasiticus* produces both 'B' and 'G' (AFG_1 and AFG_2) aflatoxins, with virtually all isolates producing toxins (Klich and Pitt, 1988). The situation for *A. nomius* appears to be similar to that for *A. parasiticus.*

AFB_1 is the most commonly occurring aflatoxin in foods and is also the compound which has been most thoroughly studied in toxicological studies.

A. flavus occurs widely in the environment, but *A. parasiticus* is considerably less common. However, some regional specificities exist and *A. parasiticus* is commonly isolated from peanuts in the United States, South Africa and Australia.

Fungal infection and consequent aflatoxin contamination can occur in field crops prior to harvest or during post-harvest storage if the moisture content of the crop exceeds critical values for fungal growth (JECFA, 1998). Fungal growth and subsequent toxin production are favoured by factors which place the host plant under stress, such as high temperature, drought, and high insect activity.

Aflatoxin contamination is most commonly associated with peanuts and peanut products, dried fruit, tree nuts, spices, figs, crude vegetable oils, cocoa beans, maize, rice, cottonseed and copra (JECFA, 1998). Consumption of aflatoxin-contaminated feed by animals can lead to occurrence of aflatoxins (mainly the hydroxylated metabolite AFM_1) in meat, eggs and milk.

Most of these crops are not grown in New Zealand. Surveillance of fungal infections of New Zealand grown grain found no *Aspergillus* species (Sayer and Lauren, 1991). This is consistent with expert opinion, that aflatoxigenic species of *Aspergillus* are unlikely to occur in New Zealand (Pitt JI, personal communication).

2.2 Hazard Characterisation: Adverse Health Effects

2.2.1 Conditions

AFB_1 has been demonstrated to exhibit both acute and chronic toxicity in a wide range of animal species (Eaton and Groopman, 1994). The liver is the principal target organ for acute (and chronic) toxicity. Effects on the lung, myocardium and kidneys have also been reported in some studies. Acute toxicity in humans has occasionally been reported in Africa and Asia following consumption of contaminated rice, maize or peanuts. Symptoms include vomiting, diarrhoea, abdominal pain and fever.

Chronic effects of aflatoxins in humans mainly relate to effects on the liver including primary liver cancer (PLC), chronic hepatitis, jaundice, hepatomegaly and cirrhosis. Most investigative studies have concentrated on the association between AFB_1 ingestion and PLC (JECFA, 1998).

Recent reviews have examined the evidence that aflatoxins also exert immunotoxicity (Bondy, 2008) and reproductive toxicity (Shuaib *et al.*, 2010).

2.2.2 Toxicological assessment

No major toxicological assessment of aflatoxins have been carried out since the previous version of this risk profile. Existing toxicological assessments were conducted by JECFA (1998 for aflatoxins and 2001 for AFM_1) (JECFA, 1998; 2001a), Food Standards Australia New Zealand (FSANZ, then operating as Australia New Zealand Food Authority (ANZFA)) (ANZFA, 1999) and IARC (2002). EFSA's assessment of the risk to consumer health of increasing the maximum limits for aflatoxins in almonds, hazelnuts, pistachios and derived products reviewed toxicity data on aflatoxins (EFSA, 2007).

Margin of Exposure (MoE) approaches have gained in popularity for assessing risk. These approaches determine a ratio (MoE) between estimated exposure and a toxiciological reference point or 'point of departure' (Dybing *et al.*, 2008). Two points of reference were determined for AFB_1:

- T25. The chronic daily dose resulting in tumours in 25% of test animals, above baseline levels.
- Benchmark dose (BMD). $BMDL_{10}$ is the lower 95th percentile confidence interval for a benchmark dose giving a 10% increase in tumour incidence.

Based on toxicological studies in Fischer rats, the T25 for AFB_1 was calculated to be 0.50 μg/kg body weight/day. $BMDL_{10}$ values were in the range 0.16-0.30 μg/kg body weight/day, depending on the method used to model the dose-response curve.

EFSA derived a similar animal $BMDL_{10}$ of 0.17 μg/kg body weight/day, but also derived a $BMDL_{10}$ and a $BMDL_1$ from human epidemiological data, with values of 0.87 and 0.078 μg/kg body weight/day, respectively (EFSA, 2007).

A range of benchmark doses were calculated for AFB_1, based on rat liver tumour data (Benford *et al.*, 2010). Depending on the model used to fit a curve to the experimental data, $BMDL_{10}$, $BMDL_5$ and $BMDL_1$ estimates were in the range 0.14-0.31, 0.07-0.25 and 0.014-0.171 μg/kg body weight/day, respectively. The lowest estimates were derived from the model giving the best fit (lowest p-value). A T25 estimate of 0.39 μg/kg body weight/day was derived.

A Malaysian study derived a higher $BMDL_{10}$ of 0.305 μg/kg body weight/day, based on the occurrence of tumours in male rats (Leong *et al.*, 2011).

2.2.3 Proposed mechanisms of carcinogenicity

No significant advances have been made in the understanding of the mechanism of carcinogenesis by aflatoxins. It is still generally considered that this occurs through induced changes in the *p*53 tumour suppressor gene (*TP53*), specifically mutations at codon 249. A review of published data concluded that in regions of high aflatoxin exposure (sub-Saharan Africa, specific regions of China) the codon 249 mutation accounts for more than 90% of *TP53* mutations found in hepatocellular carcinoma (HCC) cases (Gouas *et al.*, 2009). In

Taiwan and Hong Kong the proportion is 30-40%, while in low aflatoxin exposure regions, such as Japan and USA, the codon 249 mutation accounts for less than 6% of *TP53* mutations in HCC cases. An example of such studies was a Turkish study used polymerase chain reaction (PCR) analysis of DNA from HCC to detect codon 249 mutations in *TP53* (Özdemir *et al.*, 2010). Only 1 of 50 HCC patients was found to carry the mutation.

Current knowledge of mechanistic details of the progression from AFB_1 exposure to *TP53* mutation to HCC has been recently reviewed (Gouas *et al.*, 2009; Hussain *et al.*, 2007).

2.2.4 Carcinogenic potency of AFB_1

The carcinogenic potency of a chemical describes the mathematical relationship between exposure and response. JECFA considered available potency information and chose potency values of 0.3 cancers/year per 100,000 population per ng AFB_1/kg body weight/day for hepatitis B surface antigen positive (HBsAg+) individuals with an uncertainty range of 0.05 to 0.5, and a potency of 0.01 cancers/year per 100,000 population per ng AFB_1/kg body weight/day for HBsAg- individuals with an uncertainty range of 0.002 to 0.03 (JECFA, 1998).

The JECFA cancer potencies have not been updated and have been used in several recent risk assessments (Andrade *et al.*, 2012; Cressey and Reeve, 2013; Ding *et al.*, 2012; EFSA, 2007; Guo *et al.*, 2013b; Leong *et al.*, 2011; Liu and Wu, 2010; Shephard, 2008; Sugita-Konishi *et al.*, 2010; Zhao *et al.*, 2013).

2.2.5 Metabolites and their relative toxicity

The aflatoxins vary in their toxicity, with AFB_1 generally agreed to be the most toxic compound. AFG_1 appears to be toxicologically similar to AFB_1, although it has been tested much less extensively. AFM_1, the hydroxylated metabolite of AFB_1 appears to be approximately an order of magnitude less toxic than AFB_1 (Cullen *et al.*, 1987) and potency values for AFM_1 have been used that are 10% of those derived for AFB_1 (JECFA, 2001a). Discussion of adverse effects and toxicology of aflatoxins generally relate to AFB_1 unless stated otherwise.

2.3 Exposure Assessment

2.3.1 Aflatoxins in the New Zealand food supply

Table 1 summarises available information on levels of aflatoxin in food available in New Zealand. The method of analysis was high-performance liquid chromatography (HPLC).

Table 1: Aflatoxins in New Zealand foods (2008-2010)

Food[1]	Year of survey	Analytical LOD, µg/kg	AFB_1		Total Aflatoxin	
			Number of samples positive/ total samples (%)	Mean of positive results (range), µg/kg	Number of samples positive/ total samples (%)	Mean of positive results (range), µg/kg
Peanuts	2010	0.1	10/50 (20)	5.2 (0.1-22.7)	10/50 (20)	6.5 (0.1-26.6)
Peanut butter	2010	0.1	31/75 (41)	0.5 (0.1-2.1)	31/75 (41)	0.7 (0.1-3.4)
Peanut confectionery	2010	0.1	3/17 (18)	1.0 (0.1-2.1)	3/17 (18)	1.1 (0.5-2.3)
Peanut sauces	2010	0.1	8/24 (33)	2.0 (0.2-8.3)	8/24 (33)	2.7 (0.2-10.5)
Almonds	2010	0.1	0/10 (0)	-	0/10 (0)	-
Brazil nuts	2010	0.1	1/10 (10)	5.8	1/10 (10)	5.8
Cashews	2010	0.1	0/10 (0)	-	0/10 (0)	-
Pistachios	2010	0.1	1/20 (5)	0.6	1/20 (5)	0.7
Breakfast cereals, cornflakes	2008	0.1	1/5 (20)	0.2	1/5 (20)	0.2
Breakfast cereals, other	2008	0.1	1/11 (9)	0.9	1/11 (9)	1.1
Corn chips	2008	0.1	0/5 (0)	-	0/5 (0)	-
Extruded snack foods	2008	0.1	0/9 (0)	-	0/9 (0)	-
Popcorn	2008	0.1	0/1 (0)	-	0/1 (0)	-
Cornmeal/polenta	2008	0.1	0/4 (0)	-	0/4 (0)	-
Pasta/noodles	2008	0.1	0/7 (0)	-	0/7 (0)	-
Bakery products (bread, biscuits)	2008	0.1	1/11 (9)	0.6	1/11 (9)	0.7

Food[1]	Year of survey	Analytical LOD, µg/kg	AFB_1		Total Aflatoxin	
			Number of samples positive/ total samples (%)	Mean of positive results (range), µg/kg	Number of samples positive/ total samples (%)	Mean of positive results (range), µg/kg
Figs	2009	0.1	3/10 (30)	1.7 (0.1-3.2)	3/10 (30)	4.2 (0.1-6.7)
Dried vine fruit	2009	0.1	0/10 (0)	-	0/10 (0)	-
Prunes	2010	0.1	1/5 (20)	0.1	1/5 (20)	0.5
Dried apricots	2010	0.1	1/10 (10)	0.2	1/10 (10)	0.9
Dates	2010	0.1	0/5 (0)	-	0/5 (0)	-
Cayenne pepper	2009	0.1	4/5 (80)	3.7 (2.9-4.8)	4/5 (80)	3.8 (2.9-5.0)
Chilli powder	2009	0.1	4/5 (80)	5.1 (3.5-7.7)	4/5 (80)	5.5 (3.5-8.5)
Curry powder	2009	0.1	5/5 (100)	41.4 (0.2-202)	5/5 (100)	46.1 (0.2-225)
Ginger, ground	2009	0.1	4/5 (80)	1.4 (0.3-2.7)	4/5 (80)	2.0 (0.3-3.6)
Paprika	2009	0.1	5/5 (100)	1.5 (0.2-3.5)	5/5 (100)	1.7 (0.2-3.5)
Dried fruit and nuts	2009	0.1	3/19 (16)	0.1 (0.1-0.1)	3/19 (16)	0.4 (0.1-0.7)
Mixed nuts	2010	0.1	12/33 (36)	1.6 (0.3-9.0)	12/33 (36)	1.7 (0.3-9.7)
Snack bars	2008; 2010	0.1	4/41 (10)	1.4 (0.1-4.8)	4/41 (10)	2.1 (0.2-7.7)

AFB_1 = aflatoxin B_1 LOD = limit of detection 95% CI = 95th percentile confidence interval

[1] (Cressey and Jones, 2008; 2009; 2010)

Raw milk samples are analysed for AFM_1 as part of the Dairy National Chemical Contaminants Programme (NCCP).[2] Results available from 2011/2012 reported positive detection of AFM_1 in 2 samples of raw milk out of 301, at a level above the limit of reporting (0.01 µg/L), but below the action residue limit of 0.05 µg/L. AFM_1 was detected in 1 of 46 samples of bovine colostrum at a concentration in the same range (0.01-0.05 µg/L).

2.3.2 Aflatoxins in the Australian food supply

The Australian National Association of Commodity Marketing Agencies (NACMA) classifies maize on the basis of aflatoxin content into Milling, Prime, Feed1 and Feed2 categories. A survey of maize harvested from different Australian regions in 2004-2006 is summarised in Table 2 (Bricknell *et al.*, 2008).

Table 2: Aflatoxins detected in maize samples collected in Australia in 2004, 2005 and 2006, and compliance of samples with NACMA standards by region

State	Region	Number of samples	Number in NACMA grade (aflatoxin concentration, µg/kg)[1]				
			Milling (<)	Prime (5-15)	Feed1 (15-20)	Feed2 (20-80)	(>80)
Queensland	Far North	41	41	0	0	0	0
	Central Highlands	50	8	15	0	3	24
	Burnett	168	141	13	1	4	9
	Darling Downs	146	143	3	0	0	0
NSW	Mid	79	75	2	0	2	0
	Riverina	73	68	3	0	0	2
Victoria		5	5	0	0	0	0
Western Australia		2	2	0	0	0	0

NACMA = National Association of Commodity Marketing Agencies

[1] Analysis by 2-dimensional thin layer chromatography. Limit of reporting = 1 µg/kg

The 23rd Australian Total Diet Study (ATDS) included analysis of almonds, baked beans in tomato sauce, mixed grain breakfast cereals, single grain breakfast cereals, mixed infant cereal, rolled oats, white rice, peanut butter, meat pie, meat and savoury sauce (non-tomato) for the presence of B and G aflatoxins (Food Standards Australia New Zealand, 2011). Analysis for AFM1 was carried out on full fat milk, full fat fruit yoghurt, cheddar cheese, infant formula and milk-based infant dessert. Samples were analysed by liquid chromatography-mass spectrometry. Aflatoxins were not detected in any sample analysed. However, the limits of reporting (1-2 mg/kg) were very high. It is possible that these limits of reporting are a typographical error, as earlier ADTSs have stated a limit of reporting for aflatoxins of 0.001 mg/kg (Food Standards Australia New Zealand, 2002)

[2] http://www.foodsafety.govt.nz/industry/sectors/dairy/monitoring-testing/nccp/ Accessed 31 July 2013

2.3.3 Overseas Context

Since the previous mycotoxin risk profile, a huge body of information has been published on the prevalence and concentrations of aflatoxins in various foods. Results of such studies are only summarised here where they implicate novel foods as source of aflatoxin exposure. Overall, the pattern of publications does not suggest a change in the priority foods for aflatoxin contamination, with cereals, nuts (ground and tree) and seeds, dried fruits, spices and dairy products being the main targets of surveillance activity.

2.3.3.1 Plant foods

Wheat and wheat products

Data presented in the previous risk profile suggested that wheat is rarely contaminated with aflatoxins (Cressey and Thomson, 2006). However, a number of studies have been published reporting detection of aflatoxins in wheat and wheat products. AFB_1 was detected above 5 μg/kg in 40% of 1646 wheat grain samples from 10 Indian states (Toteja *et al.*, 2006). The maximum concentration detected was 606 μg/kg. A study in the Golestan province of Iran reported mean total aflatoxin and AFB_1 concentrations for 100 wheat flours of 1.99 and 0.53 μg/kg, respectively (Ghasemi-Kebria *et al.*, 2013). The prevalence of aflatoxins in wheat (*n* = 41) grown in Turkey was reported to be 59% (limit of detection (LOD) = 0.01 μg/kg) (Giray *et al.*, 2007). Concentrations of total aflatoxins and AFB_1 were in the range 0.01-0.64 μg/kg and 0.01-0.14 μg/kg, respectively. A study of mycotoxins in 'Mediterranean' foods detected AFB_1 in 10 of 65 wheat-based foods, with concentrations in the range 5.5-66.7 μg/kg (Serrano *et al.*, 2012). Samples were from southern European (Italy, Spain) and north African (Morocco, Tunisia) countries, with all AFB_1-containing samples from north Africa. A study in 3 regions of China (Huantai, Huaian, Fusui) detected AFB_1 in 16 of 16 samples of wheat flour, with concentrations in the range 0.1-0.9 μg/kg (Sun *et al.*, 2011).

New Zealand imports approximately half of its wheat requirements, predominantly from Australia, with a lesser amount from Canada.[3] No information was found on aflatoxins in Australian wheat. Wheat-containing foods have been analysed for aflatoxins in Australian Total Diet Studies; no aflatoxins were detected (Food Standards Australia New Zealand, 2002; 2011). A Canadian survey of aflatoxins in breakfast cereals detected aflatoxins in 4 of 48 wheat-based breakfast cereals, but at very low concentrations (0.002-0.05 μg/kg) (Tam *et al.*, 2006).

Olives

A survey of 30 Greek olive samples detected AFB_1 in all samples, with concentrations in the range 0.15-1.13 g/kg (Ghitakou *et al.*, 2006). There were some indications of varietal differences in the concentrations of AFB_1 and it was hypothesised that green olives may be more inhibitory to aflatoxin production than black olives.

AFB_1 was detected in 4 of 10 black olive samples from Morocco, with concentrations in the range 0.6-5.0 μg/kg (El Adlouni *et al.*, 2006).

[3] http://www.stats.govt.nz/infoshare/TradeVariables.aspx?DataType=TIM

Edible oils

Development of suitable analytical methods has allowed the analysis of edible oils for aflatoxins. Analysis of 30 virgin olive oils from Italy and North Africa detected AFB_1 in 3 of 4 samples from North Africa at concentrations up to 2.4 μg/kg (Ferracane *et al.*, 2007). AFB_1 was not detected in olive oil from Italy. A Sudanese study detected AFB_1 (LOD = 0.1 μg/kg), but not other B and G aflatoxins, in 8 of 56 edible oil samples (Idris *et al.*, 2010). AFB_1 was only detected in unrefined/crude oils, with sesame oil the most frequently contaminated. Concentrations of AFB_1 were in the range 0.2-0.8 μg/kg. A study in 3 regions of China (Huantai, Huaian, Fusui) detected AFB_1 in 39 of 39 samples of plant oil, with concentrations in the range 0.2-114.4 μg/kg (Sun *et al.*, 2011).

Legumes

In a study in Cameroon all soybean samples tested (n = 10) contained AFB_1 with a mean concentration of 2.6 μg/kg (range 1-3 μg/kg) (Abia *et al.*, 2013b). A Brazilian study detected total aflatoxins in 75% of 51 bean samples, with concentrations in the range 0.025-0.42 μg/kg (Jager *et al.*, 2013). The type of bean was not specified. In a Korean study, AFB_1 was not detected in any of 7 soybean, 46 hot soy paste or 7 soybean oil samples (LOD = 0.05 μg/kg), but was detected in 1 of 7 samples of soy sauce (1.8 μg/kg) and 2 of 56 samples of soybean paste (0.05 and 0.17 μg/kg) (Chun *et al.*, 2006). It is possible that the aflatoxin detected may have originated from non-soybean components of these products.

Chocolate

Chocolate (n = 25 for each of powder, milk, dark, bitter and white chocolates) was analysed for aflatoxins (Copetti *et al.*, 2012). The method used was very sensitive, with a LOD of 0.01 μg/kg. Prevalence of aflatoxins varied with chocolate type from 20% (white) to 100% (dark, bitter). The highest mean concentration was in bitter chocolate (0.66 μg/kg), while the highest individual total aflatoxin concentration was in powdered chocolate (1.7 μg/kg).

Grapes and wine

AFB_1 was detected in 19 of 47 grape musts[4] (El Khoury *et al.*, 2008). The maximum AFB_1 concentration detected was 0.46 μg/kg. Only 2 musts contained AFB_1 at concentrations greater than 0.1 μg/kg. It was not reported whether AFB_1 was detected in wine produced from the musts.

Aflatoxins were not detected in any white (n = 71) or red (n = 72) wines collected in the United States (Al-Taher *et al.*, 2012). LODs for individual aflatoxins were in the range 0.05-0.25 μg/L. Wines were from USA, Europe, South America and Australia.

[4] Must is the first stage in wine production and is used to describe the product achieved after the grapes have been pressed, but the juice still contains skin, seeds and stem material.

Tubers

A study in Benin, West Africa found *Aspergillus flavus* on stored chips of cassava and yam tubers, but no aflatoxins were detected at a LOD of 0.25 µg/kg (Gnonlonfin *et al.*, 2008). In contrast, a study in Uganda (East Africa) detected aflatoxins (LOD not stated) in 18 of 60 dried cassava samples (sliced or crushed), with a maximum concentration of 4.5 µg/kg (Kaaya and Eboku, 2010). Aflatoxin concentration was not positively correlated with visual mould rating, but was related to certain drying and storage practices.

Vegetables

An Indian study detected aflatoxins in a range of green leafy vegetables (Hariprasad *et al.*, 2013). Aflatoxin was detected in 5 of 9 cabbage samples, with concentrations in the range 0.4-26.0 µg/kg, and in 6 of 9 spinach samples, with concentrations in the range 0.9-15.3 µg/kg. The other green leafy vegetables examined are usually used as culinary herbs in New Zealand or are not consumed here.

A Turkish study detected AFB_1 in 6 of 11 dried vegetable samples (LOD = 1 µg/kg) (Hacıbekiroğlu and Kolak, 2013). The highest concentration detected (10 µg/kg) was found in dried eggplant and parsley.

Tea

Aflatoxins were detected in all of 15 samples of tea (LOD = 1.7 µg/kg for total aflatoxin) from Istanbul, Turkey (Hacıbekiroğlu and Kolak, 2013). Most samples contained more than 5 µg/kg AFB_1 and more than 10 µg/kg total aflatoxins. It appears that most of the 'tea' samples in this study were herbal products, as opposed to leaf of *Camellia sinensis.*

Aflatoxins were detected (LOD = 1 µg/kg for AFB_1 and AFG_1, 0.2 µg/kg for AFB_2 and AFG_2) in 11 of 40 black tea samples purchased in Tehran, Iran (Pouretedal and Mazaheri, 2013). AFB_1 was the predominant aflatoxin present, with concentrations up to 191 µg/kg reported. All samples were of *Camellia sinensis.* However, given that aflatoxins are lipophilic, it is uncertain how much toxin would transfer to infused tea.

2.3.3.2 Foods of animal origin

There is growing evidence that aflatoxins present in animal feed can be transmitted to human foods, such as eggs and meat. However, the concentrations ultimately present in food for human consumption are low. Animal feeding practices in New Zealand will mean that the potential for aflatoxin residues in stock animals is extremely low. The diverse nature of ingredients used in the poultry feed industry mean that there is some potential for aflatoxin residues in poultry feed and, consequently, in eggs and poultry meat, although concentrations will be very low.

Eggs

AFB_1 was not detected in Italian market eggs (n = 27; 5 organic, 7 free-range, 15 intensive farming) (Capriotti *et al.*, 2012). However, the authors do not give a LOD specific to AFB_1,

but stated that limits of detection for mycotoxins are in the range 0.5-3 μg/kg. In contrast, a Chinese study detected AFB_1 in 1 of 3 egg samples at a concentration of 0.73 μg/kg (Chen *et al.*, 2012). AFM_1 was also detected in the same sample at a concentration of 0.68 μg/kg. Analyses of 7 egg samples from Almeria, Spain did not detect aflatoxins in 2 samples, but detected trace amounts of 1 or more B or G aflatoxin in the remaining 5 samples (Frenich *et al.*, 2011). It should be noted that the detection and quantification limits in this study were quite high and a 'trace' of AFB_1 would be a concentration in the range 0.5-1.0 μg/kg. Aflatoxins were detected in 5 of 40 eggs sampled in Jordan, with concentrations in the range 0.2-5.8 μg/kg (Herzallah, 2009).

Layer chickens (White Leghorn) received diets containing 0, 2500, 3130 or 3910 μg/kg AFB_1 until 8 weeks of age (Pandey and Chauhan, 2007). Birds were transferred to a grower diet from week 9 until the end of the study at week 40. Eggs collected in week 40 contained 0.00, 1.43, 1.39 and 1.63 μg/kg AFB_1 for the 4 dose groups respectively.

Poultry meat

Broilers consuming feed material containing 134 μg/kg AFB_1 and 24 μg/kg AFB_2 resulted in mean AFB_1 concentration of 0.137 and 0.016 μg/kg in liver and breast muscle, respectively (Yang *et al.*, 2012). AFM_1 was also detected in liver (0.051 μg/kg), but not breast muscle.

The impact of bird age and feed AFB_1 concentration on the AFB_1 content of broiler liver and muscle meat was examined (Hussain *et al.*, 2010). Groups of birds (n = 80 per group) of 7, 14 or 28 days of age received feed containing 0, 1600, 3200 or 6400 μg/kg AFB_1 for 7 days. Groups of 6 birds were sacrificed at intervals and the AFB_1 content of liver and muscle meat was determined. The highest AFB_1 concentrations were attained in the youngest birds receiving the highest dose of AFB_1, at the end of the 7 day feeding period. The highest AFB_1 concentrations determined in liver and muscle meat were 5.74 and 2.18 μg/kg, respectively. Following cessation of contaminated feeding, AFB_1 concentrations in liver and muscle reduced to non-detectable concentrations within 8 days.

Layer chickens (White Leghorn) received diets containing 0, 2500, 3130 or 3910 μg/kg AFB_1 until 8 weeks of age (Pandey and Chauhan, 2007). Birds were transferred to a grower diet from week 9 until the end of the study at week 40. Mean AFB_1 concentrations in breast muscle of birds sacrificed at the end of the study were 0.00, 18.00, 25.67 and 25.70 μg/kg for the 4 dose groups, respectively. These results are in sharp contrast to those of Hussain *et al.* (2010) summarised above in terms of concentrations found and the lack of clearance of aflatoxins following cessation of contaminated feeding.

Red Meat

A Chinese study detected aflatoxins in 2 of 3 samples of pig liver and kidney, but in only 1 of 3 samples of pig muscle meat (Chen *et al.*, 2012). Total aflatoxins levels in offals were as high as 3 μg/kg, with all B and G toxins detected, while in muscle meat only AFB_1 was detected, at a concentration of 0.25 μg/kg. A study in Jordan detected aflatoxins in 12 of 80 meat samples, with total aflatoxin concentrations in the range 0.15-8.32 μg/kg (Herzallah,

2009). Mean aflatoxin concentrations were higher in Winter than Summer, presumably related to supplementary feeding.

Fresh and dried bovine meat samples (*n* = 80) from Oyo state, Nigeria were tested for aflatoxin contamination (Olufunmilayo and Oyefolu, 2010). The highest mean concentrations were detected in fresh (0.16 μg/kg) and dried (0.22 μg/kg) kidney, followed by fresh (0.13 μg/kg) and dried (0.08 μg/kg) heart. Fresh beef muscle contained 0.05 μg/kg total aflatoxin, on average, while dried beef muscle contained 0.007 μg/kg total aflatoxin. Mean concentrations of G aflatoxins were greater than mean concentrations of B aflatoxins for all sample types.

Dairy products

Cheese

An Iranian study demonstrated that the AFM_1 concentration in a brined white cheese was directly related to the AFM_1 concentration of the milk used for manufacture (Kamkar *et al.*, 2008). The toxin preferentially partitions into the curd and, on average, concentrations in the cheese were approximately twice those in the milk used for manufacture.

2.3.4 New Zealand estimates of dietary exposure

Information on the prevalence and concentration of aflatoxins in foods available in New Zealand (maize products, nuts and nut products, dried fruits and spices) was collated and combined with information on consumption of these foods and the body weights of consumers to give estimates of dietary exposure to aflatoxins (Cressey and Reeve, 2013). Exposure estimates were consistent with estimates from other developed countries and much lower than estimates from developing countries.

Due to the high proportion of left-censored ('not detected') results for the analysis of aflatoxins in foods, exposure estimates were determined as a range (lower-upper bound). Mean estimates of dietary total aflatoxin exposure from dietary modelling ranged from 0.09-0.11 ng/kg body weight/day for an adult female to 0.30-0.36 ng/kg body weight/day for a 5-6 years child. Estimates of dietary total aflatoxin exposure at the 95th percentile level were also determined and ranged from 0.35-0.44 ng/kg body weight/day for an adult female to 0.62-1.11 ng/kg body weight/day for a 5-6 years child. AFB_1 accounted for more than 80% of total aflatoxin dietary exposure. Spices contribute the greatest proportion to overall aflatoxin exposure, followed by nuts and nut products. However, the predominance of spices in the exposure calculation is mostly due to a single very high concentration of aflatoxins (225 μg/kg total aflatoxins) detected in a sample of curry powder.

2.3.5 Overseas estimates of dietary exposure

Table 3 summarises results of overseas studies that have derived estimates of dietary exposure to aflatoxins. There continues to be a significant divide between estimates of aflatoxin exposure in developing countries, where estimates may be as high as several hundred ng/kg body weight/day, and developed countries, where estimates are generally less than 1 ng/kg body weight/day (Liu and Wu, 2010).

Table 3: International estimates of dietary exposure to aflatoxins

Country	Population group	Mean exposure (total aflatoxin, unless otherwise stated), ng/kg body weight/day	Main foods contributing	Reference
African countries	Adults (60 kg) • Kenya • Ghana • Botswana • Benin • Tanzania • Gambia	 133-353 850 23 105 402 1.4-30	 Maize Kenkey Peanut butter Yam chips Beer Millet	(Shephard, 2008)
Brazil	Total population High consumers	6.6-6.8 16.3-27.6	Rice	(Andrade *et al.*, 2012)
Brazil (São Paulo)	NS (food consumption data came from dietary records for 35 'volunteers')	1.58 (range 0.04-14.0) AFM_1 0.14 (range 0.006-0.34)	Peanut products Liquid milk	(Jager *et al.*, 2013)
China[1] -Huantai -Huaian -Fusui	NS	AFB_1 median (range) 6.6 (4.5-20.3) 28.7 (3.7-830) 44.8 (16.8-242)	Corn, plant oil	(Sun *et al.*, 2011)
China Children Adults	 Children Adults	AFB_1 (high consumer) 0.218-0.222 (3.28-3.33) 0.106-0.108 (1.25-1.27)	Peanuts	(Ding *et al.*, 2012)
China	 Male, 2-4 years Female, 2-4 years Male, 4-7 years Female, 4-7 years Male, 7-11 years Female, 7-11 years Male, 11-14 years Female, 11-14 years Male 14-18 years Female, 14-18 years Male, 18-30 years Female, 18-30 years Male, 30-45 years Female, 30-45 years Male, 45-60 years Female, 45-60 years Male, 60-70 years Female, 60-70 years Male, >70 years Female, >70 years	AFM_1 mean (95^{th} percentile) 0.079 (0.289) 0.087 (0.317) 0.034 (0.126) 0.030 (0.109) 0.018 (0.067) 0.018 (0.065) 0.012 (0.044) 0.011 (0.040) 0.010 (0.037) 0.012 (0.044) 0.008 (0.031) 0.009 (0.031) 0.005 (0.019) 0.006 (0.024) 0.007 (0.025) 0.009 (0.032) 0.011 (0.042) 0.011 (0.041) 0.012 (0.045) 0.012 (0.042)	Milk and milk products	(Guo *et al.*, 2013b)
European Union	GEMS cluster diet F GEMS cluster diet E GEMS cluster diet B	0.35-0.69 0.56-1.10 0.84-1.93	Maize, oilseeds	(EFSA, 2007)
France	Children	Mean (95^{th} percentile) AFB_1 0.001-0.39 (0.08-0.74) AFB_2 0.39 (0.74) AFG_1 0.39 (0.74) AFG_2 0.39 (0.74)	 Bread, pasta Bread, pasta Bread, pasta Bread, pasta	(Sirot *et al.*, 2013)

Country	Population group	Mean exposure (total aflatoxin, unless otherwise stated), ng/kg body weight/day	Main foods contributing	Reference
	Adult	AFM_1 0.03 (0.05) AFB_1 0.002-0.22 (0.01-0.39) AFB_2 0.2 (0.3) AFG_1 0.2 (0.3) AFG_2 0.2 (0.3) AFM_1 0.054 (0.130)	Dairy products Bread, pasta Bread, pasta Bread, pasta Bread, pasta Dairy products	
Japan	 Toddlers and young children Older children Adolescents Adults	AFB_1 (95^{th} percentile) 2.34 1.78 1.33 1.20	Only rice was included in the analysis	(Sakuma *et al.*, 2013)
Japan	 1-6 years 7-14 years 15-19 years >19 years	95^{th} percentile 0.006-0.007 0.005-0.006 0.004-0.005 0.0006-0.001	Only peanut butter and bitter chocolate were included	(Kumagai *et al.*, 2008)
Malaysia	Adults, 18-59 years (63 kg)	10	Raw peanuts	(Othman and Keat, 2006)
Malaysia	Adult, 60 kg body weight	Mean (95^{th} percentile) 0.36 (8.89)	Fried peanut	(Leong *et al.*, 2011)
Morocco	NS	0.0004	Only cereals were included	(Serrano *et al.*, 2012)
Netherlands	Children	AFB_1 0.1	Duplicate diet	(Bakker *et al.*, 2009)
Serbia	 Male, 1-5 years Female, 1-5 years Male, 5-15 years Female, 5-15 years Male, 15-25 years Female, 15-25 years Male, 25-55 years Female, 25-55 years Male, >55 years Female, >55 years	AFM_1 6.45 6.26 2.34 1.86 1.26 0.42 0.49 0.56 0.51 0.69	Milk	(Kos *et al.*, 2014)
South Korea	Adult (20-64 years)	0.642	Soy sauce, soybean paste	(Chun *et al.*, 2006)
Spain (Catalonia)	Children, 4-9 years Adolescents, 10-19 years Adult males, 20-65 years Adult females, 20-65 years Immigrants, 17-51 years Coeliac sufferers, 16-75 years	0.105/0.033[3] 0.178/0.245 0.072/0.098 0.077/0.094 0.086/0.086 0.079/0.276	NS	(Cano-Sancho *et al.*, 2013a)
Tunisia	NS	0.079	Only cereals were included	(Serrano *et al.*, 2012)

AFB_1 = aflatoxin B_1 AFM_1 = aflatoxin M_1 NS = not stated

[1] Fusui county has a high prevalence of HCC, Huaian county has a high prevalence of oesophageal cancer, and Huantai County has a low prevalence of both cancer types.

[2] Published dietary exposure were in 'µg/day'. A body weight of 60 kg has been used to convert these to 'ng/kg body weight/day'.
[3] The paired exposure estimates relate to the way left-censored data were treated, with the first estimate derived by substituting left-censored values with a value equal to half the LOD. The second estimate used a Kaplan-Meier (K-M) method to calculate mean values. In our experience, the K-M method is unreliable when the proportion of left-censored values is high (>60%).

Liu and Wu (2010) consolidated aflatoxin exposure information from a number of different countries. In general, lowest exposures were in North America (0.2-1 ng/kg body weight/day) and Europe (0-4 ng/kg body weight/day). High exposure estimates (>100 ng/kg body weight/day) were reported for Malaysia, India, Sudan and a range of sub-Saharan African countries. Exposures for New Zealand are consistent with those for North America and Europe.

2.3.6 Biomarkers of exposure

Exposure to aflatoxins can be assessed either by analysis of AFB_1 or its metabolite, AFM_1, in urine or milk, measurement of AFB_1 adducts formed with DNA in urine or serum, or AFB_1-albumin adducts (Baldwin *et al.*, 2011; Wild and Gong, 2010).

A study in a cohort of pregnant Egyptian women (*n* = 98, 18-40 years) measured serum AFB_1-albumin and urinary AFM_1 (Piekkola *et al.*, 2012). Concentrations of the 2 biomarkers were positively correlated (r = 0.276, p = 0.007). Concentrations of albumin adduct were significantly associated with maize consumption. No significant associations to consumption of particular foods were seen for AFM_1.

In a study of adults from Cameroon (*n* = 175), urinary AFM_1 was detected in 16 samples (9%) with a maximum concentration of 1.38 µg/L (Abia *et al.*, 2013a). Literature values for the urinary excretion rate of AFM_1 (1-3%) and an estimate of daily urinary output (1.5 L) were used to estimate dietary exposure to aflatoxins.

The presence of the codon 249 *TP53* mutation in plasma has also been used as a biomarker of aflatoxin exposure (Hussain *et al.*, 2007; Kuniholm *et al.*, 2008).

2.4 Risk Characterisation

2.4.1 Adverse health effects in New Zealand

2.4.1.1 Incidence of primary liver cancer

No cases of acute aflatoxicosis have been reported in New Zealand. While it is not possible to definitively identify cases of chronic adverse effects from exposure to aflatoxins, it is pertinent to consider New Zealand's rates of PLC and the prevalence of hepatitis B and C infection, as these factors have all shown inter-relations in the major epidemiological studies carried out in relation to aflatoxin exposure overseas (Table 4).

Table 4: Incidence of liver cancer, hepatitis B and hepatitis C in New Zealand

Year	Liver cancer [1]		Hepatitis B[2]		Hepatitis C[2]	
	New cases	Rate (per 100,000)	New cases	Rate (per 100,000)	New cases	Rate (per 100,000)
2003	189	3.6	61	1.6	40	1.1
2004	164	3.0	38	1.0	24	0.6
2005	223	4.1	59	1.4	29	0.7
2006	231	4.1	62	1.6	35	0.8
2007	237	4.1	72	1.7	30	0.8
2008	233	3.9	38	0.9	22	0.5
2009	253	4.0	55	1.3	32	1.2
2010	NA	NA	51	1.2	17	0.4
2011	NA	NA	51	1.2	26	0.6
2012	NA	NA	39	0.9	32	0.7

NA Not available

[1] http://www.health.govt.nz/publication/cancer-historical-summary-1948-2009

[2] (ESR, 2013)

Hepatitis B notifications have declined from almost 400 per year in the late 1980s to the most recently reported incidence of 39 in 2012 (ESR, 2013). This decline has been influenced by the introduction of immunisation for infants of HBsAg+ mothers (1985), followed by immunisation of all neonates (1988).[5]

Statistics suggest that the rate of HCC is increasing in New Zealand, from less than 2 per 100,000 population to approximately 4 per 100,000 population in 2009.[6]

2.4.1.2 Risk assessment

Risk estimates were calculated using cancer potency factors derived by JECFA and estimates of mean lifetime AFB_1 exposure for New Zealanders (Cressey and Reeve, 2013). Mean risk estimates were in the range 0.0015 to 0.0022 cancer per year per 100,000 population. Risk estimates suggest that dietary exposure to aflatoxins in New Zealand would result in a negligible contribution to the burden of primary liver cancer (<1 cancer/10 years).

2.4.2 Adverse health effects overseas

2.4.2.1 Incidence of primary liver cancer

Liver cancer is the fifth most frequently occurring cancer worldwide (Bosch *et al.*, 2004). Rates of liver cancer in developing countries are generally 2 to 3 times higher than in developed countries. Regions with the highest age-adjusted incidence rates are; East Asia (27.6-36.6 per 100,000 of population), sub-Saharan Africa (20.8-38.1 per 100,000 of population) and some countries in West Africa (30-48 per 100,00 of population). The areas of lowest liver cancer risk are reported to be Northern Europe, Australia, New Zealand and the Caucasian populations of North and South America with rates for males below 5.0 per 100,00 of population.

[5] http://www.health.govt.nz/your-health/conditions-and-treatments/diseases-and-illnesses/hepatitis-b accessed 24 February 2014

[6] http://www.health.govt.nz/publication/cancer-historical-summary-1948-2009 accessed 5 August 2013

2.4.2.2 Epidemiological studies

A number of epidemiological studies have been conducted, and continue to be conducted, mainly to examine links between PLC or HCC, hepatitis B and aflatoxin exposure. While PLC may involve cell types other than the hepatocytes, it can generally be assumed that PLC and HCC are synonymous. HBsAg refers to a surface antigen of the hepatitis B virus (HBV). These studies are summarised below.

Egypt. A case-control study was carried out to compare 80 HCC cases (average age 52.9 years) and 20 healthy controls (average age 53.2 years) (Abdel-Wahab *et al.*, 2008). Serum AFB_1 concentration were significant higher ($p<0.0001$) in cases (32.5 μg/L compared to 7.3 μg/L). AFB_1 serum concentrations were significantly higher in male, rural residents and farmers ($p<0.05$). It should be noted that the number of controls is rather small for a case-control study.

A cohort study including 50 healthy lactating mothers and their exclusively breast fed infants found aflatoxin in the serum of 24 mothers (Hassan *et al.*, 2006). The mean concentration in maternal serum was 8.9 μg/L, while in maternal milk the mean was 1.9 μg/L and in infant serum was 1.8 μg/L. The presence of aflatoxin was not associated with any renal or hepatic dysfunction. This is probably not surprising as the concentrations of aflatoxin found are only slightly higher than those found in the controls in the Egyptian case-control study summarised in the previous paragraph.

Gambia. HCC is often preceded by development of cirrhosis of the liver. A case-control study of confirmed cirrhosis cases in the Gambia, West Africa looked at associations between environmental and infectious factors and cirrhosis (Kuniholm *et al.*, 2008). HBsAg seropositivity (odds ratio 8.0, 95% CI 4.4-14.7) and hepatitis C (odds ratio 3.3, 95% CI 1.2-9.5) were associated with a significant increase in cirrhosis risk. Aflatoxin exposure, as indicated by the presence of the codon 249 *TP53* mutation in plasma, (odds ratio 3.8, 95% CI 1.5-9.6) or high lifetime peanut intake (odds ratio 2.8, 95% CI 1.1-7.7) were also associated with an increased cirrhosis risk. Aflatoxin exposure and hepatitis B virus exposure appeared to be synergistic risk factors for cirrhosis.

Iran. An ecological study was carried out to determine whether the aflatoxin content of wheat flour may be a risk factor for oesophageal cancer (OC) in the Golestan region of Iran (Ghasemi-Kebria *et al.*, 2013). The Golestan region was divided into high and low-OC risk areas. The mean total aflatoxin concentration of wheat flour from silos in the high-OC risk area was 2.52 μg/kg, while the low-OC risk area had mean wheat flour aflatoxins concentrations of 1.55 μg/kg. Wheat flours from high and low-OC areas were significantly different ($p<0.05$) with respect to total aflatoxin, AFB_1 and AFG_2 concentration, but not AFB_2 or AFG_1 concentration.

Taiwan. A case-control study was conducted to examine the role of aflatoxin exposure in HCC (Wu *et al.*, 2009). AFB_1 biomarkers were examined in blood (AFB_1-albumin) and urine (AFB_1 and metabolites) of cases (n = 230) and controls (n = 1052). Odds ratios for HCC cases having aflatoxin biomarkers above the mean level were 1.54 (95^{th} percentile confidence interval 1.01-2.36) and 1.76 (95^{th} percentile confidence interval 1.18-2.58) for blood and

urinary biomarkers, respectively. There was a statistically significant increased risk of HCC with increasing urinary biomarker levels for HBV-negative cases, but not for other combinations of biomarker and HBV status.

Meta-analysis. A systematic review and meta-analysis was carried out to determine the population attributable risk (PAR) of aflatoxin-related HCC (Liu *et al.*, 2012). Seventeen studies were identified from China, Taiwan and sub-Saharan Africa, including 1680 HCC cases and 3052 controls. The overall PAR was 17% (95% CI 14-19%), with higher PAR for hepatitis B positive (HBV+, 21%), than HBV- (8.8%) cases. The PAR appears to have decreased over time in certain Chinese and Taiwanese populations, in response to public health interventions.

2.4.2.3 Risk assessments

Africa. Using JECFA cancer potency values, an assumed hepatitis B virus infection (HBV) rate of 25% and exposure estimates for aflatoxins from several African countries (Kenya, Ghana, Botswana, Benin, Tanzania, Gambia) cancer risk estimates in the range 0.1 to 70.1 cancers per year per 100,000 population were estimated (Shephard, 2008). MoE estimates were also calculated using rodent $BMDL_{10}$ and human $BMDL_{10}$ and $BMDL_1$ values derived by EFSA (EFSA, 2007). MoEs ranged from 0.1 to 621, depending on the country and the benchmark dose used.

Brazil. Using JECFA cancer potency values, an excess cancer risk of 0.073-0.075 cancers per year per 100,000 population was determined for the total Brazilian population (Andrade *et al.*, 2012). High consumers were at greater risk (0.18-0.31 cancers per year per 100,000 population). MoEs (rodent $BMDL_{10}$) were 25-26 and 6-10, respectively for total population and high consumers.

China. Separate estimates of cancer risk due to AFB_1 exposure were made for each of 4 commodities, but not for the 4 commodities combined (Ding *et al.*, 2012). Using JECFA cancer potency values and a HBV rate of 8.6%, cancer risk estimates ranged from 0.003-0.17 cancers per year per 100,000 population (peanuts) to 0.15-9.13 cancer per year per 100,000 population (maize and maize-based foods). MoE estimates ranged from 0.3-18.1 (maize and maize-based foods with human $BMDL_1$) to 154-7909 (peanuts with human $BMDL_{10}$).

Cancer risk due to exposure to AFM_1 from consumption of milk and milk products was estimated using JECFA cancer potency values (Guo *et al.*, 2013b). At the population mean level of exposure the cancer risk was 0.000029 cancers per year per 100,000 population. This compares to an incidence of liver cancer in the Chinese population of 24.6 cancers per year per 100,000 population

European Union. Using JECFA cancer potency values, excess cancer risk estimates were derived for 2 GEMS cluster diets; cluster F, including the Baltic countries, and cluster M, including the Mediterranean countries (EFSA, 2007). These clusters represent the low and high extremes, respectively, for aflatoxin exposure in Europe. Two values for the prevalence of HBV were also considered; 0.2% and 7%. The cancer risk for the low exposure, low HBV group was 0.0037-0.0073 cancers per year per 100,000 population, while the risk for the high exposure, high HBV group was 0.025-0.059 cancers per year per 100,000 population. A range of MoE approaches were also applied, with margins ranging from 40-93 for the ratio of

cluster M exposure to human $BMDL_1$ to 1270-2470 for the ratio of cluster F exposure to human $BMDL_{10}$.

Malaysia. Using JECFA cancer potency values and a HBV rate of 13%, an excess cancer risk estimate of 0.47 cancer per year per 100,000 population was derived (Othman and Keat, 2006). A later study, using the same cancer potency figure and a HBV rate of 25%, derived excess cancer risk estimates of 0.03 and 0.73 cancers per year per 100,000 population for mean and high (95^{th} percentile) consumers, respectively (Leong *et al.*, 2011). These estimates were compared to the incidence rate for PLC in Malaysia of 4.9 per 100,000 population. A $BMDL_{10}$ value of 305 ng/kg body weight/day was used to derive MoEs of 847 and 34 for mean and high consumers, respectively.

Japan. Using JECFA cancer potency values and a HBV rate of 1%, cancer risk estimates were calculated, based on 90^{th}, 95^{th} and 99.9^{th} percentile estimates of dietary AFB_1 exposure (Sugita-Konishi *et al.*, 2010). The 95^{th} percentile estimates were 0.0004-0.0005 cancer per year per 100,000 population.

International. Liu and Wu (2010) used published aflatoxin exposure estimates, HBV rates and JECFA cancer potency values to estimate the global burden of liver cancer due to aflatoxin exposure. The global estimate was 25,200-155,000 cases of HCC per annum due to aflatoxin exposure, with the majority of cases in Africa (40%), South Asia (27%) and the Western Pacific region (20%, includes China).

The Codex Committee on Contaminants in Food (CCCF) derived estimates of aflatoxin exposure from consumption of cereals (wheat, maize, rice, sorghum) using the GEMS/Food cluster diets and upper bound mean estimates of aflatoxin concentrations in cereal, based on published data (Codex Committee on Contaminants in Food, 2013b). The EFSA $BMDL_{10}$ derived from rodent studies (170 ng/kg body weight/day, EFSA (2007)) was used to estimate margins of exposure for each cluster. MoEs were in the range 0.3-7.8.

2.5 Risk Management Information

2.5.1 Relevant food controls: New Zealand

2.5.1.1 Establishment of regulatory limits

The Australia New Zealand Food Standards Code specifies a maximum limit for total aflatoxins in peanuts and tree nuts of 0.015 mg/kg (15 µg/kg), but includes no provisions for other foods.

The New Zealand Food (Prescribed Foods) Standard 2007 prescribes imported peanut and pistachio nuts, peanut butter and nutmeg; requiring their testing at time of import for the presence of mycotoxins (fungal toxins).[7]

[7] http://www.foodsafety.govt.nz/elibrary/industry/prescribed-food-standard/Food_Prescribed-Amends_Prohibited.pdf accessed 27 February 2014

2.5.2 Relevant food controls: overseas

2.5.2.1 Establishment of regulatory limits

In 2003, approximately 100 countries reported having mycotoxin regulations in place (Van Egmond and Jonker, 2004). Aflatoxins are by far the most commonly regulated mycotoxins. Regulatory limits may be expressed in terms of AFB_1, in terms of total aflatoxins or occasionally in terms of the sum of AFB_1 and AFG_1.

For regulatory limits expressed in terms of AFB_1 limits range from 1 to 20 µg/kg, with the most common limit being 2 µg/kg. This limit applies to most foods for direct human consumption within EU and associated countries (29 countries). The next most common limit for AFB_1 is 5 µg/kg (21 countries).

The range of regulatory limits for total aflatoxins found was 0-35 µg/kg, with a median of 10 µg/kg (Van Egmond and Jonker, 2004). The EU limit of 2 µg/kg for AFB_1 is also expressed as 4 µg/kg total aflatoxins and this was the most common regulatory limit for total aflatoxins (29 countries), followed by 20 µg/kg (17 countries).

Regulatory limits for AFM_1 were reported from 60 countries with the most common limit being 0.05 µg/kg (34 countries, including EU and associated countries), followed by 0.5 µg/kg (22 countries) (Van Egmond and Jonker, 2004).

In 2006, the European Commission issued new regulations for maximum levels of certain contaminants, including mycotoxins, in food (European Commission, 2006b). With respect to aflatoxins, these regulations included specific maximum limits for foods formulated for infants, specifically:

- Processed cereal-based foods and baby foods for infants and young children (ML AFB_1 = 0.1 µg/kg)
- Infant formulae and follow-on formulae, including infant milk and follow-on milk (ML AFM_1 = 0.025 µg/kg)
- Dietary foods for special medical purposes intended specifically for infants (ML AFB_1 = 0.1 µg/kg and AFM_1 = 0.025 µg/kg)

JECFA considered the impact of various maximum limits (4, 8, 10, 15, 20 µg/kg) for total aflatoxins in almonds, Brazil nuts, hazelnuts, pistachios and dried figs (JECFA, 2008). The committee concluded that in most parts of the world, as represented by GEMS/Food cluster diets, these foods contribute only a small proportion (<5%) of total aflatoxin exposure. Enforcing a maximum limit of 20 µg/kg for these foods would have some impact on dietary aflatoxin exposure, in the regions with highest consumption of these foods, but enforcement of a lower maximum limit would have little additional impact on exposure.

EFSA was asked to review the impact on dietary aflatoxin exposure of increasing the EU maximum limit for aflatoxins in dried figs (2 µg/kg for AFB_1 and 4 µg/kg for total aflatoxins) to a potential maximum of 6 µg/kg for AFB_1 and 10 µg/kg for total aflatoxins (EFSA, 2012b). It was concluded that this change would have a marginal impact on dietary aflatoxin exposure, with total aflatoxin exposure for the adult population estimated to increase by 0.15-0.26%.

The Codex Committee on Contaminants in Food (CCCF) have prepared a discussion document on aflatoxins in cereals that recommends (Codex Committee on Contaminants in Food, 2013b):

1. The Committee should request the JECFA to conduct an assessment on the effects of various MLs (maximum limits) on AF exposure, and the risk from the consumption of AF contaminated cereals and cereal products.
2. Member countries are encouraged to submit raw data to allow the assessment by the JECFA on AF contamination in rice, corn, sorghum, wheat, rye, oat and barley. These data should be submitted as complete datasets with results of individual samples and not data presented in summarized or aggregate form.

2.5.2.2 Codes of Practice

Codes of Practice (COPs) for prevention and reduction of aflatoxin contamination have been formulated by the Codex Alimentarius Commission (Codex). In the previous version of this risk profile reference was provided to COPs for peanuts, tree nuts, feed for milk producing animals and a general COP for prevention and reduction of mycotoxin contamination of cereals. Since that time, Codex have added a COP for prevention and reduction of aflatoxin contamination in dried figs.[8]

The Codex Committee on Contaminants in Foods (CCCF) are currently working on an annex to the COP for prevention and reduction of mycotoxin contamination of cereals, to cover prevention and reduction of aflatoxins (and OTA) in sorghum and sorghum products (Codex Committee on Contaminants in Food, 2013d). The proposed annex includes aspects related to planting, harvest, transport, storage, processing, and packaging and marketing.

2.5.2.3 Management of AF formation in crops

The potential for genetic modification to reduce or mitigate mycotoxin contamination of crops has been reviewed (Cary *et al.*, 2009). Three approaches are outlined:

- Detoxification of mycotoxins;
- Resistance to fungal growth through pathogenesis-related proteins; and
- Resistance to fungal growth through antifungal peptides.

A gene for RIP-1, a ribosome inactivating protein from maize, was inserted into 2 peanut cultivars (Weissinger *et al.*, 2007). Cotyledons of transgenic plants inoculated with *A. flavus* showed a statistically significant reduction in AFB_1 levels compared to control plants (Cary *et al.*, 2009).

Considerable recent research has been carried out on the use of competing microflora to control infection with aflatoxin-producing fungi and consequent aflatoxin production. Biocontrol agents may be non-aflatoxigenic strains of *A. flavus* or *A. parasiticus* (Al-Othman *et al.*, 2013; Mohale *et al.*, 2013; Rosada *et al.*, 2013) or unrelated organisms (Alaniz Zanon *et al.*, 2013; Kalantari *et al.*, 2012; Niknejad *et al.*, 2012). It should be noted that, due to the

[8] http://www.codexalimentarius.org/download/standards/11025/CXP_065e.pdf Accessed 28 November 2013

huge interest in this control approach, the references given here should be viewed as representative only.

2.5.2.4 Interventions

A variety of absorbent clays have been used to ameliorate the impact of mycotoxins on animal health. One of these clays, NovaSil, is undergoing clinical trials for its potential to bind dietary aflatoxins in humans, without impacting nutritional components of the diet (Phillips *et al.*, 2008). Daily doses of NovaSil (1.5 or 3 g/day) were shown to decrease serum AFB_1-albumin adduct levels after 3 months (Wang *et al.*, 2008). However, the decreases were not dose-dependent and after 4 months there was no significant difference between either of the dose groups and the control group (placebo).

Cost-effectiveness analysis was used to compare two interventions for the control of aflatoxin contamination in Africa and reduction of associated cases of HCC (Wu and Khlangwiset, 2010). The interventions were; application of atoxigenic strains of *A. flavus* to maize (competitive exclusion) in Nigeria, and application of a post-harvest package to peanuts (sorting, drying, storage and insect control) in Guinea. Both interventions were found to be very cost-effective (CER, cost-effectiveness ratio >1). The CER for competitive exclusion was in the range 5.1-24.8, while that for the post-harvest package was in the range 0.21-2.08.

2.5.3 Influence of food processing on aflatoxin levels

2.5.3.1 Traditional processing

Analysis of the aflatoxin content and processing practices of dried cassava chips from 90 Ugandan households found that drying chips on bare ground, storing by heaping on bare floor and storage in old containers were practices associated with aflatoxin presence (Kaaya and Eboku, 2010). Drying on tarpaulins was negatively associated with aflatoxin content.

The production of muthokoi (a traditional Kenyan dehulled maize dish) was examined for its impact on aflatoxin contamination (Mutungi *et al.*, 2008). Dehulling resulted in a mean reduction in aflatoxin content of 47%, while soaking the maize in various solutions (alkaline mineral salt, sodium hypochlorite or ammonium persulphate) for 6 or 14 hours resulted in further decreases of 28 to 72%. Boiling the resultant muthokoi in alkaline mineral salt solution for 150 minutes decreased aflatoxin content by a further 80-93%.

Analysis of aflatoxin content during traditional harvesting and processing of hazelnuts in Turkey found that the only factor associated with aflatoxin content was the nuts coming in contact with the ground during harvest (Özay *et al.*, 2008). Harvesting nuts onto canvas by shaking the tree avoided this problem and was implemented as an industry practice.

2.5.3.2 Cooking

A range of studies suggest that substantial reductions in the aflatoxin content of foods can be achieved by thermal treatment.

Heating dried wheat at 150 or 200ºC resulted in decreases in the AFB_1 content of 50 and 90%, respectively (Hwang and Lee, 2006). A greater reduction was achieved when the

moisture content of the wheat was increased by 10%. Processing of the wheat into Sujebi (a soup containing wheat flakes) or steamed bread resulted in decreases in the AFB_1 content of 71 and 43%, respectively.

Domestic cooking of rice (steaming) was reported to result in a 93.8% reduction in the AFB_1 concentration (Sakuma *et al.*, 2013).

Extrusion cooking of rice meal was shown to decrease aflatoxin content by 51 to 95% (Castells *et al.*, 2006). While patterns of reduction differed between different aflatoxins, in general higher barrel temperatures, lower residence times of higher meal moisture content resulted in greater reductions in aflatoxin content.

The impact of extrusion cooking on aflatoxins in peanut meal was examined (Saalia and Phillips, 2011). For naturally-contaminated peanut meal a maximum reduction in aflatoxin content of 59% was achieved with a high meal moisture content (35%).

2.5.3.3 Cheesemaking

During production of traditional Iranian cheese, AFM_1 was found to preferentially partition into the curd, resulting in concentrations of AFM_1 in the cheese greater than those in milk (Kamkar *et al.*, 2008).

2.5.3.4 Brewing

Transfer of AFB_1 from brewing raw material (maize grit, malted barley) to finished beer was examined (Pietri *et al.*, 2010). Levels of AFB_1 in raw ingredients were in the range 0.3 to 14.9 µg/kg, while in finished beer concentrations were 0.0015-0.022 µg/L. On average, 1.5% of the AFB_1 present in ingredients was transferred to beer. The low level of transfer was ascribed to the low aqueous solubility of AFB_1.

2.6 Conclusions

2.6.1 Description of risks to New Zealand consumers

There is consistent epidemiological evidence linking aflatoxin exposure to human PLC. Plausible mechanisms for carcinogenesis have been proposed and there is some biochemical data to support these hypotheses. The cancer risk due to aflatoxin is substantially increased in the presence of other liver diseases (hepatitis B, hepatitis C) and there are some questions concerning aflatoxin exposure as an independent risk factor.

Studies indicate that aflatoxigenic *Aspergillus* species are not present in New Zealand crops (Sayer and Lauren, 1991) and it is generally believed that these toxins only form in tropical or sub-tropical situations. The major sources of aflatoxin exposure for the general New Zealand population have been shown to be imported foods; spices and nuts, with peanuts and peanut butter being the major nut foods contributing.

Estimates of the aflatoxin exposure of New Zealanders suggest that it is at the lower end of the range of international estimates, with mean exposure estimates in the range 0.09-0.36 ng/kg body weight/day for total aflatoxins or 0.07-0.31 ng/kg body weight/day for AFB_1.

Based on the consensus carcinogenic potency values from epidemiological studies adopted by JECFA (0.01 cancers/year per 100,000 population per ng aflatoxin/kg body weight/day for HbsAg negative individuals), this level of exposure equates to a mean excess lifetime liver cancer risk of 0.0015-0.0022 cancers/100,000 population/year compared to current rates of liver cancer in New Zealand of 3-4/100,000/year. These estimates include consideration of the risk for hepatitis B positive individuals.

2.6.2 Commentary on risk management options

The current import monitoring regime is the only feasible risk management strategy available to New Zealand and assessments carried out suggest that the current approach offers a high level of protection with respect to importation of aflatoxin-contaminated peanuts and pistachios. No controls exist for aflatoxin contamination of other imported foods, such as spices.

2.6.3 Data gaps

A wider survey of aflatoxins in spices imported into New Zealand would give more statistical certainty to the finding of the limited surveys carried out to date (Cressey and Jones, 2009). Given that New Zealand imports approximately half their wheat requirements, verification that this wheat is not markedly contaminated with aflatoxins would provide further assurance that New Zealanders' exposure to aflatoxins was low. Information on aflatoxin contamination in animal feed would also provide important information for assessment of aflatoxin exposure in New Zealand through foods of animal origin.

3 OCHRATOXIN A

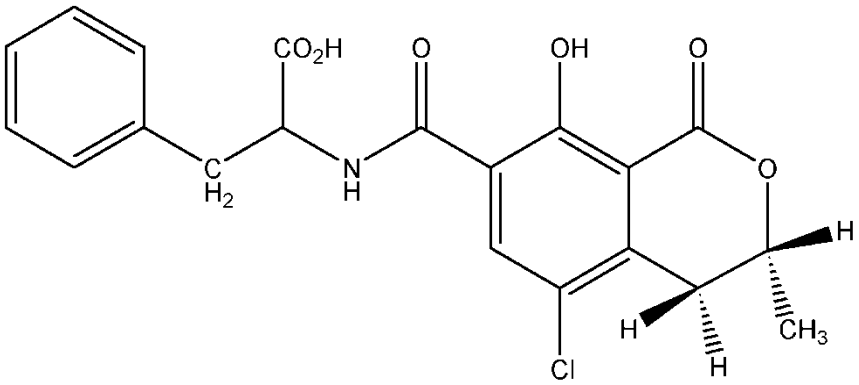
3.1 Hazard identification

Ochratoxin A (OTA), (R)-N-[(5chloro-3,4-dihydro-8-hydroxy-3-methyl-1-oxo-1H-2-benzopyran-7-yl)-carbonyl]-L-phenylalanine, is produced by *Aspergillus ochraceus* and a related *Aspergillus* species, *A. carbonarius*, as well as some isolates of *A. niger*, and by *Penicillium verrucosum* (JECFA, 2001d). These organisms differ in their geographical distribution and ecological niche, in the commodities affected, and at the point at which they are likely to infect commodities.

3.1.1 Structure and nomenclature

OTA contains a chlorinated isocoumarin moiety linked via a carboxyl group to L-phenylalanine (Figure 3). Ochratoxin B (OTB; a dechlorinated analogue of OTA) and ochratoxin C (OTC; an ethyl ester of OTA) have also been detected, but OTA is by far the major contaminant found in crop plants (Walker, 1999).

Figure 3: Structure of OTA



3.1.2 Occurrence

P. verrucosum is a cool climate organism (0-31˚C, optimum 20˚C), occurring only in cool temperate regions, and is able to grow at water activities as low as 0.8 (Pitt and Hocking, 1997). It is the source of OTA formation in stored cereals and cereal products in European countries and Canada. Due to the high stability of OTA this can also result in the presence of OTA in animals fed contaminated cereals. *P. verrucosum* does not occur in the tropics (JECFA, 2001d).

A. ochraceus grows at moderate temperatures (8-37˚C, optimum 24-31˚C) and at water activities above 0.8 (optimum 0.95-0.99) (Pitt and Hocking, 1997). It occurs occasionally on a wide range of stored food products, but is seldom the cause of substantial concentrations of OTA (JECFA, 2001d).

A. carbonarius grows at high temperatures (max 40˚C, optimum 32-35˚C) and is associated with maturing fruit, particularly grapes. It is the major source of OTA in fresh grapes, dried vine fruits and wine (JECFA, 2001d).

OTA contamination is principally found in cereals, but can also occur in coffee, cocoa, nuts, dried vine fruits, grape juice and wine, beer, and pork and pork products made from animals fed OTA contaminated feed (Walker, 1999).

Sayer and Lauren (1991) did not report isolation of any of these OTA-forming fungal species from New Zealand grain sampled at harvest. However, no information was found on occurrence of these fungal species on stored grain in New Zealand. Similarly, no information was found on *Aspergillus* infection of grapes or other fruits in New Zealand.

3.2 Hazard Characterisation: Adverse Health Effects

3.2.1 Conditions

OTA is principally nephrotoxic. Consumption of OTA-contaminated barley in Europe has been associated with a major renal disease of pigs, known as porcine nephropathy (Council for Agriculture and Technology, 2003).

A case of acute renal failure (ARF) possibly associated with inhalation of OTA has been reported (Di Paolo *et al.*, 1993). After spending 8 hours in a granary that had been closed for several months, a farmer and his wife suffered temporary respiratory distress. The woman developed nonoliguric ARF 24 hours later and biopsy revealed tubulonecrosis which healed in 24 days. Toxic substances were not found, but a strain of *A. ochraceus*, capable of producing ochratoxin, was isolated from the wheat.

OTA has been strongly implicated in a human kidney disease known as Balkan endemic nephropathy (BEN). OTA is common in foods from BEN-affected areas (former Yugoslavia, Bulgaria and Romania). Further weight is added to this hypothesis by the fact that OTA is also carcinogenic in rats and mice and patients with BEN frequently exhibit kidney tumours (urothelial urinary tract tumours) (Council for Agriculture and Technology, 2003; Pfohl-Leszkowicz *et al.*, 2002). The disease has a slow progressive course leading to renal failure. While populations in BEN unaffected areas are also exposed to OTA, there is evidence to suggest that exposure frequency and blood OTA levels are higher in those suffering BEN (Pfohl-Leszkowicz *et al.*, 2002). However, the kidney tumours apparent in BEN cases (upper urothelial) are different to those observed in OTA-exposed rodents (renal tubule) and there is evidence that aristolochic acid, rather than OTA, may be the causative agent in BEN (Haighton *et al.*, 2012; Mally *et al.*, 2007; Stefanovic *et al.*, 2011). Exposure to aristolochic acid has been hypothesised to be due to contamination of wheat with seeds of the plant *Aristolochia clematitis* (Pepeljnjak and Šegvić Klarić, 2010). Some recent reviews have argued the opposite position; that the evidence supports a causative role of OTA, not aristolochic acid (Pepeljnjak and Šegvić Klarić, 2010; Pfohl-Leszkowicz, 2009)

3.2.2 Toxicity

3.2.2.1 Acute toxicity

The LD_{50} following oral administration in laboratory animals ranges from 0.2 mg/kg body weight in dogs to 46-58 mg/kg body weight in mice (JECFA, 2001d). In rats, neonates are more sensitive than adults (JECFA, 2001d), while females are more sensitive than males (Pfohl-Leszkowicz *et al.*, 2002).

3.2.2.2 Chronic toxicity

OTA is nephrotoxic in all mammalian species tested, with the main target being the renal proximal tubule, where OTA exerts both cytotoxic and carcinogenic effects (JECFA, 2001d). In rodents, the doses causing carcinogenicity were higher than those resulting in nephrotoxicity.

OTA is genotoxic both *in vitro* and *in vivo*, however the mechanism is uncertain (JECFA, 2001d). There is evidence that the genotoxicity of OTA is threshold-based (there is a level of exposure below which it is not genotoxic) (EFSA, 2006; Haighton *et al.*, 2012). It has also been suggested that earlier studies using gavage administration optimised conditions for tumour formation, compared to administration in the diet (Mantle and Kulinskaya, 2010). The mechanism by which OTA exerts its genotoxicity is still contentious and research is ongoing (Hibi *et al.*, 2013; Mally *et al.*, 2007; Mally, 2012; Marin-Kuan *et al.*, 2008).

OTA can cross the placenta and is embryotoxic and teratogenic in rodent species. It is also immunosuppressive in rodents, inhibiting proliferation of B and T lymphocytes. All of these effects occur only at doses much higher than those causing nephrotoxicity (JECFA, 2001d).

3.2.3 Toxicological assessment

JECFA reassessed OTA at their 68th meeting (JECFA, 2008). After considering a number of new toxicological studies, the committee confirmed their previous assessment of minimal renal changes in the pig, at 8 μg/kg body weight/day, as the critical effect for risk assessment. JECFA were particularly concerned with elucidating the mechanism by which OTA causes renal tumours. A number of genotoxic and non-genotoxic mechanism have been proposed and evidence supporting these was reviewed. JECFA concluded that a number of non-genotoxic mechanisms may be contributing to tumour formation. JECFA confirmed the existing Provisional Tolerable Weekly Intake (PTWI) of 100 ng/kg body weight/week.

EFSA reviewed recent toxicological information on OTA, but concluded that the information was not relevant to the overall assessment of risk and confirmed their earlier Tolerable Weekly Intake (TWI) of 120 ng/kg body weight/week (EFSA, 2010).

A Canadian risk assessment highlighted limitations in the 90-day pig study used as the basis for the JECFA PTWI and the EFSA TWI (Kuiper-Goodman *et al.*, 2010). They derived a Negligible Cancer Risk Intake (NCRI) of 4 ng/kg body weight/day (28 ng/kg body weight/week), derived from tumour incidence in rats and using an excess cancer risk level of 1:100,000.

IARC have not reassessed OTA since the previous version of this risk profile. IARC have classified OTA as a possible human carcinogen (Group 2B; IARC, 1993).

Benchmark doses (BMD) have been determined for OTA (Muri *et al.*, 2009a). BMDs were calculated at the 1% and 5% levels (doses causing a 1 or 5% increase in the incidence of kidney adenomas or kidney carcinomas in rats). Associated BMD_1 or BMD_5 and BMDL (lower 95th percentile limit of the respect BMD estimate) for these endpoints and by rat gender are shown in Table 5.

Table 5: Benchmark doses for OTA

Endpoint	Benchmark response level (%)	Gender	BMD (µg/kg body weight)	BMDL (µg/kg body weight)
Kidney adenoma	1	M	24	17
	1	F	135	79
	5	M	86	68
	5	F	198	142
Kidney carcinoma	1	M	46	43
	1	F	67	62
	5	M	53	50
	5	F	88	78

M = male F = female BMD = benchmark dose BMDL = benchmark dose lower 95th percentile confidence limit

JECFA also calculated benchmark doses for OTA, based on total renal tumour incidence in rats (JECFA, 2008). Depending on the model used, BMD_{10} values were in the range 18-32 µg/kg body weight/day and $BMDL_{10}$ were in the range 15-25 µg/kg body weight/day. JECFA noted that the benchmark doses calculated by this method were higher than the Lowest Observed Effect Level (LOEL) used to derive the PTWI (8 µg/kg body weight/day).

3.2.2 Metabolites and their relative toxicities

OTA may co-occur in foods with a non-chlorinated analogue, OTB (EFSA, 2006). Studies in rats indicate that, while OTB may have similar cytotoxicity to OTA, it is metabolised and eliminated much more quickly and completely (Mally and Dekant, 2005). Consequently, the nephrotoxicity of OTB is much lower than OTA. Studies in cell lines and rodents suggest that OTB may be about an order of magnitude less toxic than OTA (Xiao *et al.*, 1996).

OTC, containing the chloro substituent, but having an ethyl substituent at the carboxyl group, and methyl-OTA (MeOTA), having a methyl substituent at the carboxyl group, have been reported in wine (Remiro *et al.*, 2010). Some studies have suggested that OTC has similar toxicity to OTA (Xiao *et al.*, 1996), while no toxicity studies have considered MeOTA.

A study of red wines found similar levels of OTA and OTB (median concentrations 0.0063 and 0.0076 µg/L, respectively), while OTC and MeOTA were present at much lower concentrations (median concentrations 0.0006 and 0.0002 µg/L, respectively) (Remiro *et al.*, 2010). A further study by the same group found similar results for 96 wines from a range of

Mediterranean countries (Remiro *et al.*, 2013). Methyl- and ethyl-OTB were also detected, but at much lower concentrations than the parent compound.

3.3 Exposure Assessment

3.3.1 OTA in the New Zealand food supply

Since the previous risk profile, two significant surveys of OTA in the New Zealand food supply have been carried out (Cressey and Jones, 2009; 2011). In addition, an unpublished study by ESR analysed OTA in a range of consumer foods (Darren Saunders, ESR, personal communication). Results are summarised in Table 6.

Table 6: OTA in New Zealand foods

Product type	Year of survey	Analytical LOD (µg/kg)	Number analysed	No. samples with OTA (%)	Range of positives (µg/kg)[1]
Bread, various	2007[2]	0.2	12	2 (17)	(0.20)-2.09
Bread, mixed grain	2011	0.2	8	3 (38)	(0.30)-(0.41)
Bread, wheatmeal	2011	0.2	8	2 (25)	(0.45)-(0.52)
Bread, white	2011	0.2	8	2 (25)	(0.40)-(0.55)
Biscuits, chocolate	2011	0.2	8	0 (0)	
Biscuits, cracker	2011	0.2	8	0 (0)	
Biscuits, sweet plain	2011	0.2	8	2 (25)	(0.20)-(0.42)
Cornflakes	2007[2]	0.2	6	1 (17)	0.53
Cornflakes	2011	0.2	8	0 (0)	
Bran flake cereal	2011	0.2	8	4 (50)	(0.20)-2.99
Wheat biscuit cereal	2011	0.2	8	0 (0)	
Muesli	2007[2]	0.2	9	2 (22)	0.92-2.85
Muesli	2011	0.2	8	3 (38)	(0.24)-1.42
Oats, rolled	2011	0.2	8	0 (0)	
Cake, plain	2011	0.2	8	0 (0)	
Muffin	2011	0.2	8	1 (13)	(0.33)
Noodles, instant (cooked)	2011	0.2	8	1 (13)	0.79
Pasta, dried (cooked)	2011	0.2	8	1 (13)	(0.52)
Rice, white (cooked)	2011	0.2	8	0 (0)	
Spaghetti in sauce, canned	2011	0.2	8	0 (0)	
Snack bars	2011	0.2	8	2 (25)	(0.21)-(0.30)
Snacks, flavoured	2011	0.2	8	0 (0)	
Pizza	2011	0.2	8	0 (0)	
Infant weaning food, cereal based	2011	0.2	8	0 (0)	
Coffee, various	2007[2,3]	0.2	8	5 (63)	(0.28)-1.48
Coffee, brewed	2011	0.05	8	1 (13)	(0.09)
Coffee, instant	2011	0.05	8	0 (0)	

Product type	Year of survey	Analytical LOD (µg/kg)	Number analysed	No. samples with OTA (%)	Range of positives (µg/kg)[1]
Wine, still red	2011	0.05	8	0 (0)	
Wine, still white	2011	0.05	8	0 (0)	
Beer	2011	0.05	8	0 (0)	
Dried figs	2007[2]	0.2	2	0 (0)	
Dried figs	2008-2009	0.2	10	1 (10)	73
Dried vine fruits[4]	2007[2]	0.2	3	2 (67)	(0.28)-0.74
Dried vine fruits[4]	2008-2009	0.2	10	5 (50)	(0.2)-(0.6)
Dried apricots	2007[2]	0.2	2	0 (0)	
Dried apricots	2008-2009	0.2	10	0 (0)	
Dates	2007[2]	0.2	2	1 (50)	1.02
Dates	2008-2009	0.2	5	0 (0)	
Prunes	2008-2009	0.2	5	0 (0)	
Pepper (black, white)	2008-2009	0.2	5	4 (80)	(0.7)-8.3
Chilli powder	2007[2]	0.2	4	4 (100)	(0.23)-39.9
Chilli powder	2008-2009	0.2	5	4 (80)	1.3-6.3
Cayenne pepper	2007[2]	0.2	2	2 (100)	0.83-2.74
Cayenne pepper	2008-2009	0.2	5	5 (100)	1.8-7.3
Paprika	2007[2]	0.2	4	4 (100)	13.3-50.6
Paprika	2008-2009	0.2	5	5 (100)	15-103
Ginger, ground	2007[2]	0.2	2	2 (100)	0.6-4.5
Ginger, ground	2008-2009	0.2	5	4 (80)	(0.5)-2.1
Curry powder	2008-2009	0.2	5	5 (100)	(0.2)-3.5
Nutmeg	2007[2]	0.2	2	2 (100)	4.3-23.5

LOD = limit of detection

[1] Concentration figures in brackets are indicative and relate to analytical results that were above the LOD, but below the limit of quantitation

[2] From an unpublished study (Darren Saunders, ESR, personal communication)

[3] In this study, coffee was analysed as dry beans or coffee powder. Instant coffee typically involves a dilution factor of the order of 100 (2 g instant coffee to 200 ml water)

[4] Raisins, sultanas and currants

A study of mycotoxin contamination in animal feed in Asia and Oceania reportedly included samples sourced from New Zealand (Borutova *et al.*, 2012). However, results were not reported separately by country of origin.

3.3.2 OTA in the Australian food supply

The 23rd Australian Total Diet Survey analysed bread, biscuits, rolled oats, pasta, meat pies, baked beans, chocolate, coffee, dried apricots, edible oils (canola and olive), soy beverage, sultanas and red wine for OTA (Food Standards Australia New Zealand, 2011). OTA was not detected in any samples. However, the method used for analyses and the LOD for the method were not reported.

3.3.2 Overseas Context

An enormous body of information is available on the incidence and levels of OTA in a variety of commodities and processed foods overseas. However, given that a good body of New Zealand data is now available, overseas data have only been summarised where novel

foods have been identified as sources of OTA or where data may be relevant to food imported into New Zealand.

For many of the foods discussed in the following sections, the occurrence of OTA varies significantly between different studies. It is worth noting that there is increasing evidence that tree and ground nuts may be contaminated with OTA, while the feeding of OTA-contaminated feed to pigs can result in elevated levels of OTA in meat products prepared from pigmeat.

3.3.2.1 Plant-based foods

Fruit juice

While OTA has been previously detected on grapes and in grape juice and wine, apple juice is usually considered to be more likely to be contaminated with patulin. A study in Saudi Arabia detected OTA in 15 of 51 apple juice samples, with concentrations as high as 200 μg/L (Al-Hazmi, 2010). Saudi Arabia does not have a domestic apple juice industry and all samples were imported as ready-prepared juice or made up locally from imported juice concentrate.

A study in Hong Kong detected OTA in 2 of 12 'juice drinks', with a maximum concentration of 0.22 μg/kg (Chung *et al.*, 2009).

Liquorice

OTA was been reported to occur at high concentrations in liquorice root and to persist through into liquorice confectionery (Ariño *et al.*, 2007b). All samples analysed were found to contain OTA (limit of quantification (LOQ) = 0.5 μg/kg), with 15 samples of dried liquorice root containing mean levels of OTA of 63.6 μg/kg (maximum 252.8 g/kg), while liquorice confectionery (n = 4) had a mean OTA content of 3.8 μg/kg (maximum 8.2 μg/kg). A further study of OTA in liquorice confectionery detected OTA (LOQ = 0.5 μg/kg) in 23 of 44 samples, with a maximum concentration of 12 μg/kg (Herrera *et al.*, 2009).

Cocoa and chocolate

While unroasted cocoa beans were shown to contain OTA at concentrations up to 10.8 μg/kg, the contamination tended to concentrate in the defatted solids, rather than the cocoa mass (mean OTA concentration 0.96 μg/kg) and was corresponding low (mean OTA concentration 0.61 μg/kg) in chocolate manufactured from the cocoa beans (Copetti *et al.*, 2013). A Brazilian study found a high prevalence of OTA on cocoa bean (n = 54, 38 positive at LOD of 0.07 μg/kg), but with only 4 samples having concentration greater than 2 μg/kg (de Magalhães *et al.*, 2011). A Canadian study detected OTA in 16 of 16 natural cocoa samples, with an average concentration of 0.89 μg/kg (Turcotte and Scott, 2011). OTA was detected in 14 of 14 dark chocolate samples and 5 of 7 milk chocolate samples, with mean concentrations of 0.38 and 0.11 respectively. A later study by the same group produced very similar results (Turcotte *et al.*, 2013).

Edible oils

OTA was detected (LOD = 0.1 μg/kg) in 24 of 30 virgin olive oil samples from Italy and Morocco, with concentrations in the range 0.1-17.0 μg/kg (Ferracane *et al.*, 2007). There was no correlation between quality parameters and OTA content. A smaller Chinese study did not detect OTA in 9 edible oil samples at a LOD of 0.47 μg/kg (Li *et al.*, 2014).

Nuts

OTA was detected in 30 of 72 peanut samples from the Catalonia region of Spain (Coronel *et al.*, 2012). However, concentrations were generally quite low (range 0.08-0.77 μg/kg). A study carried out in Côte d'Ivoire found similar results, with 6 of 10 peanut samples containing OTA, with concentrations in the range 0.20-0.64 μg/kg (Sangare-Tigori *et al.*, 2006). Higher concentrations of OTA were found in a study in Niger, with OTA detected in 6 of 7 samples of peanuts, with a mean concentration of 3.7 μg/kg and a maximum of 5 μg/kg (Toffa *et al.*, 2013).

OTA and OTB were detected in almonds, cashew nuts and peanuts with mean concentrations in the range 0.65-7.65 for OTA and 2.56-8.83 for OTB (Saito *et al.*, 2012). OTA and OTB were also detected in peanuts from Cameroon (n = 35), with prevalence of 26 and 31% and maximum concentrations of 23 and 16 μg/kg, respectively (Abia *et al.*, 2013b).

A study in Tunisia reported OTA concentrations in the range 11-266 μg/kg in 110 samples of almonds, peanuts and pistachios (Zaied *et al.*, 2010).

Olives

OTA was detected in all of 10 samples of black olives from Morocco, with concentrations ranging from less than the LOQ (0.2 μg/kg) to 1.02 μg/kg (El Adlouni *et al.*, 2006).

3.3.2.2 Foods of animal origin

Pork

Several studies reported greater prevalence and concentrations of OTA in the exterior of cured pork products than in the interior. It is uncertain whether this is due to migration of OTA to the exterior of the products or due to surface contamination with OTA-producing fungi during the curing process.

Pigs (n = 20) received either standard feed or feed with OTA added at a rate of 200 μg/kg for 40 days (Dall'Asta *et al.*, 2010). On average, muscle from pigs fed contaminated feed contained 2.21 μg/kg OTA, while salami made using minced muscle and fat from the same pigs had a mean OTA content of 2.65 μg/kg (inner part of salami) or 2.92 μg/kg (outer part of salami). For dry-cured hams, greater differences in mean OTA concentrations were seen between the inner and outer parts of the ham (2.18 and 3.62, respectively). In addition, dry-cured hams (n = 110) were sampled from the market, with 32 internally contaminated (mean OTA concentration 0.24 μg/kg) and 84 externally contaminated (mean OTA concentration 0.98 μg/kg).

Pigs (*n* = 24) received feed contaminated with OTA at concentrations in the range 0.4-171 µg/kg (4 dose groups) (Bertuzzi *et al.*, 2013). OTA was detected in plasma, kidney, liver, muscle and fat samples, with concentrations correlated with feed OTA concentrations. Concentrations of OTA in pig muscle were in the range 0.6-3.40 µg/kg. Pork products (dry sausage, dry-cured streaky bacon, dry-cured pork neck and dry-cured ham) all contained OTA at concentrations correlated with feed concentrations (maximum 5.62 µg/kg). Dry-cured ham was found to have considerably higher concentrations of OTA on the exterior surface (maximum 314 µg/kg), with concentrations not related to feed OTA concentrations. This was interpreted as being due to direct fungal contamination of the hams during the long curing process.

OTA was detected in the interior (2 of 10, range 0.28-1.52 µg/kg) and exterior (5 of 10, range 0.63-7.28 µg/kg) of dry-cured and smoked hams (Toscani *et al.*, 2007). The authors interpreted the higher concentrations on the outside of the hams as being due to direct contamination of the hams by OTA-producing moulds, present in the curing environment.

A small Chinese study detected OTA in 1 of 3 pig muscle samples at a concentration of 1.25 µg/kg (Chen *et al.*, 2012). A Portuguese study found a similar prevalence of contamination, with OTA being detected (LOD = 0.06 µg/kg) in 5 of 20 retail pork samples, with a maximum concentration of 0.58 µg/kg (Duarte *et al.*, 2013).

Meat

OTA was determined in a range of fermented Croatian meat products (Markov *et al.*, 2013). OTA was detected in 14 of 15 game sausages (rabbit, wild board, deer, roe deer, mixed) at concentrations in the range 0.05-3.07 µg/kg. OTA was detected in 21 of 25 semi-dry sausages (range 0.05-3.28 µg/kg) and 23 of 50 dry meat products (range 0.05-7.83 µg/kg). The dry and semi-dry meat products were made mainly from pigmeat or mixtures of pigmeat and beef.

Poultry

Tissue samples (liver, kidney, gizzard) were taken from chickens (*n* = 90) and analysed for OTA (Milićević *et al.*, 2011). OTA was detected in 23 liver, 17 kidney and 16 gizzard samples. The highest concentration measured was 9.94 µg/kg in a gizzard sample.

A study in Pakistan examined OTA in tissues (liver, breast muscle) from broiler (*n* = 131) and 'Desi' (*n* = 52) chickens (Khan *et al.*, 2013). The birds from which samples were taken were further characterised as 'healthy' or 'diseased'. Diseased birds made up 21% of the broiler samples and 25% of the Desi samples. Results are summarised in Table 7. No correlation was found between the OTA concentration of feed and tissue concentrations of OTA.

Table 7: OTA residues in tissues of chickens from Faisalabad, Pakistan

Bird/tissue type	Healthy birds		Diseased birds	
	Prevalence (%)	Maximum concentration (μg/kg)	Prevalence (%)	Maximum concentration (μg/kg)
Broiler				
- Liver	74	1.83	93	7.68
- Breast muscle	25	0.35	50	0.24
Desi[1]				
- Liver	54	1.32	92	2.16
- Breast muscle	13	0.09	54	0.21

[1] Desi chicken refers to smaller local breed of chicken that are usually raised free range

Milk

While OTA has occasionally been reported in cows' milk (Skaug, 1999), a study in Spain with extremely low limits of detection 0.0005 μg/L did not detect OTA in any of 12 samples (Bascarán *et al.*, 2007). Similar results were obtained in a second Spanish study with no OTA detected in 2 raw milk or 7 infant formula samples, although the study did not report limits of detection for OTA in these matrices (Beltrán *et al.*, 2011). A larger survey (n = 61) did not detect OTA (LOD = 0.01 μg/L) in any milk or milk substitute (soy, almond, oat, rice, wheat beverages) sample (González-Osnaya *et al.*, 2008). In contrast, a limited study in Wuhan, China detected OTA in 1 of 3 milk samples, at a concentration of 1.43 μg/kg (Chen *et al.*, 2012).

It was suggested that organic milk may have greater potential for OTA contamination than conventional milk (Pattono *et al.*, 2011). OTA was not detected (LOQ = 0.05 μg/kg) in any conventional milk samples (n = 20), but was detected in 3 of 63 organic milk samples, with concentrations in the range 0.07-0.11 μg/kg.

A review of mycotoxin carryover into milk reported that ruminant metabolism of OTA mainly resulted in conversion to the less toxic ochratoxin-α, with negligible carryover into milk (Fink-Gremmels, 2008).

Cheese

OTA was detected (LOQ = 1 μg/kg) in 6 of 40 samples of grated hard cheese, with concentrations in the range 1.6-54 μg/kg (Biancardi *et al.*, 2013). Contamination was ascribed to surface contamination of the cheese crust during ripening, rather than being due to contaminated raw materials. However, comparative analyses of the crust and the cheese interior were not carried out. OTA was detected (LOD = 0.02 μg/kg) in 30 of 92 mould-ripened blue cheeses from Europe, with concentrations in the range 0.1-3.0 μg/kg (Dall'Asta *et al.*, 2008).

Semi-hard cheeses (n = 32), hand-made from raw cows' milk, were analysed for OTA (Pattono *et al.*, 2013). The rind was removed and analysed separately to the cheese interior. OTA was detected in 6 cheese samples, with concentrations in the cheese interior in the range 18.4-146 μg/kg and in the rind in the range 1.0-262 μg/kg.

Eggs

A Chinese study detected OTA in 1 of 3 egg samples at a concentration of 1.32 μg/kg (Chen *et al.*, 2012). A multi-mycotoxin method did not detect OTA in any of 7 egg samples (Frenich *et al.*, 2011). However, the high LOD (5 μg/kg) would have made detection unlikely. OTA was not detected in eggs from layer hens received feed artificially contaminated with OTA at either 100 or 2000 μg/kg (Giancarlo *et al.*, 2011). Although the LOD was not reported, it can be inferred that it was approximately 0.1 μg/kg. A Belgian study did not detect OTA in any of 20 egg samples (Tangni *et al.*, 2009). However, the relatively high LOD (2.5 μg/kg) would have contributed to this result.

3.3.3 New Zealand estimates of dietary exposure

Thomson (1996) estimated New Zealand exposure to OTA to be 2.4 ng/kg body weight/day. This exposure estimate was based on Danish data for OTA concentrations in cereals and it should be viewed as speculative only.

A more detailed exposure assessment for New Zealand is currently underway, using New Zealand specific OTA concentration data and food consumption data from the most recent national nutrition surveys (Ministry of Health, 2003; University of Otago and Ministry of Health, 2011). Mean estimates of dietary exposure were in the range 0.28-3.17 ng/kg body weight/day, depending on age-gender and treatment of left-censored analytical data (currently unpublished data). High level (95th percentile) usual exposures were in the range 0.62-4.66 ng/kg body weight/day.

3.3.4 Overseas estimates of dietary exposure

Table 8 summarises results of overseas studies which have derived estimates of dietary exposure to OTA.

Table 8: Overseas estimates of dietary exposure to OTA

Country	Population group	Mean exposure (95th percentile), ng/kg body weight/day	Main contributing food(s)	Reference
PTWI (JECFA) = 100 ng/kg body weight/week (14.3 ng/kg body weight/day) TWI (EFSA) = 120 ng/kg body weight/week (17.1 ng/kg body weight/day)				
Belgium Czech Republic Denmark Finland France Germany Hungary Ireland Italy Netherland Sweden United Kingdom	Adults (16-64 years)	58 (131) 54 (117) 64 (130) 54 (119) 64 (130) 87 (171) 74 (139) 80 (177) 100 (184) 65 (135) 53 (103) 49 (108)	Vegetables, nuts and pulses food group	(Boon *et al.*, 2011)
Canada	Infant (1 year) Male (31-50 years) Female (31-50 years)	4.38 (12.08) 1.62 (4.04) 1.33 (3.42)	Wheat products	(Kuiper-Goodman *et al.*, 2010)

Country	Population group	Mean exposure (95th percentile), ng/kg body weight/day	Main contributing food(s)	Reference
PTWI (JECFA) = 100 ng/kg body weight/week (14.3 ng/kg body weight/day) TWI (EFSA) = 120 ng/kg body weight/week (17.1 ng/kg body weight/day)				
China, Shanghai	Male adults (16-35 years) Female adults	1.15 (4.74) 1.05 (4.37)	Cereals and derived products	(Han *et al.*, 2013)
China, Yangtze Delta	Children Adults	13.9 (27.7) 4.62 (9.23)	Only cereal consumption was considered	(Li *et al.*, 2014)
France	Adults (15+ years)	1.62-1.70 (3.28-3.88)[1]	NS	(Counil *et al.*, 2006)
France	Children Adults	0.23-2.83 (0.58-5.25)[4] 0.28-1.92 (0.61-3.23)	Bread, fruit	(Sirot *et al.*, 2013)
Japan	1-6 years 7-14 years 15-19 years >19 years	(0.011-0.012) (0.009) (0.007-0.008) (0.001)	NS	(Kumagai *et al.*, 2008)
Lebanon	Children (8-13 years) Teenagers (14-18)	17.6-38.6 (31.0-57.5)[4] 14.8-28.8 (24.0-43.6)	Cereals and cereal-based products	(Soubra *et al.*, 2009)
Netherlands	Children (*n* = 123)	4.1	Duplicate diet	(Bakker *et al.*, 2009)
Portugal	Adults (19-92 years, *n* = 104)	0.71 (range 0.19-3.35)[2]	NS	(Lino *et al.*, 2008)
Portugal	Adult (65 kg body weight)	3.98	Cereals	(Duarte *et al.*, 2010)
Spain (Lleida)	Blood donors (*n* = 279) (18+ years)	From plasma OTA 1.69 (4.94) From dietary exposure 1.96 (3.97)	Cereals and derived products, wine	(Coronel *et al.*, 2009)
Spain (Lleida)	Blood donors (*n* = 325) (18+ years)	From plasma OTA 2.66/1.57 (7.73/4.15)[3] From dietary exposure 1.60 (3.21)	NS	(Coronel *et al.*, 2011)
Spain (Catalonia)	Infants (0-3 years) Children (4-9) Adolescents (10-17) Adults (18-65)	0.28-2.42 (1.46-7.23)[4] 0.09-0.39 (0.30-0.98) 0.14-0.28 (0.44-0.68) 0.37-0.53 (1.14-1.31)	NS	(Coronel *et al.*, 2012)
Spain (Valencia)	Blood donors (*n* = 168) (18+ years)	1.47/2.16[5]	NS	(Medina *et al.*, 2010)
Tunisia	Controls[6] I II III IV	Mean (range)[2] 4.4 (5.0-24.9) 26.0 (5.4-90.0) 7.7 (6.6-29.0) 8.1 (6.6-21.8) 7.7 (5.6-21.3)	NS	(Zaied *et al.*, 2011)

[1] The range of values reflects use of 1, 3 or 7 day dietary records to estimate food consumption

[2] Dietary exposure was calculated from serum OTA using the equation of Breitholtz *et al.* (1991)

[3] Differing exposure estimate depend on whether the conversion from plasma OTA to dietary OTA is based on the coefficient of Studer-Rohr *et al.* (2000) or Miraglia *et al.* (1996)

[4] The range limits were derived by assigning analytical results below the LOD a concentration either equal to zero or equal to the analytical LOD

[5] Differing exposure estimate depend on whether the conversion from plasma OTA to dietary OTA is based on the coefficient of Breitholtz *et al.* (1991) or the Klassen equation

[6] I = cases with chronic interstitial nephropathy of unknown aetiology, II = cases with chronic interstitial nephropathy of known aetiology, III = cases of chronic glomerular nephropathy, IV = cases with chronic vascular nephropathy

3.3.5 Biomarkers of exposure

Analysis of blood or urine is being increasingly used to assess past and recent OTA exposure. However, studies of this sort usually only measure parent OTA in body fluids. It has been shown that ochratoxin-α, a metabolite produced by cleavage of OTA at the amide bond, may be present in blood and urine at much higher concentrations than the parent compound (Muñoz *et al.*, 2010).

Analysis of OTA in blood has been used in a number of studies to determine dietary exposure (see examples in Table 8).

OTA was detected in 42 of 60 urine samples taken from healthy persons in Coimbra, Portugal (Pena *et al.*, 2006). The concentrations were in the range 0.021-0.105 μg/L, with an average of 0.038 μg/L.

In a study of adults from Cameroon (n = 175) urinary OTA was detected in 28 samples (16%) with a maximum concentration of 1.87 μg/L (Abia *et al.*, 2013a). Literature values for the urinary excretion rate of OTA (50%) and an estimate of daily urinary output (1.5 L) were used to estimate dietary exposure to OTA.

3.4 Risk Characterisation

3.4.1 Adverse health effects in New Zealand

3.4.1.1 Incidence of end stage renal disease

No cases of human ochratoxicosis have been reported in New Zealand and no reports were identified linking kidney disease in New Zealand to exposure to fungal toxins.

The incidence of end stage renal disease in New Zealand appears to have stabilised since 2007, with rates in the range 111-135 per million of population for the period 2007-2011.[9] Ochratoxicosis is not listed amongst causes of kidney disease in New Zealand or Australia. In New Zealand in 2011, diabetic nephropathy is the most common type of end stage renal disease (ESRD) (42%), followed by glomerulonephritis (24%) and hypertension (11%).

3.4.2 Adverse health effects overseas

3.4.2.1 Incidence of end stage renal disease

Limited data are available for rates of kidney disease in overseas populations. In 2008, in the USA it was reported that the incidence rate of ESRD had stabilised at approximately 350

[9] http://www.anzdata.org.au/anzdata/AnzdataReport/35thReport/2012c02_newpatients_v2.5.pdf Accessed 11 December 2013

cases per million of population.[10] Age-standardised rates in Denmark are very similar to New Zealand, with rates in the range 102-140 per million during the period 2007-2011 (Heaf and Wehberg, 2012).

In areas of Croatia and Bulgaria where BEN occurs the age-adjusted incidence has been reported to be as high as 5000 per million (Pfohl-Leszkowicz *et al.*, 2002). The incidence of urothelial tumours in these regions was also high (400-700 per million compared to high incidence areas of Italy with rates of 20-60 per million).

3.4.2.2 Epidemiological studies

Croatia

Urine samples were collected from a village with endemic nephropathy (n = 45) and from a control village (n = 18) in each of 2 different years (2000 and 2005) (Domijan *et al.*, 2009). OTA was detected more frequently in samples from the endemic village (43% compared to 28% in 2000, and 18% compared to 6% in 2005). Sphingosine to sphinganine ratios in urine, a biomarker of fumonisin exposure, were also found to be higher in the endemic village.

Egypt

A case-control study was carried out involving 39 HCC cases and 22 healthy controls (Ibrahim *et al.*, 2013). The mean serum OTA concentration in the HCC cases was 1.1 ng/ml (range 0.129-10.93 ng/ml), while the mean concentration in healthy controls was 0.201 ng/ml (range 0.005-0.50 ng/ml).

Tunisia

Nephropathy cases (n = 24) were compared to healthy controls (n =44) (Hmaissia Khlifa *et al.*, 2012). OTA was detected (LOD = 0.1 ng/ml) in 80% of blood samples from cases (mean 1.25 ng/ml, range 0.12-3.8 ng/ml), compared to 34% of controls (mean 0.22 ng/ml, range 0.12-1.5 ng/ml). Differences were statistically significant. Analysis of food samples from the homes of cases and controls confirmed that cereals were the predominant source of dietary OTA. Food samples from cases had a higher prevalence and higher concentrations of OTA.

Blood OTA concentrations were compared between groups with particular renal diseases and healthy control groups (Zaied *et al.*, 2011). In the control group, 49% of samples contained detectable OTA (mean 3.3 ng/ml, range 1.7-8.5 ng/ml). The highest incidence of blood OTA was in the group with chronic interstitial nephropathy (CIN) with unknown aetiology (76%, mean 18 ng/ml, range 1.8-65 ng/ml). All groups of renal disease cases differed significantly from controls with respect to blood OTA.

[10] http://kidney.niddk.nih.gov/KUDiseases/pubs/kustats/KU_Diseases_Stats_508.pdf Accessed 11 December 2013

3.5 Risk Management Information

3.5.1 Relevant food controls: New Zealand

3.5.1.1 Establishment of regulatory limits

New Zealand does not currently have regulatory limits for OTA.

3.5.2 Relevant food controls: overseas

3.5.2.1 Establishment of regulatory limits

Regulations for 25 countries (counting the EU as a single country) which reported regulation of OTA in foods (but not feeds) were summarised in the previous risk profile (Cressey and Thomson, 2006). Regulatory limits for the EU have subsequently been updated (European Commission, 2006b; 2010). Updated EU limits are summarised in Table 9.

Table 9: Regulatory limits for OTA in EU

Commodity description	Regulatory limit (µg/kg)[1]
Unprocessed cereals	5
All products derived from unprocessed cereals, including processed cereal products and cereals intended for direct human consumption with the exception of foodstuffs listed in 9 and 10	3
Dried vine fruit (currants, raisins and sultanas)	10
Roasted coffee beans and ground roasted coffee, excluding soluble coffee	5
Soluble coffee (instant coffee)	10
Wine (including sparkling wine, excluding liqueur wine and wine with an alcoholic strength of not less than 15% vol.) and fruit wine	2
Aromatised wine, aromatised wine-based drinks and aromatised wine-product cocktails	2
Grape juice, concentrated grape juice as reconstituted, grape nectar, grape must and concentrated grape must as reconstituted, intended for direct human consumption	2
Processed cereal-based foods and baby foods for infants and young children	0.5
Dietary foods for special medical purposes intended specifically for infants	0.5
Spices (*Capsicum* spp., *Piper* spp., nutmeg, ginger, turmeric, mixtures of spices containing one or more of these)	15[2,3]
Liquorice:	
Root (for herbal infusion)	20[2]
Extract (for beverages and confectionary)	80[2]
Green coffee, dried fruit other than dried vine fruit, beer, cocoa and cocoa products, liqueur wines, meat products	-

[1] (European Commission, 2006b)
[2] (European Commission, 2010)
[3] A limit of 30 µg/kg was in place from 1 July 2010 until 30 June 2012, when the lower limit came into force

OTA limits have been proposed for adoption in Canada (Haighton *et al.*, 2012). The proposed limits are the same as those in place in the EU for unprocessed cereals, processed cereal products, grape juice, dried vine fruit, infant formulae and infant foods. Canada has not proposed maximum limits for the other foods covered by the EU regulations, but does propose an additional maximum limit for processed cereal products from wheat bran of 7 µg/kg.

3.5.2.2 Codes of practice

The Codex Committee on Contaminants in Foods (CCCF) are currently working on an annex to the COP for prevention and reduction of mycotoxin contamination of cereals, to cover prevention and reduction of OTA (and aflatoxins) in sorghum and sorghum products (Codex Committee on Contaminants in Food, 2013d). The proposed annex includes aspects related to planting, harvest, transport, storage, processing, and packaging and marketing.

CCCF are also in the process of developing a COP for prevention and reduction of OTA in cocoa (Codex Committee on Contaminants in Food, 2013c). The draft code covers aspects related to pre-harvest, harvest, storage and pod opening, fermentation of cocoa beans, drying process, storage, transportation and trading of dried cocoa beans, and cargo ship loading and transport.

The International Organisation of Vine and Wine (OIV) have developed a COP for minimising the level of OTA in vine-based products.[11] The code covers:

- Cultivation practices in the vineyard;
- Practices at harvest; and
- Treatment at the winery.

3.5.2.3 Integrated approaches

The Ecuadorian coffee industry have adopted an integrated approach to management of OTA residues in coffee, based on Hazard Analysis Critical Control Point (HACCP) principles (Lopez-Garcia *et al.*, 2008). Critical control points (and critical limits) identified were:

- Drying, on the farm or after wet processing (to <15% moisture);
- Drying, before storage (to <12% moisture); and
- Reception at the processing facility (screening for percentage defects).

3.5.2.4 Management of OTA formation in crops

The use of chemical fungicides to control infection with OTA-producing fungi and reduce OTA contamination has proved effective in grapes, with the actives cyprodinil and fludioxonil reported to be particularly efficacious (Valero *et al.*, 2007; Varga and Kozakiewicz, 2006). Carbendazim was reported to provide control of *A. carbonarius*, but stimulate production of OTA (Medina *et al.*, 2007).

Biocontrol strategies for managing OTA formation are gaining some attention. In *in vitro* and detached grape berry studies, addition of yeast strains (*Kluyveromyces thermotolerans*) controlled growth of *Aspergillus carbonarius* and *A. niger* and reduced OTA accumulation by 3-100% (Ponsone *et al.*, 2011). Similarly, application of atoxigenic *Penicillium jantinellum* reduced infection with *A. nigri* and OTA accumulation in grapes (Valero *et al.*, 2007).

[11] http://www.oiv.int/oiv/files/6%20-%20Domaines%20scientifiques/6%20-%208%20Guides%20OIV/EN/VITI-OENO%201-2005_EN.pdf Accessed 12 December 2013

3.5.3 Influence of processing on OTA levels

3.5.3.1 Wheat

OTA concentrations were reported to decrease by approximately 30% during bread dough fermentation and by a similar amount during baking (Valle-Algarra *et al.*, 2009).

3.5.3.2 Coffee

The impact of degree of roasting (light, medium and dark) and grinding particle size (fine, medium and coarse) on residual OTA concentrations in coffee beans were examined (Oliveira *et al.*, 2013). Roasting at a higher temperature, to give a darker roast, combined with a coarse grind, resulted in approximately 97% reduction in OTA content. A light roast with a fine grind results in 56% reduction in OTA content. Degree of roasting had a greater impact of OTA content than grinding particle size.

3.5.3.3 Wine

Alcoholic fermentation of white or red grape juice was shown to decrease the OTA concentration of the must in a linear fashion over time (up to 300 hours) (Esti *et al.*, 2012). Depletion of OTA commenced more quickly in red wine must, reportedly due to absorption of OTA on to grape skin present. While some difference was observed between different yeast strains, reductions of 57-79% in OTA concentration were achieved during alcoholic fermentation.

Quintela *et al*. reviewed methods for removing OTA from wine (Quintela *et al.*, 2013). A variety of wine fining agents are able to absorb and remove OTA, but the degree of removal depends on the concentration of OTA, the type of fining agent and its concentration. Often conditions that result in good removal of OTA impact negatively on wine quality parameters. Some fining agents used at concentrations usually employed for fining achieved OTA reductions of about 40%.

3.5.3.4 Beans

Various types of dried edible beans (e.g. lima, fava, cannellini, navy, pinto), either naturally or artificially contaminated with OTA, were subjected to washing, soaking and cooking for various lengths of time (Iha *et al.*, 2009). The combined treatments were shown to reduce the OTA content of beans by up to 50%.

3.5.3.5 Spices

Gamma irradiation (^{60}Co) of black and white pepper was applied to assess its effectiveness for decontaminating OTA (Jalili *et al.*, 2012). Maximum OTA reduction (55.2%) was achieved at the highest moisture content (18%) and the highest irradiation dose (30 kGy).

3.5.3.6 Cocoa

Reduction in OTA content during the processing of cocoa beans into chocolate was examined (Manda *et al.*, 2009). The process included roasting, shelling, grinding, additive addition and

moulding. The full process resulted in an average 91% reduction in the OTA content. The majority of the reduction occurred during the shelling stage, which resulted in a 75% reduction in OTA content.

3.6 Conclusions

3.6.1 Description of risks to New Zealand consumers

Despite several decades of research, evidence for a role for OTA in the causation of human kidney disease is suggestive, but not conclusive. The progression of the condition known as Balkan Endemic Nephropathy (BEN) is similar to effects observed in laboratory animals exposed to OTA. However, differences in the types of tumour formed have been noted and an alternative hypothesis, implicating aristolochic acid, has gained traction.

New Zealand does not exhibit regions of endemic kidney disease and the general incidence of kidney disease in New Zealand is not high. Major causes of kidney disease in New Zealand are well characterised, and do not include food contaminants.

OTA has been detected in a range of domestically produced and imported foods available in New Zealand, although levels of contamination are not high by international standards.

Estimates of exposure to OTA by New Zealanders are similar to or lower than estimates for other developed countries and are well below health-based exposure limits derived by JECFA and EFSA.

A Health Canada risk assessment derived a lower limit, based on a conclusion that OTA was a non-threshold carcinogen. Upper 95th percentile New Zealand exposure estimates for some children 5-6 years just exceed the Canadian Negligible Cancer Risk Intake of 4 ng/kg body weight/day. Although the exact mechanism by which OTA exerts genotoxicity has still not been confirmed, there is evidence to suggest that a range of mechanisms, that are likely to have a toxicity threshold, probably contribute.

3.6.2 Commentary on risk management options

New Zealand does not currently exercise direct risk management measures to control the entry of OTA into the human food chain. Control of OTA in New Zealand-produced food is likely to occur as a consequence of GAP and GMP practices, designed to achieve other quality and safety objectives.

3.6.3 Data gaps

The major data gap at present is the establishment of a definitive link between OTA exposure and adverse human health effects, although expert bodies such as JECFA and EFSA feel that there is sufficient evidence to recommend that exposure be kept as low as possible.

4 TRICHOTHECENE MYCOTOXINS

4.1 Hazard identification

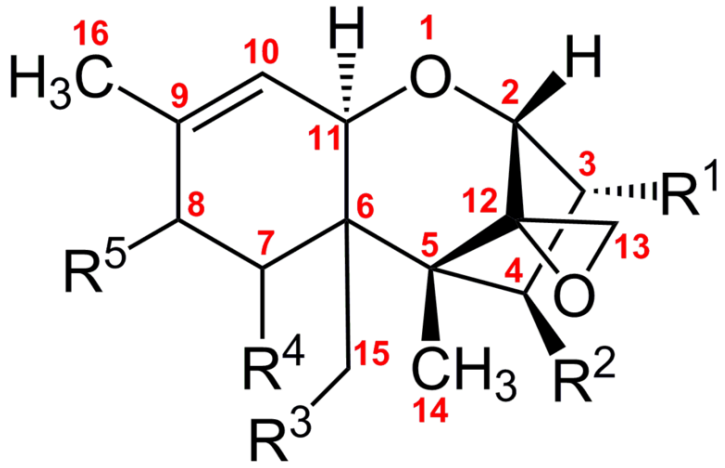
The trichothecenes are a family of approximately 150 structurally related compounds produced by fungi of the genera *Fusarium, Cephalosporium, Myrothecium, Stachybotrys, Trichoderma* and others. Trichothecenes of significance in food are produced by *Fusarium* species, including *F. poae, F. sporotrichioides, F. acuminatum, F. graminearum, F. culmorum, F. crookwellense, F. avenaceum* and *F. equiseti* (Council for Agriculture and Technology, 2003). The toxins in this group that have received the most attention are deoxynivalenol (DON), nivalenol (NIV), T-2 toxin (T2) and HT-2 toxin (HT2), with lesser attention paid to diacetoxyscirpenol (DAS) and other trichothecene toxins. Focus on these toxins has been due to the fact that they are the major toxins formed in foods and/or there is evidence for their involvement in human disease. The current analysis will mainly focus on DON, NIV, T2 and HT2. Trichothecene mycotoxins have been reported in cereal grain crops worldwide (Schothorst and Van Egmond, 2004).

4.1.1 Structure and nomenclature

The trichothecene mycotoxins are sesquiterpenoids possessing a tetracyclic 12,13-epoxytrichothecene skeleton. They can be conveniently divided into 4 categories according to similarity of functional groups. The first class is characterised by a functional group other than a ketone at C-8 (type A) and include T2 and HT2, DAS, monoacetoxyscirpenol (MAS) and neosolaniol (NEO). The second category of trichothecenes usually has a carbonyl function at C-8 (type B), typified by DON and NIV. The third category is characterised by a second epoxide group at C-7,8 or C-9,10 (type C), and the fourth contains a macrocyclic ring system between C-4 and C-15 with 2 ester linkages (type D). Type C and type D trichothecenes are not normally associated with food.

Structural summaries are shown in Figure 4 for type A and B trichothecene mycotoxins.

Figure 4: Structure of type A and B trichothecene mycotoxins



Type A: T2 (R_1 = OH, R_2 = OAc, R_3 = OAc, R_4 = H, R_5 = $OCOCH_2CH(CH_3)_2$), HT2 (R_1 = OH, R_2 = OH, R_3 = OAc, R_4 = H, R_5 = $OCOCH_2CH(CH_3)_2$), DAS (R_1 = OH, R_2 = OAc, R_3 =

OAc, R_4 = H, R_5 = H), MAS (R_1 = OH, R_2 = OH, R_3 = OAc, R_4 = H, R_5 = H), NEO (R_1 = OH, R_2 = OAc, R_3 = OAc, R_4 = H, R_5 = OH)

Type B: DON (R_1 = OH, R_2 = H, R_3 = OH, R_4 = OH, R_5 = O), NIV (R_1 = OH, R_2 = OH, R_3 = OH, R_4 = OH, R_5 = O), 3-acetylDON (R_1 = OAc, R_2 = H, R_3 = OH, R_4 = OH, R_5 = O), 15-acetylDON (R_1 = OH, R_2 = H, R_3 = OAc, R_4 = OH, R_5 = O), DON-3-glucoside (R_1 = $OC_6H_{11}O_5$), R_2 = H, R_3 = OH, R_4 = OH, R_5 = O), Fusarenon X (R_1 = OH, R_2 = OAc, R_3 = OH, R_4 = OH, R_5 = O)

Structure-activity relationship (SAR) analysis has been used to relate structural features of trichothecene mycotoxins to mammalian toxicity (Wu *et al.*, 2013a):

- The double bond at C9-C10 and the epoxide ring at C12-C13 are essential elements for trichothecene toxicity;
- Toxicity is increased by a hydroxyl group at C3, compared to a hydrogen or acetoxy group;
- Toxicity is increased by an acetoxy group at C4 and/or C15, compared to a hydroxyl group or hydrogen; and
- Toxicity requires an oxygenated functional group at C8.

This analysis suggests that T2 and NEO will potentially be the most toxic of the A and B trichothecene mycotoxins.

4.1.2 Occurrence

Type A trichothecenes (T2, HT2) are frequently associated with *F. tricintum, F. poae, F. sporotrichioides, F. acuminatum, F. equiseti* and *F. semitectum* (WHO, 1990). Trichothecene mycotoxin formation by these fungal species has been reported in Europe and North America and occasionally in Asia, but not in Africa or Australia (Council for Agriculture and Technology, 2003). Type B trichothecenes (DON, NIV) are frequently associated with *F. graminearum* and *F. culmorum* (WHO, 1990). Trichothecene mycotoxin formation by these species, particularly *F. graminearum* appears to be almost universal (Council for Agriculture and Technology, 2003).

Table 10 summarises information on *Fusarium* species occurring and production of trichothecene mycotoxins in New Zealand crops. It should be noted that no additional information has been published since the previous version of this risk profile and this table is reproduced for convenience.

Table 10: Trichothecene production by *Fusarium* species in New Zealand crops

Crop	Fungal species ('>' indicates order of detection frequency)	Trichothecenes detected	Study reference
Maize (Manawatu)	*F. graminearum* *F. culmorum* *F. subglutinans* *F. acuminatum*	T2, DON, DAS detected, but no details of which species produced which mycotoxins	(Hussein *et al.*, 1987)
Maize (Waikato)	*F. graminearum* >*F. semitectum* >	No analyses	(Sayer, 1991)

Crop	Fungal species ('>' indicates order of detection frequency)	Trichothecenes detected	Study reference
	F. crookwellense[1]	carried out for mycotoxins	
Wheat (Waikato) Wheat (East Coast) Wheat (Manawatu) Wheat (South Island) Barley (Waikato) Barley (East Coast) Barley (Manawatu) Barley (South Island) Oats (East Coast) Oats (South Island) Maize (North Island)	*F. graminearum >F. avenaceum, F. crookwellense, F. poae* *F. culmorum > F. poae* *F. graminearum, F. culmorum > F. avenaceum, F. crookwellense, F. poae* *F. avenaceum > F. poae, F. culmorum* *F. graminearum >F. avenaceum, F. crookwellense, F. poae* *F. avenaceum, F. culmorum, F, equiseti,> F. poae* *F. poae > F. avenaceum, F. crookwellense, F. culmorum, F. graminearum* *F. avenaceum, F. poae > F. culmorum, F. graminearum* *F. poae > F. avenaceum* *F. avenaceum > F. culmorum > F. poae* *F. graminearum > F. crookwellense > F. semitectum*	No analyses carried out for mycotoxins	(Sayer and Lauren, 1991)
Maize, wheat, barley, oats (all New Zealand)	*F. graminearum* *F. culmorum* *F. avenaceum* *F. crookwellense* *F. poae* *F. semitectum* *F. equiseti* *F. tricinctum*	NIV, DON NIV, (DAS)[2] NIV, (DAS)[2] DAS	(Lauren *et al.*, 1992)
Wheat, barley (North Island)	*F. graminearum > F. avenaceum > F. poae > F. crookwellense > F. culmorum*	No analyses carried out for mycotoxins	(Cromey *et al.*, 2001)
Wheat, barley (South Island	*F. avenaceum > F. culmorum > F. graminearum > F crookwellense*	No analyses carried out for mycotoxins	(Cromey *et al.*, 2001)
Maize (Manawatu)	*F. graminearum > F. culmorum > F. acuminatum, F. subglutinans*	No analyses carried out for mycotoxins	(Hussein *et al.*, 2003)

[1] Order given here is for field maize. In stored maize the proportion of *F. semitectum* was greater than *F. graminearum.*
[2] Detections of DAS were infrequent in comparison to detections of NIV

While there are differences between different studies, *F. graminearum* appears to be the *Fusarium* species that most commonly infects grain crops in the North Island. *F. graminearum* is associated with production of Type B trichothecenes (NIV, DON). Monds *et al.* (2005) examined the mycotoxin-producing potential of a number of *F. graminearum* isolates from New Zealand grains and found that the isolates either produced NIV or DON or neither, but rarely both NIV and DON in significant amounts.

South Island crops are more likely to be infected with *F. avenaceum*. Bosch *et al.* (1989) demonstrated significant rodent toxicity in extracts from *F. avenaceum* and found high levels of moniliformin in these extracts and a haemorrhagic factor (wortmannin) in 1 extract. There

have been no reports of significant trichothecene production by *F. avenaceum* isolates in New Zealand. *F. avenaceum* is the most common *Fusarium* species infecting crops in Northern Europe and has been reported to produce the mycotoxins moniliformin, beauvericin and enniatins (Morrison *et al.*, 2002).

Other species common in New Zealand grain are known trichothecene producers, including *F. culmorum* (DON, NIV), *F. poae* (HT2, T2, DAS, NIV), and *F. crookwellense* (NIV, DAS).

The study of Hussein *et al*. (1987) is unique in reporting detection of T2. Although T2 has been looked for, it has not been detected in subsequent studies and there must be some questions regarding these early findings.

4.2 Hazard Characterisation: Adverse Health Effects

A number of incidents of human toxicosis have been associated with trichothecene contaminated foods. However, it should be noted that in most cases the implicated food may contain more than 1 known mycotoxin and may potentially contain other, as yet uncharacterised, toxins.

No new case or outbreak reports of human toxicosis due to trichothecene mycotoxins have been published since the previous version of this risk profile.

4.2.1 Conditions

4.2.1.1 DON

No human deaths attributed to DON have been reported (JECFA, 2001c).

The acute effects of DON intoxication are similar to microbial food poisoning (nausea, vomiting, diarrhoea, abdominal pain, headaches, dizziness and fever). The condition is sometimes known as red mould toxicosis (JECFA, 2001c).

Epidemiological studies in China have associated consumption of DON-contaminated maize or wheat with chronic conditions, such as oesophageal cancer, gastric cancer and endemic osteoarthritis (JECFA, 2001c). There was consistent evidence of higher levels of DON in grains in affected areas compared to control areas. However, IARC classified DON in 1993 as not classifiable as to its carcinogenicity to humans (Group 3) (IARC, 1993). Subsequent studies support its non-carcinogenicity (JECFA, 2011).

4.2.1.2 NIV

No information is currently available on human health effects of NIV (EFSA, 2013b). Studies, that have attempted to relate the presence of DON to high incidence of some cancers, have also noted the presence of NIV in foods.

EFSA concluded that, on the overall weight of evidence, NIV is unlikely to be genotoxic (EFSA, 2013b).

4.2.1.3 T2

T2 has been implicated in a condition called alimentary toxic aleukia (ATA), incidents of which were reported in the former USSR during the period 1931-1947 following consumption of mouldy over-wintered wheat (JECFA, 2001e). Moulds were reported to be *F. poae* and *F. sporotrichioides*. The symptoms included necrotic lesions of the oral cavity, oesophagus and stomach and pronounced leucopenia (low white blood cell count) and resulted in high mortality rates.

No new cases or outbreaks of human toxicosis due to T2 have been reported since the previous version of this risk profile.

IARC categorised T2 in 1993 as not classifiable as to its carcinogenicity to humans (Group 3) (IARC, 1993).

4.2.1.4 HT2

No reports were found linking exposure to HT2 to human disease. However, HT2 is a major metabolite of T2 and the 2 toxins are generally considered together when being evaluated (EFSA, 2011b; JECFA, 2001e).

4.2.1.5 Other trichothecene mycotoxins

No information was found linking other trichothecene mycotoxins to particular human diseases.

4.2.2 Toxicity

The toxicities of DON (JECFA, 2011; Pestka, 2010a; b), NIV (EFSA, 2013b; Pestka, 2010b) and T2/HT2 (EFSA, 2011b) have been extensively reviewed since the previous version of this risk profile. Limited information is available on the toxicity of other trichothecene mycotoxins, but has been reviewed for fusarenon X (FX), DAS, NEO, 3-acetyl-DON (3ADON) and 15-acetyl-DON (15ADON) (Pronk *et al.*, 2002).

4.2.2.1 Acute toxicity

The previous version of this risk profile presented a summary of animal LD_{50} information. Oral LD_{50} values were in the range 46-140 mg/kg for DON, 20-39 mg/kg for NIV, 1.8-10 mg/kg for T2 and 7.2 mg/kg for HT2.

A more recent estimate of LD_{50} for T2 of 3.7 mg/kg was within the range previously determined (McKean *et al.*, 2006).

Trichothecene mycotoxins are known to induce emesis (vomiting) in a range of animal species and emesis in pigs was used as the pivotal endpoint to derive a human acute reference dose (JECFA, 2011). Mink were used to examine the comparative emetic potential of DON, 3ADON, 15ADON, NIV and FX (Wu *et al.*, 2013c). Emesis was found to be dose dependent for all toxins and 2 routes of administration (intraperitoneal and oral). Increasing doses decreased the latency period to emesis and increased the duration and number of emetic

events. The relative emetic potency by the intraperitoneal route was NIV > FX > DON > 15ADON > 3ADON, while by the oral route the relative potency was DON = FX > 15ADON >> NIV > 3ADON. These results were reported to be consistent with findings in pigs and dogs.

Further studies on emesis due to DON identified 2 peptide hormones, associated with satiety, that were elevated during DON-induced emesis (Wu *et al.*, 2013b). Pretreatment with antagonists to the peptide receptors prevented induction of emesis.

4.2.3 Chronic toxicity

The toxic effects of trichothecenes are due to their ability to bind to ribosomes and inhibit protein synthesis (Scientific Committee on Food, 2002; Shuhmacher-Wolz *et al.*, 2010). Trichothecene mycotoxins also have an inhibitory effect on RNA and DNA synthesis and exert toxic effects on cell membranes. Trichothecenes are also immunotoxic, although effects on the immune system are strongly dose dependent and they may be immunostimulatory at low concentrations (Pestka *et al.*, 2004).

There is some evidence that DON reaches the brain and interferes with central neuronal networks dedicated to food intake regulation (Girardet *et al.*, 2011). In a rat model, DON administration decreased the frequency of feeding and the amount of food consumed at each feed.

4.2.4 Toxicological assessment

4.2.4.1 DON

JECFA have reviewed the Provisional Maximum Tolerable Daily Intake (PMTDI) for DON of 1 μg/kg body weight/day (1000 ng/kg body weight/day) set in 2001, based on a NOEL of 100 μg/kg body weight/day for reduced body weight gain in a 2-year mouse feeding study (JECFA, 2011). The PMTDI was confirmed as still appropriate and was extended to be a group PMTDI for DON and its acetylated derivatives (3ADON and 15ADON). An acute reference dose (ARfD) was also derived from the lowest $BMDL_{10}$ of 0.21 mg/kg body weight for emesis in pigs. A safety factor of 25 was applied to give an ARfD of 8 μg/kg body weight. Data from earlier human outbreaks concluded that a lower dose that might cause emesis in human might be 50 μg/kg body weight. This suggests that the derived ARfD should be suitably protective.

The Food Safety Commission of Japan (FSCJ) used the same toxicological endpoint (decrease in body weight gain in mice) to derive a TDI of 1 μg/kg body weight/day for DON (Food Safety Commission of Japan, 2010).

JECFA reported a BMD_{05} and associated $BMDL_{05}$ (lower 95th percentile confidence limit for the BMD_{05}) for chronic DON exposure of 8.6 and 0.6 μg/kg body weight/day, respectively (JECFA, 2011). It should be noted that this benchmark dose includes an 'extrapolation' from the animal benchmark dose to a human equivalent benchmark dose. The animal BMD_{05} for reduced body weight gain has been estimated as 0.236 mg/kg body weight/day, with an associated $BMDL_{05}$ of 0.219 mg/kg body weight/day (Muri *et al.*, 2009a; Pieters *et al.*,

2001). Data to derive benchmark doses came from the same study used to determine the PMTDI for DON (Iverson *et al.*, 1995). For acute exposure, a lowest $BMDL_{10}$ of 0.21 mg/kg body weight was derived from studies of emesis in pigs.

4.2.4.2 NIV

EFSA reviewed public health risks associated with NIV in 2013 (EFSA, 2013b). Decreases in white blood cell (WBC) counts in a 90-day rat study were considered to be the most appropriate endpoints for benchmark dose determination. A TDI of 1.2 µg/kg body weight/day (1200 ng/kg body weight/day) was derived for NIV. This is higher than the temporary TDI derived in 2000 of 700 ng/kg body weight/day (Scientific Committee on Food, 2000a).

The Food Safety Commission of Japan (FSCJ) used the same toxicological endpoint (decrease in rat WBC counts) to derive a TDI of 400 ng/kg body weight/day (Food Safety Commission of Japan, 2010). The difference between the EFSA and FSCJ TDI estimates was an additional uncertainty factor of 3 applied by EFSA due to:

- Extrapolation from subchronic to chronic duration in rodents (x 2 factor); and
- Limitations in available reproductive and developmental toxicity data for NIV (x 1.5 factor).

Decreased WBC count data from a 90 day rat study was also used to derive benchmark doses for NIV (EFSA, 2013b). BMD_{05} and $BMDL_{05}$ estimates were 0.46 and 0.35 mg/kg body weight/day, respectively.

4.2.4.3 T2/HT2

EFSA reviewed public health risks associated with T2 and HT2 in 2011 (EFSA, 2011b). The conclusions were largely consistent with earlier assessments of these toxins:

- As T2 is metabolised to HT2, the toxic effects of the toxins cannot be distinguished; and
- The most sensitive species to the toxic effects of T2/HT2 is the pig and the most sensitive endpoints are immunotoxicity and haematotoxicity.

A MoE approach was used to derive a group TDI for the sum of T2 and HT2 of 100 ng/kg body weight/day. This is an increase on the previous temporary TDI of 60 ng/kg body weight/day derived by the EU Scientific Committee on Food in 2001 (Scientific Committee on Food, 2001) and the provisional maximum TDI of the same value derived by JECFA in 2001 (JECFA, 2001e).

EFSA derived a BMD_{05} and associated $BMDL_{05}$ for T2, using anti-horse globulin titres (a measure of immunotoxicity) in pigs (Rafai *et al.*, 1995a; Rafai *et al.*, 1995b). The best fitting model gave a BMD_{05} value of 15 µg/kg body weight/day and a $BMDL_{05}$ of 10.3 µg/kg body weight/day (EFSA, 2011b). Using this model the corresponding BMD_{10} and $BMDL_{10}$ values would be 31.6 and 21.7 µg/kg body weight/day, respectively.

4.2.5 Metabolites and their relative toxicities

Studies in recent years have highlighted that trichothecene mycotoxins may be extensively metabolised by the mycotoxin-producing fungi or in plants to produced so-called masked forms of the toxins. Glucosides of the major type A trichothecenes (T2, HT2, DAS, NEO) have been reported in naturally- or artificially-infected cereals (De Angelis *et al.*, 2012; Lattanzio *et al.*, 2012; Nakagawa *et al.*, 2012; 2013; Veprikova *et al.*, 2012). Triol and tetraol metabolites of T2 have been reported in naturally-contaminated cereal samples (Gottschalk *et al.*, 2009).

Similarly, glucosides of NIV and FX have recently been reported, with the authors estimating that levels of the glucoside were greater than 15% of those of the parent toxin (Nakagawa *et al.*, 2011).

By far the best characterised masked trichothecenes are metabolites of DON. The most prominent of these are the acetylated derivatives, 3ADON and 15ADON and a glucoside, DON-3-glucoside (DON-3-G). 3ADON and 15ADON appear to be fungal metabolites, while DON-3-G appears to be a plant metabolite and may be associated with *Fusarium* head blight (FHB) resistance in some cereal varieties (Berthiller *et al.*, 2013).

DON-3-G has been shown to release the aglycone (DON) under simulated human intestinal conditions (Berthiller *et al.*, 2011; Dall'Erta *et al.*, 2013) and in *in vivo* rat studies (Nagl *et al.*, 2012). However, other studies simulating human digestion showed little production of DON from DON-3-G (De Nijs *et al.*, 2012). An *in vivo* study in a human volunteer did not detect intact DON-3-G or 3ADON in urinary output (Warth *et al.*, 2013). However, concentrations of these metabolites were low in the test diet.

Rapid hydrolysis of 3ADON and 15ADON in rat stomach has been demonstrated (Veršilovskis *et al.*, 2012).

On the basis of currently available information, it appears prudent to assume that 3ADON, 15ADON and DON-3-G present in food samples will be converted quantitatively to DON in the human digestive tract and should be considered as being equivalent to DON, in terms of toxicity.

A recent consolidation of European data concluded that 3ADON and 15ADON were detected less frequently than DON and at lower concentrations (EFSA, 2013c). On average, the contribution of 3ADON to total DON was less than 2% for lower bound estimates (not detected = zero) and 13-20% for upper bound estimates (not detected = LOD). 15ADON contributed 10-15% to total DON for both lower and upper bound estimates. Few data were provided on DON-3-G. However, it almost always co-occurred with DON and on average represented 5.6% of the lower bound sum of DON and DON-3-G.

The metabolism of DON in animals has been reviewed (Dänicke and Brezina, 2013). In pigs, cattle and poultry DON can be de-epoxidised in the gut to form de-epoxy-DON. There is some evidence to suggest that this process is carried out by the microbial population in the lower intestine. Both DON and de-epoxy-DON form conjugates in the liver, mainly with glucuronic acid. The limited toxicity testing carried out on these metabolic forms of DON

suggest that de-epoxy-DON and the glucuronides of DON and de-epoxy-DON are less toxic than parent DON.

4.3 Exposure Assessment

4.3.1 Trichothecenes in New Zealand cereal grains

No new information on trichothecene mycotoxins in New Zealand cereal grains has been published since the previous version of this risk profile.

4.3.2 Trichothecenes in the New Zealand food supply

Since the previous risk profile, a survey of trichothecene mycotoxins in the New Zealand food supply have been carried out (Cressey *et al.*, 2014). In addition, an unpublished study was carried out by a student at ESR analysing DON and NIV in a range of consumer foods (Eva Kosanic, unpublished study). It should be noted that the study of Cressey *et al.* (2014) contained 2 sets of samples; 176 composite samples taken in 2009 and 24 single samples taken in 2014. These 2 components have been reported separately. Results are summarised in Table 11.

Table 11: Trichothecene mycotoxins in New Zealand foods

Food	Year of survey	Toxin	Analytical limit of detection, µg/kg	Number of samples positive/ total samples (%)	Mean of positive results (range), µg/kg
Cornflakes	2009[1]	DON NIV	40 50	1/3 (33) 1/3 (33)	44 31[2]
Cornflakes	2009	DON[3] DAS	0.2 0.1	8/8 (100) 1/8 (13)	4.7 (2.4-9.5) 0.2
Bran flake cereal	2009	DON[3]	0.3	8/8 (100)	13.7 (8.9-22)
Bran flake cereal	2014	DON[3]	0.3	4/4 (100)	8.1 (5.2-10.6)
Wheat biscuit cereal	2009[1]	DON NIV	12 70	0/3 (0) 0/3 (0)	- -
Wheat biscuit cereal	2009	DON[3]	0.2	8/8 (100)	3.4 (2.4-5.0)
Muesli	2009[1]	DON NIV	33 32	0/3 (0) 0/3 (0)	- -
Muesli	2009	DON[3]	0.2	8/8 (100)	3.7 (1.3-9.5)
Muesli	2014	DON[3]	0.2	4/4 (100)	1.4 (1.0-1.8)
Oats, rolled (uncooked)	2009[1]	DON NIV	19 21	0/3 (0) 0/3 (0)	- -
Oats, rolled (cooked)	2009	No toxins detected[3]	-	-	-
Bread, various	2009[1]	DON NIV	27 32	0/3 (0) 1/3 (33)	- 100
Bread, mixed grain	2009	DON[3] NIV	0.3 0.2	8/8 (100) 5/8 (63)	5.3 (2.0-10.4) 3.3 (2.7-3.8)
Bread, mixed grain	2014	DON[3]	0.3	4/4 (100)	10.1 (7.2-14.5)
Bread, wheatmeal	2009	DON[3] NIV	0.3 0.2	7/8 (88) 4/8 (50)	4.6 (2.6-7.4) 4.8 (3.5-6.6)
Bread, wheatmeal	2014	DON[3] NIV	0.3 0.2	4/4 (100) 3/4 (75)	8.3 (3.6-10.7) 3.8 (2.5-4.8)

Food	Year of survey	Toxin	Analytical limit of detection, µg/kg	Number of samples positive/ total samples (%)	Mean of positive results (range), µg/kg
Bread, white	2009	DON[3] NIV	0.3 0.2	6/8 (75) 3/8 (38)	3.2 (1.3-5.4) 2.8 (2.5-3.8)
Bread, white	2014	DON[3]	0.3	4/4 (100)	1.8 (1.4-2.2)
Biscuits, chocolate	2009	No toxins detected[3]	-	-	-
Biscuits, cracker	2009	DON[3] NIV	0.2 0.2	8/8 (100) 8/8 (100)	8.1 (4.8-22) 8.7 (5.8-13.5)
Biscuits, sweet plain	2009	DON[3] NIV	0.2 0.4	7/8 (88) 6/8 (75)	5.3 (2.4-13.0) 10.6 (6.9-16.4)
Cake	2009	DON[3] NIV	0.3 0.3	2/8 (25) 3/8 (38)	4.9 (2.0-7.8) 4.2 (2.3-7.0)
Muffin	2009	No toxins detected[3]	-	-	-
Noodles, instant (cooked)	2009	DON[3] NIV	0.2 0.1	7/8 (88) 4/8 (50)	9.2 (4.5-25) 1.5 (1.2-1.8)
Pasta, dried (cooked)	2009	DON[3] NIV	0.2 0.1	8/8 (100) 1/8 (13)	16.8 (3.0-38) 1.7
Spaghetti in sauce, canned	2009	DON[3] NIV	0.3 0.1	6/8 (75) 3/8 (38)	10.4 (5.6-22) 1.6 (1.1-2.6)
Rice (uncooked)	2009[1]	DON NIV	18 19	0/3 (0) 1/3 (33)	- 28
Rice, white (cooked)	2009	NIV[3] DAS	0.2 0.3	1/8 (13) 1/8 (13)	3.9 1.2
Snack bars	2009	DON[3] NIV	0.2 0.3	1/8 (13) 1/8 (13)	2.5 2.5
Extruded snack foods	2009	DON[3] NIV	0.2 0.3	4/5 (80) 3/5 (60)	6.7 (3.4-9.0) 5.5 (5.0-6.1)
Extruded snack foods	2014	DON[3] NIV	0.2 0.3	2/2 (100) 1/2 (50)	1.4 (1.1-1.7) 7.4
Corn chips	2009	DON[3] NIV 15ADON T2	0.2 0.3 6 0.04	3/3 (100) 2/3 (67) 1/3 (33) 1/3 (33)	166 (26-410) 6.8 (5.0-8.6) 41 0.4
Corn chips	2014	DON[3] NIV	0.2 0.3	2/2 (100) 1/2 (50)	2.5 (2.4-2.6) 10.1
Pizza	2009	DAS[3]	0.2	1/8 (13)	0.3
Cornflour	2009[1]	DON NIV	14 25	1/3 (33) 1/3 (33)	108 112
Cereal-based infant weaning food	2009	NIV[3]	0.3	1/8 (13)	4.6
Beer	2009	DON[3]	0.4	1/8 (13)	10.9

DON = deoxynivalenol, NIV = nivalenol, T2 = T-2 toxin, HT2 = HT-2 toxin, NEO = neosolaniol, DAS = diacetoxyscirpenol, FX = Fusarenon X, 3ADON = 3-acetyldeoxynivalenol, 15ADON = 15-acetyldeoxynivalenol

Results are from (Cressey *et al.*, 2014), unless otherwise specified

[1] From (Kosanic, 2009)

[2] Result was reported even though it was below the LOD given

[3] The survey included analyses for DON, 3ADON, 15ADON, NIV, FX, T2, HT2, DAS and NEO. If any of these toxins are not listed in the table in relation to a food then it was not detected in that food.

4.3.3 Trichothecenes in Australian cereal grains

Following an isolated occurrence of *Fusarium* head blight in Western Australia during 2003, the main mycotoxins detected in the grain were DON, 3ADON, zearalenone (ZEA), enniatins and chlamydosporol (Tan *et al.*, 2012).

The 23rd Australian Total Diet Survey analysed bread (white and multigrain), savoury biscuits, breakfast cereals, rolled oats, pasta and meat pies for DON (Food Standards Australia New Zealand, 2011). DON was not detected in any samples. However, the method used for analyses and the LOD for the method were not reported.

4.3.4 Overseas context

While a large body of information has been published on trichothecene mycotoxins in food, the majority of this information confirms that these mycotoxins are principally found in cereals and foods derived from cereals, including beer. The following sections summarise studies in which trichothecene mycotoxins were detected in non-cereal foods. Further information on trichothecene mycotoxins in beer is also summarised here.

4.3.4.1 Foods of plant origin

Nuts and seeds

A study in Saudi Arabia detected T2 in 1 of 11 pumpkin seed samples at a concentration of 140 µg/kg, while DAS was detected in 1 of 7 peanut samples at a concentration of 120 µg/kg (Alwakee and Nasser, 2011). Neither toxin was detected in samples of chickpeas (n = 4), pine nuts (n = 3), almonds (n = 3), pistachios (n = 5), Karela seeds (n = 2), sunflower seeds (n = 2), walnuts, cashews or hazelnuts (all n = 1). The thin layer chromatography (TLC) method used did not distinguish any other trichothecene mycotoxins.

Single samples of peanuts, almonds, sunflower seeds, pumpkin seeds, walnuts, macadamia nuts, pistachios, hazelnuts and pine nuts were analysed by a multi-mycotoxin method that included DON, FX, T2 and HT2 (Arroyo-Manzanares *et al.*, 2013). DON was detected in the walnut sample at a concentration of 346 µg/kg and FX was detected in the macadamia nut samples at a concentration of 2470 µg/kg.

Spices

DON was detected in 2 of 11 samples of chilli powder and 1 of 17 paprika samples (Santos *et al.*, 2011). The authors report maximum concentrations of DON in these sample types of 0.1 and 0.3 **g/kg**, respectively (100,000 and 300,000 µg/kg), although comments in the text suggest they mean 100 and 300 µg/kg. T2 was detected in 2 of 11 chilli samples.

Soybeans

DON, DON-3-G and FX were detected in all of 10 soybean samples from Cameroon, while NIV was detected in 9 of 10 samples (Abia *et al.*, 2013b). DON-3-G was only present at low concentrations (maximum 1 µg/kg) compared to DON (range 56-75 µg/kg). FX

concentrations were in the range 33-42 μg/kg, while only very low concentrations of NIV (0.3-0.5 μg/kg) were detected.

Analysis of soy products (*n* = 45) was carried out for a range of trichothecene mycotoxins (A and B types) (Schollenberger *et al.*, 2007b). The most commonly detected toxin was DON (6/45 samples, 11-260 μg/kg), followed by MAS (4/45 samples, 5-34 μg/kg) and HT2 (3/45 samples, 5-11 μg/kg). Several toxins were only detected in single samples, including DAS (21 μg/kg), T2 tetraol (32 μg/kg), 15ADON (11 μg/kg) and 3ADON (14 μg/kg).

Tubers

Fusarium sulphureum is a major cause of rot in stored potatoes in China (Xue *et al.*, 2013). FX, 3ADON, DAS and T2 were detected in potato tubers inoculated with *F. sulphureum* and stored at 5-8ºC for 60 days. FX was present at the highest concentration, with concentrations in lesions in the range 20.8 to 36.9 mg/kg and 0.16 to 0.51 mg/kg in the asymptomatic flesh. The study only examined these 4 trichothecene mycotoxins and it is uncertain whether *F. sulphureum* produces other mycotoxins, or whether mycotoxin contamination occurs in naturally infected potatoes. A further paper by the same group reported that *F. solani* and *F. sambucinum* are also capable of producing these 4 mycotoxins when inoculated onto potatoes (Xue *et al.*, 2014).

Edible oils and oil products

DON was detected (LOD = 40 μg/kg) in 2 of 25 corn oil samples, but was not detected in any of 25 corn oil margarines (Escobar *et al.*, 2013). The maximum concentration detected in corn oil was 216 μg/kg.

Beer

While DON has previously been reported to occur in beer, a major European study also detected T2 and HT2 in a sample of 393 commercial beer samples (Cantrell, 2008). While the presentation of this study does not allow the prevalence of T2/HT2 contamination to be determined, it was reported that HT2 was detected in the majority of samples. The mean and maximum concentrations of T2 plus HT2 were 0.30 μg/L and 3.12 μg/L, respectively. DON was detected in approximately half of the samples analysed, while NIV was only detected in 3% of samples. ADON was detected in less than 1% of samples, while DAS, MAS, FX, NEO and T2-triol were not detected at all.

This contrasts to a study which did not detect T2 or HT2 in any of 106 European beers (Bertuzzi *et al.*, 2011). However, the disparity between these 2 studies is likely to be largely due to the higher LOD (1.5 μg/L) in the study of Bertuzzi *et al*. than the study of Cantrell (0.03-0.05 μg/L).

T2, HT2 and DON were not detected in any beer sample (*n* = 76) at limits of detection of 0.01, 0.1 and 0.1 μg/L, respectively (Al-Taher *et al.*, 2012).

Analysis of mainly Austrian and German beers (*n* = 374) found that DON-3-G was the most commonly detected trichothecene mycotoxin (93% of samples) when compared to DON

(77% of samples) and 3ADON (not detected in any sample) (Varga *et al.*, 2012a). The average concentrations of the 2 toxins were 6.9 and 8.4 µg/L for DON-3-G and DON, respectively. The molar ratio of DON-3-G to DON varied from 0.11 to 1.25 for samples that contained both compounds.

This is consistent with a Czech study that detected DON-3-G in 74% of beer samples (*n* = 176), while DON was only detected in 64% of samples and ADON conjugates in 50% of samples (Kostelanska *et al.*, 2009). Other trichothecene mycotoxins (NIV, FX, T2, HT2) were not detected in any beer sample. Mean concentrations of DON and DON-3-G were correlated with the alcohol content of the beer and were higher in dark beers than light beers. The mean concentration of DON ranged from 1.6 µg/L in low alcohol light beer to 11.2 µg/L in high alcohol dark beer. Mean DON-3-G concentrations ranged from 1.7µg/L to 7.8 µg/L. ADON concentrations were particularly high in high alcohol dark beers (13.7 µg/L).

A Korean study detected DON in 3 of 26 beer samples with concentrations in the range 8.4-28.6 µg/kg (Ok *et al.*, 2009a).

Wine

T2 was detected in 22% of 71 samples of white wine (Al-Taher *et al.*, 2012). T2 was present in trace amounts (0.1-0.3 µg/L) in 8 samples and at concentrations in the range 0.40-0.76 µg/L in a further 8 samples. No other trichothecene mycotoxins (HT2, DON) were detected in white wine and no trichothecene mycotoxins were detected in red wine (*n* = 72). Wines were from USA, Europe, South America and Australia.

4.3.4.2 Foods of animal origin

Poultry

T2, HT2 and DAS were analysed for in tissue samples from 2 broilers (42 days old) fed a diet containing *F. poae*-contaminated maize (Yang *et al.*, 2013). T2 and HT2 were detected in heart, liver, spleen, lung, kidney, glandular stomach, muscular stomach, small intestine, muscle, bone and brain from both broilers. DAS was only detected in heart, bone and brain from 1 broiler. T2 and HT2 concentrations in the most commonly consumed tissues (muscle and liver) were amongst the lowest tissue concentrations measured, with T2 concentrations in the range 1.1-2.4 µg/kg and HT2 in the range 0.06-1.2 µg/kg. The highest concentrations measure were in brain, heart, lung, kidney and small intestine.

Pigmeat

A Chinese study detected T2, but not HT2, in 2 of 10 pigmeat samples, with concentrations in the range 1.2-4.6 µg/kg (Chen *et al.*, 2013). The metabolite, T2 tetraol, was also detected in 2 samples, with concentrations in the range 2.7-3.5 µg/kg. Other trichothecene mycotoxins analysed (DON, NIV, 3ADON, 15ADON, DAS, MAS, NEO, FX, T2-triol and de-epoxy-DON were not detected. In 10 porcine liver samples, T2 (2 samples, 1.5 µg/kg), HT2 (1 sample, 2.5 µg/kg), T2-tetraol (4 samples, 3.0-5.2 µg/kg), DON (1 sample, 3.1 µg/kg) and de-epoxy-DON (2 samples, 2.8 µg/kg) were detected.

Pigs (n = 6) were fed a diet containing 6.68 mg/kg DON (Goyarts *et al.*, 2007). DON and de-epoxy-DON were detected in muscle at mean concentrations of 13.8 and 0.3 μg/kg, respectively. The highest concentrations of mycotoxins were seen in bile (427.6 and 80.2 μg/kg) and kidney (79.0 and 6.2 μg/kg), while neither toxin was detectable in back fat.

Milk

Rumen metabolism results in substantial conversion of DON to the apparently less toxic de-epoxy-DON (Dänicke and Brezina, 2013; Fink-Gremmels, 2008). Rates of carryover of DON and de-epoxy-DON from feed into milk have been reported to be low, with percentage carryover of 0.0001-0.0002% and 0.0004-0.0024% respectively (Fink-Gremmels, 2008).

A Chinese study detected HT2 (3.1 μg/kg) and T2-tetraol (2.4 μg/kg) in 1 of 5 market milk samples (Chen *et al.*, 2013). None of the other trichothecene mycotoxins analysed for (see under 'Pigmeat' above) were detected.

Cows were fed a diet delivering 16.6 to 75.6 mg/day DON (Seeling *et al.*, 2006). Analysis of duodenal, serum and urine samples indicated near completed biotransformation of DON to de-epoxy-DON. Daily excretion of DON and de-epoxy-DON in milk was 1 to 10 μg and 14 to 104 μg, respectively.

DON was detected in the milk of sheep consuming feed containing 1600 μg/kg DON (Jolánkai *et al.*, 2008). DON was detected in ewes' milk at concentrations in the range 0.4-7.2 μg/L, but not in a product (kefir) produced from the milk.

Eggs

A Chinese study did not detect any trichothecene mycotoxins (see under 'Pigmeat' above for the range of analytes) in 5 egg samples (Chen *et al.*, 2013).

In contrast, a Belgian study detected DON in 17 of 20 home-produced egg samples, with concentrations range from a trace (0.6-2.0 μg/kg) and 17.9 μg/kg (Tangni *et al.*, 2009). De-epoxy-DON was less frequently detected (4 of 20 samples, range 2.4-23.7 μg/kg). The sample with the highest DON concentration was also the sample with the highest de-epoxy-DON concentration. Feedstuffs were obtained from some, but not all, of the egg producers. The highest level of DON in feed (1230 μg/kg) was from the producers with the highest concentration of DON and de-epoxy-DON in their eggs.

4.3.4.3 Other trichothecene mycotoxins

A review has recently been published on the occurrence of the scirpentriol subgroup of trichothecene mycotoxins (Schollenberger *et al.*, 2007a). The most commonly reported compounds in this group are DAS, MAS and scirpentriol.

DAS has been occasionally detected in wheat, barley, oats, maize, soybean and potatoes, although the majority of surveys reviewed did not detect DAS. Concentrations of DAS as high as 1000 μg/kg have been reported in maize from Canada. DAS concentrations of 900 μg/kg have been reported in maize in New Zealand (Hussein *et al.*, 1989).

MAS has also been occasionally detected in wheat, barley, oats, maize, potato products and soy products. However, when detected, concentrations are generally low (<50 μg/kg).

Scirpentriol has been detected in wheat, barley, oats, maize, soy products and potato products. Concentrations greater than 900 μg/kg have been reported, but most studies report concentrations of less than 100 μg/kg.

4.3.5 New Zealand estimates of dietary exposure

Table 12 summarises New Zealand estimates of dietary exposure to trichothecene mycotoxins, derived in a recent study (Cressey, 2014). Exposure estimates are presented here for DON and NIV. In the survey that these exposure estimates are based on T2 and 15ADON were detected in 1 food sample, while DAS was detected at very low concentrations in 3 food samples. These concentration data were considered to be insufficient to derive dietary exposure estimates for T2, 15ADON and DAS. However, even using upper bound estimates of concentration for all foods in which T2 and DAS were not detected results in mean estimates of exposure of less than 1 ng/kg body weight/day for all age-gender groups. The 'usual' exposures in Table 12 are determined using statistical techniques that remove intra-person variability in food consumption from the distribution of exposures.

Table 12: Estimated trichothecene mycotoxin dietary exposure for various New Zealand population subgroups

Age-gender group	**Estimated dietary trichothecene mycotoxin exposure, lower bound – upper bound, ng/kg body weight/day**		
	Mean	**95th percentile**	**95th percentile usual**
Deoxynivalenol (DON)			
PMTDI/TDI (JECFA/EFSA) = 1000 ng/kg body weight/day			
Child (5-6 years)	76-77	206-208	NC
Female (11-14 years)	38-39	102-103	75-76
Male (11-14 years)	44-45	129-131	86-88
Male (19-24 years)	30-33	103-103	NC
Female (25+ years)	16.6-17.1	51-54	NC
Male (25+ years)	23.6-25.1	68-72	NC-51
Nivalenol (NIV)			
TDI (EFSA) = 1200 ng/kg body weight/day			
Child (5-6 years)	21.9-23.7	51-54	36-38
Female (11-14 years)	10.3-11.3	26.8-28.4	15.5-15.9
Male (11-14 years)	12.8-14.1	29.4-31.2	21.4-23.9
Male (19-24 years)	3.7-5.3	11.0-13.7	NC
Female (25+ years)	3.6-4.2	9.2-10.2	NC-7.9
Male (25+ years)	4.0-5.3	10.5-12.5	NC-9.1

NC: usual intakes could not be calculated

PMTDI = provisional maximum tolerable daily intake, TDI = tolerable daily intake, JECFA = Joint FAO/WHO Expert Committee on Food Additives, EFSA = European Food Safety Authority

No previous New Zealand estimates of dietary exposure to trichothecene mycotoxins are available for comparison.

While the analytical method used to generate the concentration data used in the current exposure assessment was extremely sensitive for the detection of DON, it was less optimal for detection of the conjugated forms of DON (3ADON, 15ADON and DON-3-G). These conjugated forms would have been present, at some level, in foods analysed. Based on information presented in EFSA's exposure assessment of DON, the total exposure of DON from these three conjugated is likely to be less than 50% of the exposure to parent DON (EFSA, 2013c). A 50% increase in the dietary exposure estimates in Table 12 would still result in estimates that were well below the health-based exposure limits.

4.3.6 Overseas estimates of dietary exposure

A summary of exposure estimates for trichothecene mycotoxins and, in some cases, selected metabolites published since the previous version of this risk profile is given in Table 13.

Table 13: Overseas estimates of dietary exposure to trichothecenes

Country	Population group	Mean (95th percentile) exposure, ng/kg body weight/day	Reference
DON TDI (EFSA) or PMTDI (JECFA) = 1000 ng/kg body weight/day			
Argentina	Males - 18-24 years - 25-50 years Females - 18-24 years - 25-50 years	 135 95 75 92	(Pacin *et al.*, 2011)
Belgium	Adults - DON - 3ADON - 15ADON - DON-3-G - Total DON	 35-40 (80-91)[1] 23-24 (53-55) 9-16 (21-35) 21-25 (48-56) 89-104 (202-237)	(De Boevre *et al.*, 2013)
Brazil (Paraná state)	Individuals, 8-76 years (*n* = 260)	1130 (range 0-5090)[2]	(Sifuentes dos Santos *et al.*, 2013)
Denmark	Total population Children	170 320	(Rasmussen *et al.*, 2007)
European Union	Infants Toddlers Other children Adolescents Adults Elderly Very elderly	160-730 (920-1610)[3] 480-1020 (880-1810) 430-970 (760-1650) 280-580 (590-1080) 170-460 (310-1020) 160-310 (310-620) 210-330 (400-590)	(EFSA, 2013c)
France	Adult females - Before pregnancy - Third trimester	 253-282 (554-619)[1] 198-221 (428-475)	(Chan-Hon-Tong *et al.*, 2013)
France	Children - DON - 3ADON - 15ADON Adults - DON	 540-560 (1020-1030)[1] 0.1-29 (0. 8-54) 0.7-30 (2.8-57) 370-380 (720)	(Sirot *et al.*, 2013)

Country	Population group	Mean (95th percentile) exposure, ng/kg body weight/day	Reference
	- 3ADON - 15ADON	0.3-16 (1.6-29) 0.2-16 (0.9-27)	
GEMS/Food cluster diets	General population	190-14500	(JECFA, 2011)
Hungary	Adults (from white bread)	260-490 (560-1050)[1]	(Ambrus *et al.*, 2011)
India	General population	3200 (7720; 90th percentile)	(Mishra *et al.*, 2013)
Japan	From consumption of wheat products only - 1-6 years - 7-14 years - 15-19 years - Over 19 years	95th percentile 718 511 404 249	(Nakatani *et al.*, 2011)
Korea	Male, 3-6 years Female, 3-6 years Male, 7-12 years Female, 7-12 years Male, 13-19 years Female, 13-19 years Male, 20-29 years Female, 20-29 years Male, 30-49 years Female, 30-49 years Male, 50-64 years Female, 50-64 years Male, 65+ years Female, 65+ years	142 (292) 144 (302) 95 (200) 96 (200) 77 (162) 65 (138) 66 (139) 66 (132) 68 (143) 68 (141) 73 (156) 72 (155) 70 (154) 70 (154)	(Ok *et al.*, 2009b)
Korea	Population, 3-85 years (mean body weight = 57.6 kg)	9.8	(Ok *et al.*, 2009a)
Korea	Population, 3-85 years (mean body weight = 57.6 kg) - DON - 3ADON - 15ADON	 47.6 1.8 6.2	(Ok *et al.*, 2011)
Lebanon	Children, 8-13 years Teenagers, 14-18 years	545 (975) 409 (664)	(Soubra *et al.*, 2009)
Morocco	General population	0.2[4]	(Serrano *et al.*, 2012)
Netherlands	Children (*n* = 123, duplicate diet)	291	(Bakker *et al.*, 2009)
Serbia	Children Adults	1700 1500	(Škrbić *et al.*, 2012)
South Africa[5]	Infants, 1-5 years, rural Infants, 1-5 years, urban Young children, 6-9 years, rural Young children, 6-9 years, urban Adults, 10+ years, rural Adults, 10+ years, urban	3800 2780 2730 1960 1770 1450	(Shephard *et al.*, 2010)
Spain	Infants, 0-3 years Children, 4-9 years Adolescents, 10-19 years Adult males, 20-65 years	740 360 150 100	(Cano-Sancho *et al.*, 2011a)

Country	Population group	Mean (95th percentile) exposure, ng/kg body weight/day	Reference
	Adult females, 20-65 years Seniors, 65+ years Coeliac sufferers Ethnics	90 40 130 570	
Spain	DON + 3ADON - Infants (0-3 years) - Children (5-12 years) - Adults (18-65 years)	 77.3 63.3 9.1	(Rodríguez-Carrasco *et al.*, 2013)
Tunisia	General population	189	(Serrano *et al.*, 2012)
United Kingdom	Pregnant women (n = 55)	168 (range 23-982)[6]	(Hepworth *et al.*, 2011)
NIV TDI (EFSA) = 1200 ng/kg body weight/day			
France	Children Adults	31-59 (72-119)[1] 20-34 (45-67)	(Sirot *et al.*, 2013)
European Union	Infants Toddlers Other children Adolescents Adults Elderly Very elderly	2.4-140 (16-389)[3] 4.3-202 (12-484) 1.3-132 (3.0-259) 1.0-80 (3.0-147) 0.4-75 (1.1-224) 0.8-55 (2.3-127) 0.8-58 (1.9-111)	(EFSA, 2013b)
Korea	Population, 3-85 years (mean body weight = 57.6 kg)	76.6	(Ok *et al.*, 2011)
Morocco	General population	6.1[4]	(Serrano *et al.*, 2012)
Spain	General population	433	(Serrano *et al.*, 2012)
Spain	Infants (0-3 years) Children (5-12 years) Adults (18-65 years)	67.5 62.7 7.5	(Rodríguez-Carrasco *et al.*, 2013)
Tunisia	General population	3411	(Serrano *et al.*, 2012)
T2 toxin TDI (EFSA) = 100 ng/kg body weight/day (combined with HT2)			
Belgium	Adult	6-12 (15-28)[1]	(De Boevre *et al.*, 2013)
European Union	Infants Toddlers Other children Adolescents Adults Elderly Very elderly	5.9-16 (19-51)[3,7] 12-43 (23-91) 10-39 (21-71) 4.4-24 (12-47) 3.4-18 (7.2-39) 3.3-14 (6.7-26) 2.8-15 (5.3-25)	(EFSA, 2011b)
France	Adult females - Before pregnancy - Third trimester	 1.95-16.62 (4.56-35.40)[1] 1.55-12.97 (3.61-27.57)	(Chan-Hon-Tong *et al.*, 2013)
France	Children Adults	4.0-38 (9.0-73)[1] 1.8-20 (4.8-37)	(Sirot *et al.*, 2013)
Morocco	General population	0.4[4,7]	(Serrano *et al.*, 2012)
Serbia	Children Adults	20 20	(Škrbić et al., 2012)
Spain	Children, 4-9 years	56-79[2,7]	(Cano-Sancho *et al.*,

Country	Population group	Mean (95th percentile) exposure, ng/kg body weight/day	Reference
	Adolescents, 10-19 years Adult male, 20-65 years Adult female, 20-65 years	27-40 12-19 11-16	2012b)
Spain	Infants (0-3 years) Children (5-12 years) Adults (18-65 years)	85.9[7] 79.2 9.5	(Rodríguez-Carrasco *et al.*, 2013)
Tunisia	General population	43.6[7]	(Serrano *et al.*, 2012)
HT2 toxin	**TDI (EFSA) = 100 ng/kg body weight/day (combined with T2)**		
Belgium	Adults	10-18 (23-41)[1]	(De Boevre *et al.*, 2013)
France	Adult females - Before pregnancy - Third trimester	 4.33-22.18 (9.43-46.38)[1] 3.70-17.98 (7.94-37.35)	(Chan-Hon-Tong *et al.*, 2013)
France	Children Adults	11-53 (22-104)[1] 7.2-32 (15-59)	(Sirot *et al.*, 2013)
Other			
Korea	Population, 3-85 years (mean body weight = 57.6 kg) - FX	 4.2	(Ok *et al.*, 2011)
Morocco	General population - DAS	 0.1	(Serrano *et al.*, 2012)
Spain	Infants (0-3 years) - FX - DAS - NEO Children (5-12 years) - FX - DAS - NEO Adults (18-65 years) - FX - DAS - NEO	 40.0 8.6 53.5 36.1 5.8 23.7 4.5 1.1 7.5	(Rodríguez-Carrasco *et al.*, 2013)
Tunisia	General population - DAS	 24.7	(Serrano *et al.*, 2012)

TDI = Tolerable Daily Intake DON = deoxynivalenol 3ADON = 3-acetylDON
15ADON = 15-acetylDON DON-3-G = DON-3-glucoside NIV = nivalenol
FX = fusarenon X DAS = diacetoxyscirpenol NEO = neosolaniol

[1] The range covers different approaches for dealing with left censored analytical data

[2] Exposures were calculated for consumption of bread and pasta. However, the DON concentration used was for harvest wheat

[3] The ranges presented are from the lower bound exposure estimate for the minimum EU estimate to the upper bound estimate for the maximum EU estimate

[4] Exposure estimates for Morocco were based only on consumption of rice

[5] Exposures were calculated separately for consumption of maize meal and wheat flour. These separate estimates have been summed, but more than 95% of exposure is due to consumption of maize meal

[6] The published exposures were in units of μg/day. These were converted to ng/kg body weight/day assuming a body weight of 60 kg

[7] Sum of T2 and HT2

4.3.7 Biomarkers of exposure

It has been estimated that approximately 70% of dietary DON is excreted in urine, with approximately three-quarters of excreted DON conjugated, mainly with glucuronic acid (Warth *et al.*, 2013).

A cohort of pregnant woman (n = 85, aged 21-44 years) from Bradford, England provided urinary samples for DON analysis and completed a concurrent food frequency questionnaire (FFQ) (Hepworth *et al.*, 2011). Urinary DON was measured as free DON plus a DON-glucuronide. Urinary DON was detected in all subjects, with concentrations in the range 0.5-116.7 ng/mg creatinine. De-epoxy-DON was not detected in any sample. Urinary DON was statistically significantly correlated with dietary DON intake, determined from FFQ and 'typical' DON concentrations for foods.

Urinary DON was measured in 3 cohorts of 100 adults (total n = 300) (Turner *et al.*, 2008). The 3 cohorts represented low (mean 107 g/day), medium (mean 179 g/day) and high (mean 300 g/day) cereal intake groups, as assessed by 7-day dietary records. DON was measured in 24-hour urine after enzymatic conversion of glucuronides to free DON. DON was detected in 296 of 300 urine samples. Urinary DON output for the 3 cohorts was significantly correlated with cereal intake. In multivariate analysis, consumption of wholemeal bread, white bread, 'other' bread, buns/cakes, high-fibre breakfast cereals and pasta were all statistically significantly ($p < 0.05$) associated with urinary DON. Further analysis of the data from this study concluded that urinary DON variation was better explained by recent (day of urine sampling) cereal consumption, than usual (previous 7 days) cereal consumption (Turner *et al.*, 2009).

The same research group examined this issue by analysing urinary DON and DON dietary exposure in a cohort during periods of normal diet, wheat restriction intervention and partial wheat restriction intervention (Turner *et al.*, 2010). DON was detected in 198 of 210 urinary samples under normal diet conditions (geometric mean 10.1 ng/mg creatinine, range not detected to 70.7 ng/mg), in 94 of 98 samples under partial intervention (mean 5.9 ng/mg, range not detected to 28.4 ng/mg), and in 17 of 40 samples under full intervention (mean 0.5 ng/mg, range not detected to 3.3 ng/mg). A strong correlation was found between urinary DON and dietary exposure to DON.

Analysis of urine samples from the Shanghai Women's Health Study cohort (n = 60) detected DON (free DON plus DON-glucuronides) in 97% of samples (Turner *et al.*, 2011). Mean concentrations (5.9 ng/mg creatinine) were approximately half those for a similar cohort in the United Kingdom (Turner *et al.*, 2008). It was suggested that this may be due to the lower consumption of wheat in Shanghai (25% of consumption in the United Kingdom), but a higher level of DON contamination in wheat consumed. However, urinary DON concentrations were not significantly correlated with total cereal consumption, wheat consumption or rice consumption.

In Egypt, DON was detected in urine from 63 of 93 (68%) pregnant women (age range 18-40 years), with concentrations in the range 0.5-59.9 ng/mg creatinine (Piekkola *et al.*, 2012). Urinary DON was measured as free DON plus a DON-glucuronide.

A similar study of 40 non-smoking pregnant women in Croatia detected DON, DON-3-glucuronide and DON-15-glucuronide in 76, 83 and 98% of urinary samples respectively (Šarkanj *et al.*, 2013). DON-15-glucuronide was not only the species most commonly detected, but also the species detected at the highest concentrations. Total DON (DON plus glucuronides) concentrations were in the range 6.7-903.7 ng/mg creatinine. Urinary DON output was used to estimate dietary exposure by including a measure of the volume of urine produced per day, the urinary DON elimination rate (72%), body weight and a concentration factor to account for first void urine being more concentrated than 24-hour urine. The mean estimated dietary DON exposure was 2500 ng/kg body weight/day (range 100 to 33,100).

DON was detected in urine from 5 of 40 volunteers from Belgium, with concentrations in the range 3.7-67 ng/mg creatinine (Njumbe Ediage *et al.*, 2012). DON-3-G was not concurrently present in any of these urine samples. This method was applied to a cohort of 220 children in Cameroon (Njumbe Ediage *et al.*, 2013). DON was detected in 17% of urinary samples, With concentrations in the range 0.1 to 77 ng/ml. Urinary DON concentrations were significantly lower in female children than males. DON-3-G was detected in 1% of samples.

In a study of adult from Cameroon (n = 175) urinary total DON (DON + DON-3-glucuronide + DON-15-glucuronide) was detected in 73 samples (42%) with a maximum concentration of 74.7 μg/L of DON equivalents (Abia *et al.*, 2013a). DON-15-glucuronide was the most commonly detected form of DON, followed by DON-3-glucuronide and parent DON. Literature values for the urinary excretion rate of DON (72%) and an estimate of daily urinary output (1.5 L) were used to estimate dietary exposure to DON. NIV was detected in 25 samples (14%) with a maximum concentration of 22.0 μg/L.

Nuclear magnetic resonance (NMR) spectroscopy was used to examine the metabolome in urine of subjects with low and high DON exposure (Hopton *et al.*, 2009). Hippurate content of urine was found to be significantly elevated in subject with high DON exposure compared to those with low DON exposure, suggesting this compound may have potential to be used as a biomarker of DON exposure.

A recent review of the toxicity of T2 and HT2 concluded that there are no established methods for the determination of biomarkers of exposure or effects for these trichothecene mycotoxins (Shuhmacher-Wolz *et al.*, 2010). Studies in Cynomolgus monkey suggest that T2 tetraol may have potential as a blood or urinary biomarker (EFSA, 2011b).

The presence of NIV in human urinary samples has been demonstrated (Warth *et al.*, 2012b). However, concentrations were not quantifiable and it is uncertain whether urinary levels correlate with exposure.

4.4 Risk Characterisation

4.4.1 Adverse health effects in New Zealand

No cases of trichothecene intoxication have been reported in New Zealand.

4.4.2 Adverse health effects overseas

4.4.2.1 Epidemiological studies

No epidemiological studies on adverse health effects due to trichothecene mycotoxins have been reported since the previous version of this risk profile.

4.5 Risk Management Information

4.5.1 Relevant food controls: New Zealand

4.5.1.1 Establishment of regulatory limits

Trichothecenes are not currently regulated in New Zealand.

4.5.2 Relevant food controls: overseas

4.5.2.1 Establishment of regulatory limits

In 2006, the European Commission enacted regulations setting maximum limits for several mycotoxins, including DON (European Commission, 2006b). Maximum limits were (in μg/kg):

Unprocessed cereals, other than durum wheat, oats and maize	1250
Unprocessed durum wheat and oats	1750
Unprocessed maize	1750
Cereals intended for direct human consumption, cereal flour (including maize flour, maize meal and maize grits), bran as end product marketed for direct human consumption and germ, with the exception of foodstuffs for infants and young children	750
Pasta (dry)	750
Bread (including small bakery wares), pastries, biscuits, cereal snacks and breakfast cereals	500
Processed cereal-based foods and baby foods for infants and young children	200

Provisions for maximum limits for T2 and HT2 were indicated in these regulations, but were not established, pending further assessment by EFSA.

A further regulation, issued in 2007, amended the limits for DON (in μg/kg) in unprocessed maize (European Commission, 2007):

Unprocessed maize, with the exception of unprocessed maize intended to be processed by wet milling	1750
Milling fractions of maize with particle size > 500 micron falling within CN code 1103 13 or 1103 20 40 and other maize milling products with particle size > 500 micron not used for direct human consumption falling within CN code 1904 10 10	750
Milling fractions of maize with particle size ≤500 micron falling within CN code 1102 20 and other maize milling products with particle size ≤500 micron not used for direct human consumption falling within CN code 1904 10 10	1250

CN = Combined Nomenclature

The setting of limits for DON was considered to also be protective against potential impacts of 3ADON, 15ADON and NIV, due to co-occurrence with DON.

The Code Committee on Contaminants in Food are currently developing a proposal for maximum levels of DON in cereals and cereal-based foods (Codex Committee on Contaminants in Food, 2013e). The proposed limits are (μg/kg):

Raw cereal grains (wheat, maize and barley)	2000
Flour, semolina, meal, flakes (and possibly grits and starch) derived from wheat, maize or barley	1000
Cereal-based foods for infants and young children	500

The 7th Session of CCCF agreed to the limits for raw and processed cereals and agreed to establish the maximum limit for foods for infants and young children at 200 μg/kg (Codex Alimentarius Commission, 2013). A maximum limit for bran products was not proposed, but member countries were encouraged to collect and submit data on DON in bran products. An electronic working group (EWG), led by Japan and Canada, was formed to prepare a working paper on the extension of the maximum limits for DON to its acetylated derivatives

As part of an assessment of public health risks associated with T2 and HT2, EFSA reviewed regulatory limits for these toxins in non-EU countries (EFSA, 2011b). Limits for cereals and cereal products were most commonly 100 μg/kg, except for Hungary, where the limit was 300 μg/kg. In Armenia, Moldova, the Russian Federation and Ukraine the limit applies to T2 toxin, while in Norway it applies to the sum of T2 and HT2. Norway also has a separate limit of 50 μg/kg for cereals and cereal products for infants and young children.

A socio-economic impact assessment was carried out for potential regulatory options for T2 and HT2 in the EU, using a multi-criteria assessment approach (Ragona *et al.*, 2011). Under this analytical approach the 'do nothing' (no regulatory limits) approach was the preferred option. However, the application of 'strict' maximum limits was preferable to the application of 'soft' maximum limits.

4.5.2.2 Codes of practice and related initiatives

The European Commission published recommendations on the prevention and reduction of *Fusarium* toxins in cereals and cereal products (European Commission, 2006a). Recommendations include:

- Crop rotation with non-cereal crops;
- Choice of variety/hybrid with increased suitability for the growing environment, to decrease plant stress;
- Crop planning, to avoid extended ripening in the field and avoid drought stress;
- Soil and crop management, including removal of infected plant material and minimising plant stress;
- Harvesting, including segregation of suspected infected grain, harvesting at appropriate grain moisture content and avoiding mechanical damage to grain;
- Drying, including drying as soon as possible to a moisture content below that necessary for fungal growth;
- Storage, including hygiene and temperature control and use of appropriate preservatives; and
- Transport from storage, including hygiene and protection of the grain from moisture and vermin.

4.5.2.3 Management of trichothecene formation in crops

Several models have been developed to forecast DON content of cereal crops, based on weather factors (temperature, humidity, rainfall), cultivar/hybrid type, variables related to the length of the growing period, spray application and insect pest pressure (van Asselt *et al.*, 2012; Van Der Fels-Klerx *et al.*, 2010; van der Fels-Klerx *et al.*, 2012). A similar model is under development for prediction of DON in durum wheat (Gourdain *et al.*, 2011). Models were generally considered to be adequate to forecast trends, but not to predict actual mycotoxin levels. Models for DON and wheat were generally consider to provide better prediction than those for maize. Models for winter wheat and maize in the Netherlands were combined with climate change models, to predict the potential impact of climate change on mycotoxin contamination (van der Fels-Klerx *et al.*, 2013). These analyses suggest that crops will mature earlier and that DON contamination with decrease accordingly, although considerable regional variability is forecast. Data from Norway, Sweden and Finland was added, to develop a model of the impact of climate change on DON contamination of wheat in northwestern Europe (van der Fels-Klerx *et al.*, 2012).

It has been suggested that plant breeding, to increase cultivar resistance to *Fusarium* head blight (FHB) and associated trichothecene mycotoxin production, is the most effective means of decreasing trichothecene mycotoxin exposure (Foroud and Eudes, 2009). Several components of resistance are recognised; resistance to initial infection, resistance to the spread of infection within the plant, resistance to kernel infection, tolerance to FHB and trichothecenes, and resistance to trichothecene accumulation. While several genes contributing to resistance have been identified, attempts to introduce these genes into new cultivars by conventional plant breeding have met with limited success and it has been suggested that genetic modification may be a better approach.

Within a FHB resistance breeding programme, the best performing wheat cultivars were shown to accumulate 50% less DON than reference standards (Lehoczki-Krsjak *et al.*, 2010). The differences were even greater between the resistant cultivars and susceptible cultivars that were registered for cultivation.

Crop rotation and the nature of the preceding crop have been identified as important factors in the control of trichothecene contamination in cereals. A survey of DON in winter wheat in Luxembourg found that maize as a preceding crop was a predictor for DON contamination, although the relationship was only statistically significant at the p = 0.1 level (Giraud *et al.*, 2010).

A Swiss study examined the ability of different treatments to reduce the DON content of wheat, where maize was the preceding crop (Vogelgsang *et al.*, 2011). Treatments were mainly different protocols for mulching the left-over maize material, to reduce the size of remaining maize fragments. On average, the various mulching approaches decreased the DON content of wheat by 21 to 38%, compared to controls (no treatment). Apart from treatment of maize residues, year and cultivar were significant influencers of *F. graminearum* infection and DON concentration in grain.

The impact of various fungicide treatments and a foliar fertiliser application to winter wheat at anthesis on DON contamination was examined (Blandino and Reyneri, 2009). Application of a triazole fungicide was effective in reducing *Fusarium* head blight (FHB) and DON concentrations in grain. However, co-application of a triazole and strobilurin fungicide reduced FHB to a similar degree, but resulted in increased concentrations of DON, sometimes to concentrations above those in untreated controls. Foliar fertilisation had no additional impact on DON levels.

Initial trials of the impact of fungicide application on the DON content of wheat showed little improvement, optimisation of the spraying coverage resulted in decreases of up to 90% in DON content (Lehoczki-Krsjak *et al.*, 2010). This optimised procedure was scaled up to farm level and demonstrated 70% reduction in DON contamination over 3 years. Best DON reduction required near-horizontal spraying of wheat heads with the most effective fungicides. The most effective fungicides were Prosaro (active prothioconazole and tebuconazole) and Nativo (tebuconazole and trifloxystrobin).

A French study reported similar findings, with a combination of prothioconazole and terbuconazole producing a greater decrease in DON levels in wheat than 'reference fungicides' (Dubournet *et al.*, 2008). Both fungicide treatments reduced DON levels by 50-70% compared to untreated controls.

The DON and DON-3-G content of wheat field-treated with either Prosaro (active prothioconazole and tebuconazole) or Fandango (active prothioconazole and fluoxastrobin) was compared (Kostelanska *et al.*, 2011). Use of Prosaro did not result in any significant decrease in DON levels, while use of Fandango resulted in a mean 28% reduction in DON concentrations in the grain.

Electrolysed oxidised water (EOW) was found to be capable of controlling growth of *Fusarium* spp. during grain transport and storage (Audenaert *et al.*, 2012). However,

application of EOW at sublethal levels stimulated DON production and, particularly, production of 15ADON.

A comparison of oats produced under conventional or organic agricultural systems (n = 98) for each system) found generally higher prevalence of trichothecene mycotoxins (DON, 3ADON, NIV, T2, HT2, DAS, MAS) in oats produced conventionally, although the authors did not comment on the statistical significance of differences (Twarużek *et al.*, 2013). Concentrations of NIV, T2 and HT2 were significantly higher in conventional oats, while DON concentrations were higher in organic oats.

The potential for genetic modification to reduce or mitigate mycotoxin contamination of crops has been reviewed (Cary *et al.*, 2009). Identified approaches are outlined in section 2.5.2.3. *Fusarium* species contain a 'self-defence' gene, expressing an acetyltransferase enzyme, that detoxifies DON (Alexander, 2008). This gene has been inserted into wheat, barley and rice. However, only the rice transgenic demonstrated resistance to DON.

4.5.3 Influence of processing on trichothecene levels

4.5.3.1 Cleaning and milling

High-speed optical sorting was examined as a means of reducing the DON content of wheat (Delwiche *et al.*, 2005). The DON concentrations of unsorted wheat samples were in the range 0.6-20 mg/kg, while sorted samples had a DON range of 0.2-12 mg/kg and rejected grain from those samples contained DON in the range 3.4-58 mg/kg. On average, the DON content of sorted grain was 51% of that in unsorted grain. Re-sorting of the sorted grain resulted in further decreases in the DON content and, on average, reduced the DON content to 37% of the original unsorted samples.

Sieving, scouring and polishing of wheat, prior to milling, resulted in reductions in DON concentrations of 45-59% (Lancova *et al.*, 2008a). Other trichothecene mycotoxins were almost universally not detectable in cleaned grain. Milling of cleaned grain resulted in 37-50% of the remaining DON being partitioned into the bran fraction, with a further 17-21% in the first reduction stream and 5-11% in the first break flour stream.

Milling of 2 samples of Japanese wheat produced similar results to above for the most contaminated sample (1890 μg/kg DON, 1470 μg/kg NIV), with 51% of DON and 72% of NIV recovered in the bran fraction (Zheng *et al.*, 2014). However, for a less-contaminated wheat (900 μg/kg DON, 720 μg/kg NIV), only 24% of DON and 26% of NIV were recovered in bran, with the greatest proportion (69% of DON, 65% of NIV) recovered in the patent flour. The patent flour was a blend of first and second break and reduction flour streams. These results suggest significant internalisation of the toxins in the second wheat sample.

Milling of wheat resulted in 45-60% of DON and DON-3-G present in the wheat being partitioned into the bran fraction (Kostelanska *et al.*, 2011). There was no marked differences in the pattern of partitioning of DON and its conjugate.

The distribution of DON in mill streams was examined for durum wheats with very different DON contents (382 and 4203 μg/kg) (Ríos *et al.*, 2009). For both samples, DON was

disproportionately distributed into the bran and shorts fraction. This fraction is 16-17% of the total milling output, but contained 50.8% (low DON) and 42.6% (high DON) of the DON present in the unmilled grain. Semolina, which made up approximately 76% of milling output contained 40.8% (low DON) and 49.6% (high DON) of the DON present in the unmilled grain.

While no mass balance was carried out, the concentrations of DON and DON-3-G in milled flour were shown to be 38 and 76% of the concentrations in whole wheat, while the concentrations in the bran fraction were 270 and 155% of those in whole wheat, respectively (Simsek *et al.*, 2012).

While cleaning of oats had no significant impact on the T2/HT2 content, dehulling reduced toxin content by more than 90% (Schwake-Anduschus *et al.*, 2010). A British study found similar results, with dehulling of oats reducing the content of HT2 and NIV by more than 90% and the content of DON and T2 by more than 80% (Scudamore *et al.*, 2007).

4.5.3.2 Storage of milled flour

The impact of storage of white or wholemeal (organic and industrial) wheat flour for 120 days in food grade paper or polypropylene plastic bags at 10 or 25ºC on DON and NIV was examined (Kolmanič *et al.*, 2010). For DON, significant decreases in concentration after 120 days were seen at 25ºC (4%), for storage in food grade paper (7%), and for organic wholemeal flour (4%). For NIV, temperature, packaging and flour type all had an impact, with a maximum decrease of 30% observed for organic wholemeal flour stored in food grade paper at 25ºC.

4.5.3.3 Baking and cooking

Flour naturally contaminated with DON at either low (100 or 160 μg/kg) or high (967 μg/kg) concentrations was used to produce bread (Bergamini *et al.*, 2010). The impact of variation in the fermentation time (45, 65 or 85 minutes) and temperature (30 or 40ºC) and the baking time (8 or 16 minutes) and temperature (180 or 210ºC) was examined. For low contamination concentration flours, DON concentrations increased by 31-46% during the breadbaking process. This was presumed to be due to release from conjugated forms of DON. For high contamination flours there was no consistent impact of the breadmaking process on DON concentrations. Both laboratory and industrial scale baking processes showed an increase in DON concentrations during dough fermentation, due to enzymatic release of parent DON from conjugated forms.

DON content was examined at 5 stages during the production of bread; the flour, the kneaded dough, the fermented dough, dough after proofing and bread (Lancova *et al.*, 2008a). Compared to the DON content of the flour, DON content increased during kneading, decreased during fermentation and increased again during proofing. On average, the DON content of the bread was not different to that of the flour, with a maximum decrease of 6%. Changes through the dough preparation process presumably reflect interchange between conjugated and free forms of DON.

DON and DON-3-G content were monitored at the same 5 stages in the production of bread from naturally-contaminated wheat flour (Kostelanska *et al.*, 2011). A slightly (5%), but not

statistically significant increase in DON was observed during dough development. There was also a non-significant decrease (13%) in DON-3-G. The baking process resulted in further decreases in both DON and DON-3-G, but these changes were not statistically significant. The addition of commercial bread improvers resulted in a significant increase in DON-3-G content, but not DON content, of the proofed dough.

Vidal *et al*. (2014) reported an increase in DON levels in dough during the kneading and fermentation processes, but a decrease during baking. By contrast, DON-3-G content increased throughout the breadmaking process.

An Italian study found the DON content of bread baked from flours with DON contents in the range 950-1800 µg/kg to be approximately 18% higher than the DON content of the flours (De Angelis *et al.*, 2012). This coincided with an approximate 50% decrease in the DON-3-G content of the bread, compared to the flour. Similar results were obtained by Simsek *et al*. (2012), with DON concentrations increasing through the baking process, while DON-3-G concentrations decreased. Breadbaking resulted in a 63-74% reduction in T2 content and a more modest reduction in HT2 (18-25%) (De Angelis *et al.*, 2012).

A Spanish study found no significant changes in DON content during the breadmaking process (Cano-Sancho *et al.*, 2013b). In contrast, the same study found that boiling pasta made with DON-contaminated flour resulted in decreases in DON content of about 75%. Measurement of DON in the cooking water confirmed that the mycotoxin was not destroyed, but was solubilised into the water.

A Japanese study produced similar results, with a slight increase in DON content of bread compared to flour, but an approximate 70% decrease in DON during cooking of noodles (Sugita-Konishi *et al.*, 2006). Changes in the cytotoxicity of noodles paralleled changes in DON content, while production of bread resulted in a small decrease in cytotoxicity.

A kinetic model was developed to predict the impact of breadbaking on the DON concentration in bread made from naturally-contaminated maize flour (Numanoglu *et al.*, 2011). Baking at 250ºC for 70 minutes resulted in a 6% increase in DON concentration in the bread crumb, where the temperature would have reached a maximum of 100ºC, and a decrease of 12% in the crust, where the temperature would have reached a maximum of 150ºC. These reductions were consistent with the predictions from the kinetic model.

In contrast to the studies summarised above, dough fermentation was found to have little impact on levels of DON, 3ADON and NIV spiked into wheat flour, but breadbaking resulted in average decreases of 48, 66 and 77% respectively (Valle-Algarra *et al.*, 2009). While this study differs from many others in reporting substantial decreases in DON during baking, it does support the study of Scudamore *et al*. (2009a) in suggesting that NIV is more heat labile than DON (see next paragraph).

On average, baking of bread from flour naturally contaminated with DON (61-284 µg/kg) had no significant impact on DON content, although changes in individual baking runs ranged from a decrease of 38% to an increase of 40% (Scudamore *et al.*, 2009a). Baking of cakes by a short time-high temperature method resulted in no change in DON concentration, while a long time-low temperature method resulted in increases in DON content (20-180%).

Biscuit making (semi sweet or cracker) did not impact the DON content, but resulted in an approximate 30% reduction in NIV content.

Using mass balance, production of baked products from DON-contaminated flour was found to either reduce (bread, 50% of DON in flour; cracker, 76%; cookie, 96%) or increase (pretzel, 107%; donut, 120%) the mass of DON in the finished product (Voss and Snook, 2010).

During production of wholegrain crackers, baking time and temperature were found to be the most significant variables for decreasing the DON content of crackers compared to parent flour (Suman *et al.*, 2012). None of the factors examined (presence of sodium bicarbonate, fermentation time, fermentation temperature, baking time, baking temperature) were found to have a significant impact on DON-3-G content.

On average, preparation of porridge from rolled oats and baking of bread containing 20% oats had no significant impact on the T2/HT2 content (Schwake-Anduschus *et al.*, 2010).

Extrusion cooking had little impact on the DON content of maize flour and grits (Scudamore *et al.*, 2008b). Addition of salt (2%) further stabilised the toxin. Similarly, extrusion cooking of wheat flour had little impact on DON content, with the possible exception of decreases of about 20% at low (15%) flour moisture content (Scudamore *et al.*, 2008a). NIV content increased by up to 40% during extrusion cooking.

Higher rates of DON degradation were seen in a set of experiments on extrusion cooking of wheat grits (Wu *et al.*, 2011). Increasing temperature, residence time and screw compression resulted in greater DON reductions. Lower moisture content (17%) of grits resulted in greater reductions at low temperatures (120ºC), while higher moisture contents (34%) gave greater reductions at high temperatures (170ºC). The maximum reduction in DON content was 60%.

The fate of DON during production of maize-based snack foods was examined (Scudamore *et al.*, 2009b). Three product types were examined; expanded snacks via direct extrusion processing, expanded snacks via pellet processing, and tortilla chips. While there was considerable batch to batch variability, on average the DON content of the final products was 103, 83 and 68% of the DON content of the ingredients. However, these changes were measured on an ‘as is’ basis and the authors commented that reductions were likely due to dilution, rather than degradation of DON.

4.5.3.4 Malting and brewing

Barley, either naturally or artificially contaminated with *Fusarium* toxins (DON, DON-3-G, ADONs, HT2), was subjected to a malting process (Lancova *et al.*, 2008b). Levels of all toxins increased during the process, particularly during the germination phase. It was speculated that this may be due to either fungal growth and consequent mycotoxin production or freeing of bound mycotoxins by lytic enzymes, active during the germination phase. In particular, DON-3-G concentrations increased to a greater extent than other trichothecene mycotoxins. During brewing, there was no significant change in the total amount of ADONs, while DON content decreased by up to 30%. The total mass of DON-3-G in the finished beer was approximately 6 times the mass in the malt and DON-3-G was the dominant toxin in beer.

Comparison of the concentrations of DON and its conjugates in beer to the ingredients used for manufacture of that beer (malt, wort) showed increases in DON, DON-3-G and ADONs (Kostelanska *et al.*, 2009). Maximum relative amounts of DON, DON-3-G and ADONs in beer were 536, 210 and 657% of the amount in the ingredients.

4.6 Conclusions

4.6.1 Description of risks to New Zealand consumers

Trichothecene mycotoxins have been associated with outbreaks of acute human illness, including outbreaks with high rates of mortality (alimentary toxic aleukia). The critical toxicological effects are similar for all trichothecenes (general toxicity, immunotoxicity, haematotoxicity) and are related to the ability of trichothecene mycotoxins to inhibit protein synthesis. While some epidemiological studies have attempted to relate trichothecene exposure to oesophageal cancer, gastric cancer and endemic osteoarthritis, the evidence is inconclusive. Tests on laboratory animals generally do not suggest that the trichothecenes are carcinogenic.

While no cases of trichothecene intoxication have been documented in New Zealand, the symptoms of acute intoxication mean that cases are likely to be ascribed to microbial sources.

Fusarium species have been found in a range of New Zealand cereal crops and production of trichothecene mycotoxins by these fungal species has been demonstrated. In a recent survey of trichothecene mycotoxins in consumer foods in New Zealand DON was frequently detected in cereal-based foods, but the concentrations detected were generally low. NIV, DAS, 15ADON and NEO were detected occasionally, also at low concentrations. The associated exposure assessments suggest that dietary exposure to trichothecene mycotoxins in New Zealand is low by international standards and in comparison to health-based exposure limits.

4.6.2 Commentary on risk management options

Trichothecenes are not currently regulated in New Zealand. Agronomic research conducted in New Zealand demonstrates a good awareness of the deleterious effects of *Fusarium* infection and the connection between *Fusarium* infection and trichothecene production (Cromey *et al.*, 2002; Cromey *et al.*, 2004).

4.6.3 Data gaps

Recently completed projects have addressed previously identified data gaps related to the occurrence of trichothecene mycotoxins in New Zealand foods and dietary exposure of New Zealanders to these toxins (Cressey, 2014; Cressey *et al.*, 2014).

5 FUMONISINS

5.1 Hazard Identification

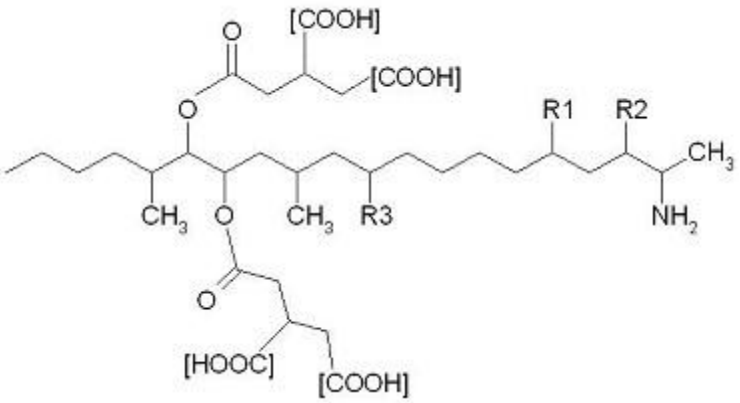
Fumonisins are mycotoxins produced predominantly by *Fusarium verticillioides* (*F. moniliforme*) and *F. proliferatum.* These fungal species are endemic in maize worldwide, but are rarely found in other crops (Pitt and Tomaska, 2001). The fungi grow optimally at about 25ºC and will grow at temperatures up to 32-37ºC (Pitt and Tomaska, 2001). While at least six fumonisins are known, fumonisin B_1 and B_2 (FB_1, FB_2) are the most important.

It has recently been discovered that *Aspergillus niger* strains are also capable of producing fumonisin mycotoxins (Frisvad *et al.,* 2007; Scott, 2011). This discovery had led to the detection of fumonisins in foods not previously considered as vehicles for these toxins. *A. niger* produces predominantly FB_2 and FB_4.

5.1.1 Structure and nomenclature

Fumonisins consist of a 20 carbon aliphatic chain with 2 ester-linked hydrophilic polyol side chains. Structural details for FB_1 – FB_4 are shown in Figure 5.

Figure 5: Structure of major fumonisins



Fumonisin B_1: R1= OH; R2= OH; R3= OH; Fumonisin B_2: R1= H; R2= OH; R3= OH; Fumonisin B_3: R1= OH; R2= OH; R3= H; Fumonisin B_4: R1= H; R2= OH; R3= H

Fumonisins C_1-C_4 are identical to the corresponding B fumonisin, except the aliphatic carbon chain does not have the terminal methyl group on the right hand end (Soriano and Dragacci, 2004). Concentrations of B and C series fumonisins in maize have been shown to be correlated, but with the C series fumonisin present at concentrations 5% or less of the corresponding B series fumonisin (Shephard *et al.*, 2011).

5.1.2 Occurrence

F. verticillioides and *F. proliferatum* are amongst the most common fungi associated with maize worldwide and can be recovered from most maize kernels, even when the kernels appear healthy (WHO, 2000). *F. verticillioides* is considered to be the major cause of *Fusarium* kernel rot in maize, a significant plant disease occurring in warm, dry weather

(JECFA, 2001b). *Fusarium* kernel rot, and associated fumonisin synthesis, is also strongly associated with insect damage of kernels, as this provides an entry point for the fungus (WHO, 2000). Thin kernel pericarp (greater susceptibility to insect injury), propensity to kernel splitting, and previous infection with other *Fusarium* species, such as *F. graminearum*, all increase the risk of *F. verticillioides* infection and fumonisin formation (WHO, 2000).

F. verticillioides is widespread in the tropics and humid temperate zones, but is uncommon in cooler temperate zones (Pitt and Hocking, 1997). Surveys of *Fusarium* species in New Zealand maize are supportive of this observation, as the fungus is only rarely isolated (Hussein *et al.*, 2003; Sayer, 1991; Sayer and Lauren, 1991). *F. proliferatum* has not been reported in New Zealand maize.

Although fumonisin-producing fungi appear to be relatively rare in New Zealand, FB_1 was reported in New Zealand pasture grasses, at concentration in the range 1-9 mg/kg (Mirocha *et al.*, 1992b). The pastures analysed were associated with an idiopathic disease of wapiti (elk) and wapiti hybrids grazed on the pastures.

5.2 Hazard Characterisation: Adverse Health Effects

Incidents of human toxicosis have been associated with fumonisin-contaminated foods. However, it should be noted that in most cases the implicated food may contain more than 1 known mycotoxin and may potentially contain other, as yet uncharacterised, toxins.

5.2.1 Conditions

Interest in the impact of fumonisin exposure on human health continues to focus on possible associations with oesophageal cancer, with lesser attention on a role in liver cancer and neural tube defects.

5.2.2 Toxicity

While no significant new insights into the toxicity of fumonisins have been published since the previous version of this risk profile, the epidemiological and toxicological evidence has recently been reviewed (Gelderblom and Marasas, 2012; Stockmann-Juvala and Savolainen, 2008).

Short-term and chronic toxicity in experimental animals due to FB_1 is primarily due to its ability to interfere with synthesis of complex glycol-sphingolipids, through inhibition of the enzyme ceramide synthase. This has effects on cellular processes such as cell growth, cell differentiation and morphology, endothelial cell permeability and apoptosis (Scientific Committee on Food, 2000b). This mode of action is believed to explain most of the toxic effects exhibited by FB_1, including hepatotoxicity, nephrotoxicity and tumour formation in the liver and kidneys (JECFA, 2001b).

5.2.3 Toxicological assessment

There has been no update to the group PMTDI for FB_1, FB_2 and FB_3, singly or in combination, of 2 µg/kg body weight/day (2000 ng/kg body weight/day) reported in the previous version of this risk profile.

There has also been no update to the IARC classification of FB_1 as a possible human carcinogen (Group 2B).

Benchmark doses have been derived for FB_1 based on either change to sphinganine-sphingosine ratio (kidney or urinary) or occurrence of kidney carcinoma in rats (Muri *et al.*, 2009a). The lowest $BMDL_5$ estimate are derived from kidney sphinganine-sphingosine ratio data, with values of 63 μg/kg body weight for males and 117 μg/kg body weight for females. $BMDL_1$ values for kidney carcinoma were 1110 μg/kg body weight for males and 1820 g/kg body weight for females.

5.2.4 Metabolites and their relative toxicity

Under some food processing conditions the B fumonisins (FB) may be converted to a hydrolysed form (HFB), with the same backbone structure as the parent fumonisin, but with the tricarballylic side-chains hydrolysed to leave hydroxyl groups (Dall'Asta *et al.*, 2009; Zimmer *et al.*, 2008). Hydrolysed fumonisins have only 30-40% of the toxic potential of the parent compounds (Stockmann-Juvala and Savolainen, 2008).

There is also evidence that fumonisins may become bound to other macromolecules in the food matrix during even quite mild food processing (Dall'Asta *et al.*, 2009). It was suggested that the binding is associative, rather than covalent and fumonisins can be released by digestion. There has been no suggestion that the adducts formed have toxicological implication, but may lead to underestimation of the contamination level of commodities, particularly maize.

A more recent study by the same group made a distinction between 'hidden' fumonisins (associated with other molecules, but easily released) and 'bound' fumonisins (covalently bound to other molecules and not easily released) (Falavigna *et al.*, 2012). The authors of this study concluded that hidden fumonisins could be easily released during gastrointestinal digestion and should be included in a consideration of the fumonisin content of foods. Putative bound fumonisins (*N*-alkyl and acyl conjugates) were stable under digestive conditions and it was suggested that further work was required on the potential toxicity of these compounds.

5.3 Exposure Assessment

Although *F. verticillioides* and *F. proliferatum* are known to cause diseases in crops other than maize (sorghum, rice), fumonisin mycotoxin occurrence is most commonly reported in maize.

5.3.1 Fumonisins in the New Zealand food supply

There has been no new information published on fumonisins in the New Zealand food supply since the previous version of this risk profile.

Maize and maize products are imported into New Zealand mainly from Australia and USA.[12] Fumonisin contamination has been reported in maize from both of these countries and it is probable that there is some contamination in maize used for human and animal food in New Zealand.

5.3.2 Fumonisins in the Australian food supply

The 23rd Australian Total Diet Study included analysis of baked beans, breakfast cereals, meat pie and frozen sweet corn kernels for FB_1 and FB_2 (Food Standards Australia New Zealand, 2011). Fumonisins were not detected in any food sample analysed. However, the analytical method and the LOD were not reported.

5.3.3 Overseas context

While the vast majority of data available relate to fumonisins in maize and foods derived from maize, other foods have occasionally been analysed for fumonisins. While fumonisins have been detected in an increasingly wide range of foods, the concentrations found are generally much lower than those found in maize and/or the food is not consumed in large quantities. Two points are worth noting:

- Although concentrations of fumonisins found in wheat are mostly much lower than those found in maize, high concentrations (>1000 μg/kg) have occasionally been reported; and
- The discovery that *Aspergillus niger* is able to produce fumonisins has led to detection of these toxins in a range of fruits and fruit-based foods. The occurrence of fumonisins in wine may be of relevance to New Zealand.

5.3.3.1 Plant-based foods

Nuts and nut products

A study conducted in Cameroon detected FB_1, FB_2 and FB_3 in 51%, 34% and 43% respectively of peanut samples (n = 35), with concentrations in the range 0.4-10 μg/kg (Abia *et al.*, 2013b). A study in Côte d'Ivoire found similar results with FB_1 detected in 7 of 10 peanut samples, with concentrations in the range trace-6 μg/kg (Sangare-Tigori *et al.*, 2006).

In contrast, fumonisins were not detected in any of 10 peanut samples from Nigeria (LOD 2-4 μg/kg, depending on the toxin) (Kayode *et al.*, 2013).

Soybeans

A study in the Cameroon detected FB_1, FB_2 and FB_3 in all 10 samples of soybeans, with mean concentrations of 49 μg/kg (FB_1), 11 μg/kg (FB_2) and 7.5 μg/kg (FB_3) (Abia *et al.*, 2013b).

[12] http://www.stats.govt.nz/ Accessed 18 February 2014

A 4-year surveillance programme of retail foods in Japan detected FB_1 in 13 of 82 soybean samples, with a maximum concentration of 8 μg/kg (Aoyama *et al.*, 2010). FB_2 was detected in 3 samples, with a maximum concentration of 4.8 μg/kg.

Wheat

There is mixed information concerning fumonisin contamination of wheat.

A US study detected fumonisins in 9 of 43 samples with black point due to fungal infection (Busman *et al.*, 2012). Total fumonisin concentrations were in the range 5-2600 μg/kg.

A study in Iran detected FB_1 (LOD = 10 μg/kg) in 56 of 82 (68%) wheat samples, with concentrations in the range 15-155 μg/kg (30-235 g/kg total fumonisins) (Chehri *et al.*, 2010).

The FB_1 concentration of Croatian wheat samples was determined as part of a trial to determine the impact of different fungicide regimes on *Fusarium* Head Blight (FHB) (Ivić *et al.*, 2009). The study stated that test plots were 'exposed to natural FHB infections'. However, it is uncertain whether these samples would be typical of the Croatian wheat supply. The mean FB_1 concentration across all wheat samples tested was 308 μg/kg. Similar results were reported from a study of Croatian wheat sampled at harvest, with fumonisins detected (LOD = 24.5 μg/kg) in 69% of samples (n = 51), with a maximum concentration of 203 μg/kg (Pleadin *et al.*, 2013). The maximum concentration detected in wheat was about 5% of the maximum concentration detected in maize in the same study.

A study on Serbian winter wheat reported very high concentrations and prevalence of FB_1, with 92 of 103 samples containing detectable FB_1 (LOQ = 750 μg/kg) (Stanković *et al.*, 2012). A maximum concentration of 5400 μg/kg was reported and annual mean concentrations of 2080 μg/kg (2005) and 920 μg/kg (2007). This study suggests that FB_1 contamination levels in wheat may approach those reported for maize. However, the very high LOQ for this study and the lack of any quality assurance data means there must be some questions about the quality of these results. A further Serbian survey of fumonisins in wheat produced more expected results, with 51% of wheat samples containing fumonisins, with concentrations in the range 27-614 μg/kg (Jakšić *et al.*, 2012).

Fumonisins (FB_1 and FB_2) were detected in 131 of 135 common wheat samples and 31 of 40 durum wheat samples from Argentina (Cendoya *et al.*, 2014). FB_1 was the most frequently detected fumonisin and was also detected at the highest concentrations. FB_1 concentrations ranged from 0.2 to 680 μg/kg in common wheat and from 0.2 to 1304 μg/kg in durum wheat.

Tuberous vegetables

FB_1 was detected in yam samples from Nigeria, with maximum concentrations of 91 μg/kg (Somorin *et al.*, 2012). A study in Benin also detected FB_1 in all 4 cassava flours analysed at concentrations in the range 4-21 μg/kg (Njumbe Ediage *et al.*, 2011).

Onions

Analysis of mouldy onions from Hungary found that they were mainly infected with strains of *Aspergillus awamori* (Varga *et al.*, 2012b). Two onion sample were found to contain fumonisins at concentrations of about 300 μg/kg. FB_2, FB_3 and FB_4 were detected, but not FB_1.

Dried figs

A survey of dried figs (*n* = 115) from the Aegean region of Turkey detected FB_1 in 74.7% of samples, with a mean concentration of 315 μg/kg (range 50-3650 μg/kg) (Heperkan *et al.*, 2011; Karbancioglu-Güler and Heperkan, 2009). A further study in the same region detected fumonisins in 67.5% of samples (*n* = 262*)* (Kosoglu *et al.*, 2011). The maximum concentration of FB_1 detected was 332 μg/kg, while the maximum concentration of FB_2 detected was 198 μg/kg.

Dried vine fruits

A Greek study detected FB_2 (LOQ = 7 μg/kg) in 29% of raisin samples (*n* = 41), with concentrations in the range 7.1-25.5 μg/kg (Perrone *et al.*, 2013).

Analysis of retail raisin samples from Denmark, Germany and the Netherlands detected fumonisins (B_2 and B_4) in 10 of 21 samples, with maximum concentrations of 13 and 1.3 μg/kg, respectively (Knudsen *et al.*, 2010).

Dried vine fruit samples (raisins and sultanas, *n* = 7) from several different countries were analysed for fumonisins (Varga *et al.*, 2010). Total fumonisin concentrations were in the range 455-35,500 μg/kg. In some samples FB_1 was the dominant toxin, while in others FB_2 was the dominant toxin. Concentrations of fumonisins found in this study are dramatically higher than those found in the studies reported above.

FB_1 and FB_2 were detected in dried grapes from Slovak vineyards, with concentrations in the range 500-2040 μg/kg (Mikušová *et al.*, 2013).

Wine

FB_2 and FB_4 have recently been reported as potential contaminants wine (Logrieco *et al.*, 2010). A survey of 51 Italian wines (45 red, 5 white, 1 rosé) did not detect FB_4 in any sample (LOD = 0.7 μg/L), but detected FB_2 (LOD = 0.25 μg/L) in 9 samples, with concentrations in the range 0.5-2.4 μg/L.

Analysis of 77 wine samples from 13 countries found FB_2 in 18 (23%) samples, with concentrations in the range 1-25 μg/L (Mogensen *et al.*, 2010).

A Japanese study detected FB_1 in 4 of 14 red wines and 2 of 13 white wines (Tamura *et al.*, 2012). FB_2 was detected in 2 red wines, while FB_3 was detected in 1 red wine. All positive finding were at concentrations below the LOQ of 1 μg/L. It should be noted that this study differs from those above in identifying FB_1 as the main fumonisin contaminant in wine.

In contrast, neither FB_1 nor FB_2 were detected in white (n = 71) or red (n = 72) wines collected in the United States (Al-Taher *et al.*, 2012). The LOD was 1 µg/L. Wines were from USA, Europe, South America and Australia.

Pineapple

A study on pineapple from Costa Rica and Ecuador reported FB_1 concentration in pineapple juice in the range 8200-23,700 µg/L and in pineapple skin samples in the range 25,700-248,000 µg/kg (Stępień *et al.*, 2013). No other studies could be found to substantiate these results.

Coffee

Thai coffee beans were analysed for fumonisins by LC-MS (Noonim *et al.*, 2009). FB_2 was detected (LOD = 0.5 µg/kg) in 7 of 12 samples, with a maximum concentration of 9.7 µg/kg. FB_4 was also detected in 2 samples, but the concentrations were not reported.

Spices and flavourings

A preliminary study reported detection of FB_1 in garlic and onion powder (Boonzaaijer *et al.*, 2008). However, results were below the LOQ of 100 µg/kg.

The fumonisin content of red chilli, black pepper and white pepper (n = 10 for each) from Sri Lanka was determined (Yogendrarajah *et al.*, 2013). Neither FB_1 nor FB_2 were detected in any white pepper sample. FB_1 was detected in 1 black pepper samples at a concentration of 135 µg/kg. FB_2 was detected in 1 sample of red chilli at a concentration below the LOQ (64 µg/kg). The latter result is consistent with fumonisin contamination of fruit being largely due to infection by *Aspergillus niger*.

5.3.3.2 Animal-based foods

There is little information on fumonisins in foods of animal origin and it is generally believed that there is negligible transmission of fumonisins.

Milk

Using a highly sensitive method (LOD = 0.1 µg/kg), FB_1 was detected in 8 of 10 commercial milk samples, with a mean concentration in positive samples of 0.33 µg/kg (range 0.26-0.43 µg/kg) (Gazzotti *et al.*, 2009).

Animal tissues

A sensitive (LOD = 0.05 g/kg) LC-MS method was used to detect FB_1, FB_2 and their hydrolysed metabolites in pig liver (Gazzotti *et al.*, 2011). FB_1 was detected in all of 7 samples, with concentrations ranging from a trace (0.05-0.10 µg/kg) to 43 µg/kg. HFB_1 was detected in 1 sample at a concentration of 17 µg/kg, while only traces of FB_2 and no HFB_2 were detected.

Weaned pigs received a diet containing FB_1 (45 mg/kg), FB_2 (8.6 mg/kg) and FB_3 (4.6 mg/kg) for 10 days, followed by 10 days of an elimination (fumonisin-free) diet (Szabó-Fodor *et al.*, 2008). At the end of the intoxication period, the mean FB_1 concentration in muscle was 11.2 μg/kg. Significant concentrations of FB_2 (7.9 μg/kg) and partially hydrolysed FB_1 (8.8 μg/kg) were also present. However, concentrations dropped sharply during the elimination period to 0.95 μg/kg FB_1 and 0.23 μg/kg FB_2. Partially hydrolysed FB_1 was not detectable in muscle meat at this time.

Ducks received single doses of FB_1 equivalent to 5 and 40 mg/kg body weight (Tardieu *et al.*, 2008). Birds were euthanised 2 hours later. The highest concentrations of FB_1 were found in the liver (6.7 and 3.9 mg/kg in high dose birds and 0.3 and 0.4 mg/kg in low dose birds), followed by the kidneys (2.2 and 1.0 mg/kg in high dose birds and 0.07 and 0.11 mg/kg in low dose birds). The lowest concentration were found in muscle tissue (0.73 and 0.22 mg/kg in high dose birds and <LOD and 0.08 mg/kg in low dose birds). The high dose levels and the short interval between dosing and testing make this study difficult to interpret in a food safety context, but does demonstrate the potential for fumonisins from feed to be transferred to edible animal tissues.

FB_1 and FB_2 were not detected in any of 22 retail meat samples, although the relatively high LOD for FB_1 (64 μg/kg) meant low level contamination (<20 μg/kg) would not have been detected (Sørensen *et al.*, 2010).

5.3.4 New Zealand estimates of dietary exposure

No new information on the dietary exposure of New Zealanders to fumonisins has been published since the previous version of this risk profile.

5.3.5 Overseas estimates of dietary exposure

Estimates of fumonisin exposure in developed countries are generally less than 0.5 μg/kg body weight/day (500 ng/kg body weight/day; 25% of the PMTDI). Exposure in developing countries, particularly in regions where maize is a dietary staple may exceed the PMTDI by an order of magnitude. National estimates of fumonisin exposure are summarised in Table 14.

Table 14: Overseas estimates of dietary exposure to fumonisins

Country	Population group	Mean (95th percentile) exposure, ng/kg body weight/day	Reference
PMTDI (JECFA) = 2000 ng/kg body weight/day			
Brazil[1]	Total population	FB_1 + FB_2 477	(Caldas and Silva, 2007)
Brazil (Parana)	Adult (60 kg)	FB_1 + FB_2 120 (90th percentile 260)	(Martins *et al.*, 2012)
China - Huantai - Huaian - Fusui	Adult (60 kg)	FB_1 (median)[1] 1500 7700 2300	(Sun *et al.*, 2011)
France	Children		(Sirot *et al.*, 2013)

Country	Population group	Mean (95th percentile) exposure, ng/kg body weight/day	Reference
PMTDI (JECFA) = 2000 ng/kg body weight/day			
	- FB_1 - FB_2 Adults - FB_1 - FB_2	15-45 (50-106) 6.5-30 (24-83) 7.5-29 (23-66) 2.4-16 (10-42)	
Germany	NS[2] - Mean case - Bad case	$FB_1 + FB_2 + FB_3$ 16 303	(Zimmer *et al.*, 2008)
Guatemala	Adult women - Urban - Central Highlands - Rural	$FB_1 + FB_2 + FB_3$ 3500 11100 15600	(Torres *et al.*, 2007)
Italy	 Coeliac patients Controls	$FB_1 + FB_2 + FB_3$ 395 29	(Dall'Asta *et al.*, 2012)
Italy	Infant consuming: Conventional corn Organic corn Adult consuming: Conventional corn Organic corn	$FB_1 + FB_2 + FB_3$ 5 - 7 20	(D'Arco *et al.*, 2009)
Iran	Average person Mazandaran Province Isfahan Province	FB_1 215 11	(Yazdanpanah *et al.*, 2006)
Morocco	Average adult	$FB_1 + FB_2$ 0.04	(Serrano *et al.*, 2012)
Netherlands	Children (*n* = 123, duplicate diet)	$FB_1 + FB_2$ 28	(Bakker *et al.*, 2009)
South Africa (rural)	Males consuming: Commercial maize Home grown maize Females consuming: Commercial maize Home grown maize Males or females consuming maize beer:	$FB_1 + FB_2 + FB_3$ 1300 12,100 1100 6700 6900-12,000[3]	(Burger *et al.*, 2010)
South Africa (Transkei)	Bizana region: Children 1-9 years Adolescents 10-17 years Adult males 18-65 years Adult females 18-65 years Centane region: Children 1-9 years Adolescents 10-17 years Adult males 18-65 years Adult females 18-65 years	$FB_1 + FB_2$ 6600 (13,600) 4100 (7800) 3800 (6600) 3000 (6000) 14,100 (27,900) 8300 (16,000) 9200 (14,300) 8200 (13,500)	(Shephard *et al.*, 2007a)
South Korea	Population 3-85 years (average body weight 57.6 kg)	$FB_1 + FB_2$ 0.087	(Seo *et al.*, 2009)
Spain	Adult (70 kg body weight)	$FB_1 + FB_2$ 4.1 (conventional corn consumption) 3.4 (organic corn consumption)	(Ariño *et al.*, 2007a)

Country	Population group	Mean (95th percentile) exposure, ng/kg body weight/day	Reference
PMTDI (JECFA) = 2000 ng/kg body weight/day			
Spain (Catalonia)		$FB_1 + FB_2$	(Cano-Sancho *et al.*, 2011b)
	Infants	156	
	Children	63	
	Adolescents	37	
	Adult Males	63	
	Adult Females	35	
	Immigrants	65	
	Coeliac sufferers	41	
Spain	Infant consuming:	$FB_1 + FB_2 + FB_3$	(D'Arco *et al.*, 2009)
	Conventional corn	2	
	Organic corn	720	
	Adult consuming:		
	Conventional corn	2	
	Organic corn	4	
Tanzania	Adult (60 kg)	$FB_1 + FB_2 + FB_3$	(Kimanya *et al.*, 2009)
	Fresh maize (n = 67)	10,200 (range 200-135,400)	
	Stored maize (n = 55)	2900 (range 100-10,400)	
Tunisia	Average adult	$FB_1 + FB_2$	(Serrano *et al.*, 2012)
		50	

[1] The study reported exposures in terms of 'µg/day'. However, an average body weight of 54.5 kg was provided to allow recalculation of exposures to 'ng/kg body weight/day'

[2] The study reported exposures in terms of 'µg/day'. A 60 kg body weight was used in the current report to convert exposures to 'ng/kg body weight/day'

[3] The study reported exposures in terms of 'µg/day'. A 70 kg body weight was used in the current report to convert exposures to 'ng/kg body weight/day'. Two 'cases' were defined; a mean case (mean food consumption, median fumonisin concentration), and a bad case (mean food consumption, 90th percentile fumonisin concentration).

[4] Per maize beer-consuming event

5.3.6 Biomarkers of exposure

FB_1 is poorly absorbed from the gastrointestinal tract and does not undergo major metabolism and intact FB_1 has been proposed as a possible biomarker (Shephard *et al.*, 2007b; Silva *et al.*, 2009). Serum, urine, faeces, hair and nail have all been proposed as potential matrices for FB_1 determination. However, the low absorption of FB_1 means concentrations in these matrices will generally be very low and present analytical challenges. None of these matrices have been validated for biomarkers of fumonisin exposure.

Effect-based biomarkers have been proposed, measuring elevated levels of the sphingoid base, sphinganine, or its ratio with sphingosine (Shephard *et al.*, 2007b). However, attempts to correlate these parameters with fumonisin exposure have mostly been unsuccessful (van der Westhuizen *et al.*, 2008; van der Westhuizen *et al.*, 2010a; Xu *et al.*, 2010), probably due to the fact that levels of these compounds can be influenced by factors other than fumonisin exposure.

The kinetics of urinary fumonisin excretion were examined, as a prelude to using this measure as a biomarker of exposure (Riley *et al.*, 2012). FB_1, but not FB_2, FB_3 or HFB_1, was detected in urine of volunteers (n = 10) following consumption of maize products. Excretion of FB_1 peaked soon after consumption began and decreased rapidly after consumption ceased.

FB_1 was not detectable in urine 5 days after consumption ceased. On average, urinary excretion of FB_1 was 0.5% of intake.

In a study of adults from Cameroon (n = 175) urinary FB_1 and FB_2 were detected in 6 (3%) and 1 (0.6%) samples, respectively (Abia *et al.*, 2013a). The maximum concentration of FB_1 detected was 14.8 μg/L. FB_2 was detected at a concentration below the LOQ (1.7 μg/L). Literature values for the urinary excretion rate of FB_1 (0.3%) and an estimate of daily urinary output (1.5 L) were used to estimate dietary exposure to FB_1. The low observed prevalence of fumonisins in urinary samples is unlikely to represent the true prevalence of exposure and is likely to be related to the low level of urinary excretion of this toxin.

Urinary FB_1 concentration was shown to be significantly positively correlated with tortilla consumption in a cohort of Mexican women (Gong *et al.*, 2008). For groups of women categorised as low, medium and high tortilla consumers, mean urinary FB_1 concentrations were 35.0, 63.1 and 147.4 ng/L, respectively. The correlation remained significant after adjustment for age, education and place of residence. Tortilla were the major source of maize consumption for this cohort. Due to the short half-life of urinary FB_1 this biomarker will only be an indicator of recent exposure. Other studies have also suggested urinary FB_1 as a potential exposure biomarker (Shirima *et al.*, 2013; Xu *et al.*, 2010).

Due to the poor absorption of FB_1 from the gastrointestinal tract, faecal FB_1 has been used as an indicator of recent FB_1 exposure (Phoku *et al.*, 2012).

5.4 Risk Characterisation

5.4.1 Adverse health effects in New Zealand

No cases of fumonisin intoxication have been reported in New Zealand. Internationally, FB_1 has been implicated in human oesophageal cancer. This cancer is moderately common in New Zealand, with 296 new registrations in 2010, a rate of 4.4 per 100,000 population (Ministry of Health, 2013).

5.4.2 Adverse health effects overseas

Oesophageal cancer is the eighth most common cancer worldwide, with 462,000 new cases in 2002 (Evans and Crosby, 2008).

5.4.2.1 Epidemiological studies

Iran

Maize and rice samples were taken from districts in the Golestan province where there was a high risk of oesophageal cancer and districts where the risk was low (Alizadeh *et al.*, 2012). FB_1 concentrations were significantly higher in rice samples from the high risk area than the low risk area (mean concentration 43.8 mg/kg compared to 8.9 mg/kg) and a significant greater proportion of rice samples were contaminated with FB_1 (75% compared to 21%). The concentration and prevalence of FB_1 in maize was higher in the high risk region, but not significantly.

China

Two nested case-control studies were carried out in Haimen city and Linxian to examine the potential involvement of FB_1 as a risk factor for liver cancer (HCC) (Persson *et al.*, 2012). Nail FB_1 was used as a marker of long term FB_1 exposure, although this marker hasn't been formally validated. No significant associated between nail FB_1 and HCC was found in either study population. The studies did not include any measurement of concurrent aflatoxin exposure.

Tanzania

A cohort of infants (n = 215) was examined (Kimanya *et al.*, 2010). Fumonisin exposure was determined for each infant by combining 24-hour (parent) dietary recall of feeding of maize as a complementary food, with fumonisin content of maize samples from participating households. At 12 months of age, infant fumonisin exposure above the provisional maximum tolerable daily intake of 2 μg/kg body weight/day was significantly associated with shorter (1.3 cm) and lighter (328 g) growth indices.

5.5 Risk Management Information

5.5.1 Relevant food controls: New Zealand

5.5.1.1 Establishment of regulatory limits

Fumonisins are not currently regulated in New Zealand.

5.5.2 Relevant food controls: overseas

5.5.2.1 Establishment of regulatory limits

In a 2003 compendium of mycotoxin regulatory limits, eight countries were identified as having guidelines or maximum limits for fumonisins (Van Egmond and Jonker, 2004). The most commonly reported limit was 1000 μg/kg for the sum of FB_1 and FB_2 in maize.

In 2006, the European Commission established maximum limits for fumonisins (sum of FB_1 and FB_2 in μg/kg) in maize and maize products (European Commission, 2006b):

Unprocessed maize	2000
Maize flour, maize meal, maize grits, maize germ and refined maize oil	1000
Maize based foods for direct human consumption, excluding foods listed in other categories	400
Processed maize-based foods and baby foods for infants and young children	200

European regulatory limits for fumonisins were amended in 2007 (European Commission, 2007):

Unprocessed maize, with the exception of unprocessed maize intended to be processed by wet milling	4000
Maize intended for direct human consumption, maize-based foods for direct human consumption, with the exception of foodstuffs listed in other categories	1000
Maize-based breakfast cereals and maize-based snacks	800
Processed maize-based foods and baby foods for infants and young children	200
Milling fractions of maize with particle size > 500 micron falling within CN code 1103 13 or 1103 20 40 and other maize milling products with particle size > 500 micron not used for direct human consumption falling within CN code1904 10 10	1400
Milling fractions of maize with particle size ≤500 micron falling within CN code 1102 20 and other maize milling products with particle size ≤ 500 micron not used for direct human consumption falling within CN code 1904 10 10	2000

CN = Combined Nomenclature

The Codex Committee on Contaminants in Food (CCCF) proposed maximum levels for fumonisins in unprocessed maize of 5000 µg/kg and 2000 µg/kg for maize flour/meal (Codex Committee on Contaminants in Food, 2013a). However, delegations from some African countries, where maize is a staple, did not support these maximum limits. They expressed a view that the setting of limits to cover both countries where maize was a staple and countries where it was a minor dietary component was not possible.

The desirability of country-specific maximum limits and the tension between food safety and food security in countries where maize is a staple have been discussed in a recent scientific paper (Shephard *et al.*, 2013).

5.5.2.2 Codes of practice and related initiatives

The European Commission published recommendations on the prevention and reduction of *Fusarium* toxins in cereals and cereal products (European Commission, 2006a). An outline of the EC recommendations is given in the chapter on trichothecene mycotoxins.

CCCF are currently reviewing the Code of Practice for Prevention and Reduction of Mycotoxin Contamination in Cereals to determine if additional measures can be added for specific control of fumonisins (Codex Committee on Contaminants in Food, 2013a). Measures under consideration include:

- Biological control;
- Predictive models; and
- Food processing, including sorting and cleaning, and wet and dry milling.

CCCF have recommended that a revision of the Code of Practice be considered, to include the use of predictive models, when available for a specific region, and sorting and cleaning, as an essential part of Good Manufacturing Practice procedures.

5.5.2.3 Management of fumonisin formation in crops

Sowing date and timing of insecticide (lambda cyhalothrin) treatment against European corn borer were both shown to have an impact on the fumonisin concentration of maize (Blandino *et al.*, 2008). Earlier sowing date and insecticide treatment 7 days after insect flight resulted in a 67% reduction in fumonisin concentration compared to untreated and later sown maize.

A decision support tool for fumonisin contamination of maize produced similar conclusions, with early planting, insecticide treatment and early harvest date all being associated with lower levels of fumonisin contamination (Maiorano *et al.*, 2009). Early harvest date was also reported to be associated with lower fumonisin levels in a Turkish study (Yılmaz and Tuncel, 2010).

A logistic regression model for fumonisin content of maize grown in Northern Italy was able to account for approximately 60% of the variability in fumonisin concentration (Battilani *et al.*, 2008). Factors that significantly influenced fumonisin content of maize were:

- Preceding crop. Rotational cropping and, particularly, growing of wheat prior to maize decreased fumonisin concentrations in maize crops.
- Maturity class. The longer the time between emergence and kernel ripeness, the higher the fumonisin content.
- Later sowing, later harvesting and higher kernel moisture at harvest were all associated with higher fumonisin concentrations.
- Nitrogen fertiliser. High nitrogen fertiliser (>325 kg/ha) was associated with increased fumonisin content, but moderate fertilisation (200-324 kg/ha) was associated with decreased fumonisin contamination, compared to low fertilisation (<200 kg/ha).

An American study also found that an earlier planting date resulted in lower maize fumonisin content (Parsons and Munkvold, 2012).

5.5.2.4 Control of fumonisins post-harvest

The time period between corn harvesting and drying was found to be positively correlated with total fumonisin content in Brazilian corn (Da Silva *et al.*, 2008). Fumonisin contamination appeared to be very sensitive to this time period, with samples with a time period of greater than 8 hours having fumonisin contamination levels approximately 5-times those that were dried in less than 3 hours.

Corn was stored for six months in 3 different types of traditional storage structure in Uganda (Atukwase *et al.*, 2012). The prevalence of *Fusarium* on corn kernels increased during the first 2 months then decreased to an average of 32% at six months. Fumonisin concentrations decreased steadily during storage, from a mean of 5.7 mg/kg at the beginning of the study to a mean of 2.8 mg/kg after six months storage. In contrast, a 9-month storage trial found no significant change of total fumonisin concentration during storage (Gregori *et al.*, 2013).

Irradiation decreased both *Fusarium* counts and fumonisin concentrations in wheat, maize and barley grain (Aziz *et al.*, 2007). Irradiation at 5 kGy inactivated FB_1 by 96.6%, 87.1% and 100% in wheat, maize and barley, respectively. A dose of 7 kGy was sufficient to completely destroy FB_1 in wheat and maize.

5.5.3 Influence of processing on fumonisin levels

5.5.3.1 Sorting and washing

Development of simple methods to remove visibly mouldy maize kernels and wash the remaining kernels was effective in reducing fumonisin exposure by 62% for subsistence households in a high oesophageal cancer region of South Africa (van der Westhuizen *et al.*, 2010b). On average, the sorting resulted in discarding of 3.9% by weight of the maize kernels.

5.5.3.1 Nixtamalisation

Nixtamalisation or 'masa-type' processes involves alkaline cooking and heating of maize for the production of tortillas and related products (Saunders *et al.*, 2001). While nixtamalisation has been shown to significant reduce the FB_1 content of corn, it was not known what the toxiciological implications of the reaction products were. A study was carried out in male Sprague-Dawley rats, comparing the impact of uncooked (U) and nixtamalised (C) maize at 3 dose levels (L, M, H) (Voss *et al.*, 2012). FB_1 concentrations were 0.08, 0.13 and 0.37 mg/kg in the LC, MC and HC diets, respectively, and 1.8, 3.5 and 4.2 mg/kg in the uncooked equivalent diets. Kidney lesions of the type associated with FB_1 exposure were not found in the LC and MC groups and were minimal and less severe in the HC group, compared to all groups receiving uncooked corn diets. Changes in sphinganine and sphingosine concentrations showed a similar pattern. Based on this study, nixtamalisation appears to be an effective measure for reducing the toxicity of fumonisin-contaminated corn.

5.5.3.2 Cooking, canning and extrusion

The impact of conventional cooking (boiling), autoclaving and dry heat treatment on FB_1 concentrations in rice were examined (Becker-Algeri *et al.*, 2013). Conventional cooking reduced FB_1 concentrations by approximately 80%. It was suggested that this may have been due to starch gelatinisation resulting in better heat transmission to the interior of the rice grain. Autoclaving had no significant impact, whole dry heating to temperatures of 150-200ºC resulted in an approximate 70% reduction in natural FB_1 contamination levels.

A study in the former Transkei region of South Africa found that traditional preparation of maize porridge from naturally-contaminated maize (n = 10) resulted in a mean reduction in total fumonisin content of 11.3% (Shephard *et al.*, 2012).

Fumonisin reduction during extrusion was studied (Scudamore *et al.*, 2008b). Fumonisin reduction was found to be greater at lower material moisture contents and higher barrel temperatures. Addition of salt appeared to lower the fumonisin reductions, but no mechanism for this observation was proposed. Maximum reductions of 85% were achieved at 13.5% moisture and 180ºC. A further study on extrusion found that the presence of reducing sugars resulted in greater fumonisin reductions, due to the formation of a fumonisin-sugar reaction

product (Jackson *et al.*, 2012). Reductions in excess of 90% were achieve using a twin-screw extruder in the presence of 10% glucose. Rat toxicity studies were used to confirm that the apparent reductions in fumonisin levels resulted in a dose-dependent decrease in kidney lesions.

The fate of fumonisins (FB_1 + FB_2) during production of maize-based snack foods was examined (Scudamore *et al.*, 2009b). Three product types were examined; expanded snacks via direct extrusion processing, expanded snacks via pellet processing, and tortilla chips. While there was considerable batch to batch variability, on average the fumonisin content of the final products was 11, <4 and 41% of the fumonisin content of the ingredients, respectively.

The impact of breadbaking on free and bound fumonisins was examined (Bryła *et al.*, 2013). Baking reduced the total fumonisin content of corn flour bread by 23-25%, but reduced bound fumonisins by 30-32%. This increased the ratio of free to total fumonisins from 0.72 to 0.83-0.95.

5.5.3.3 Fermentation

A study on the transfer of FB_1 from brewing raw materials to beer concluded that approximately 50% of the FB_1 in the raw ingredients was present in the brewed beer (Pietri *et al.*, 2010). This compared to only 1.5% transfer for AFB_1. The difference was ascribed to the greater water-solubility of FB_1. Reductions in FB_1 through the process were determined to be due to small losses at a number of steps, rather than a major reduction due to any one step.

5.5.3.2 Other

Treatment of bread artificially infected with *Gibberella moniliformis* (an FB_2 producer) with gaseous isothiocyanates (allyl-, phenyl- or benzyl-) resulted in a 73-100% decrease in fumonisin content, depending on the concentration of isothiocyanate and the contact time (Azaiez *et al.*, 2013).

5.6 Conclusions

5.6.1 Description of risks to New Zealand consumers

Further epidemiological evidence has been presented for an association between fumonisin exposure and oesophageal cancer, but not liver cancer. However, the available evidence is not definitive.

While *Fusarium* species capable of fumonisin production (*F. verticillioides, F. proliferatum*) have occasionally been found in New Zealand cereal crops, these fungal species appear to be relatively rare in New Zealand crops.

The available evidence suggests that New Zealanders will primarily be exposed to fumonisins through consumption of imported corn. As New Zealanders are generally low level consumers of maize products, the risk due to fumonisin exposure in New Zealand is likely to be low. Some of the processes used on maize (extrusion, nixtamalisation) will tend to further decrease the fumonisin content of the food in New Zealand.

While indications are that New Zealanders exposure to fumonisins will be very low, there is insufficient New Zealand specific information on the fumonisin content of available foods to define the level of risk.

5.6.2 Commentary on risk management options

Fumonisins are not currently regulated in New Zealand. Agronomic research conducted in New Zealand demonstrates a good awareness of the deleterious effects of *Fusarium* infection, but without specific reference to fumonisins (Cromey *et al.*, 2002; Cromey *et al.*, 2004). There is little evidence to suggest that fumonisin-producing *Fusarium* species occur commonly in New Zealand.

5.6.3 Data gaps

General information on the fumonisin content of the New Zealand food supply. Particularly, the emergence of *Aspergillus niger* as a producer of fumonisins in fruit may have implications for the New Zealand wine industry.

6 ZEARALENONE

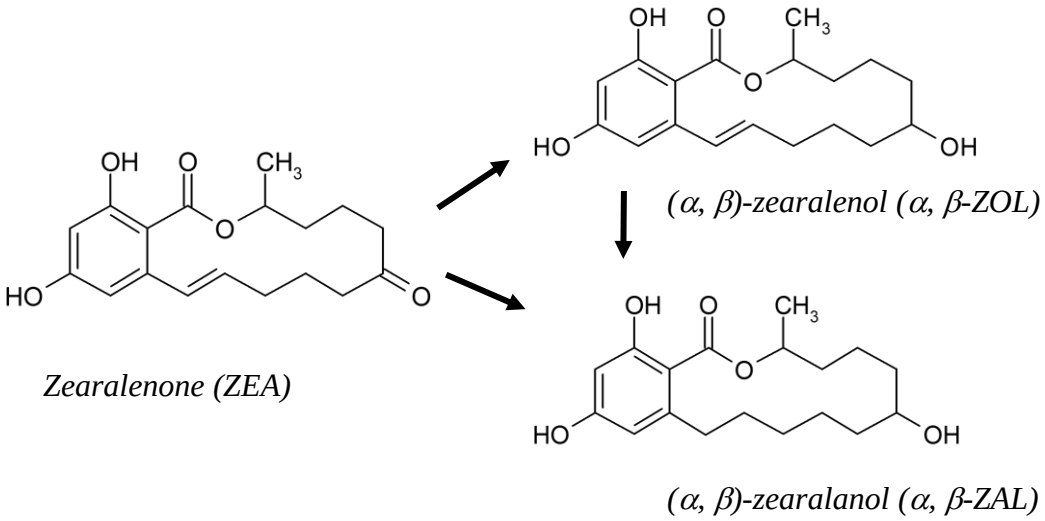
6.1 Hazard identification

Zearalenone (ZEA), (3*S*,11*E*)-14,16-dihydroxy-3-methyl-3,4,5,6,9,10-hexahydro-1*H*-2-benzoxacyclotetradecine-1,7(8*H*)-dione, is a nonsteroidal estrogenic mycotoxin produced by several *Fusarium* species that proliferate in poorly stored grains, oilseeds and hay. *Fusarium* infection tends to develop during prolonged cool, wet, growing and harvest seasons (EFSA, 2011c). ZEA occurs in both temperate and warm regions of the world in cereal crops such as corn or maize, barley, oats, wheat, rice and sorghum but also in bread and bananas. The highest reported incidence rates have been in North America, and central and northern Europe although the occurrence of ZEA has also been reported in Egypt, South Africa, Italy South America and New Zealand. ZEA is stable during storage and milling and processing or cooking of food and does not degrade at high temperatures. In plants and animals, ZEA may be metabolised to the stereoisomers, α- and β- zearalenol (α-ZOL and β-ZOL) and α- and β- zearalanol (α-ZAL and β-ZAL) (Figure 6). The α-isomer of zearalanol (α-ZAL), also known as zeranol, has been used as a growth promoter in beef cattle and feedlot lambs in the United States and Canada (IARC, 1993; Kuiper-Goodman *et al.*, 1987), but is not registered for veterinary use in New Zealand.

6.1.1 Structure and nomenclature

ZEA shows some structural similarities to the female sex hormone, 17β-estradiol, with 2 distally located oxygen-containing groups. The chemical structures of ZEA and its major metabolites are shown in Figure 6.

Figure 6: Structure of ZEA and its major metabolites



6.1.2 Occurrence

Fusarium taxonomy is complex and some early identifications have been questioned. ZEA is now regarded as being produced by *F. graminearum*, *F. culmorum*, *F. equiseti* and *F. verticillioides* (EFSA, 2011c). Other species have been reported to produce ZEA, however, they appear to be less important with respect to formation of ZEA in crops (Pitt and Hocking, 1997). All these *Fusarium* species been detected in New Zealand food crops, with *F. graminearum* seemingly the most prevalent species in the North Island and *F. culmorum* the most prevalent species in the South Island (see Table 10 and associated references).

6.2 Hazard Characterisation: Adverse Health Effects

6.2.1 Conditions

ZEA has been implicated in several incidents of adverse human health effects, but on the present evidence base, the impact on human health is speculative.

6.2.2 Toxicity

6.2.2.1 Acute toxicity

There have been no reports of acute human toxicity caused by ZEA.

ZEA has low acute toxicity after oral administration in mice, rats and guinea pigs, with LD_{50} values 2000 mg/kg body weight (EFSA, 2011c).

6.2.2.2 Chronic toxicity

The health concerns of exposure to ZEA relate to its estrogenic activity. Effects in female laboratory animals have included decreases in fertility, reproductive tract alterations, increases in embryonic resorptions, reductions in litter size, changes in weight of adrenal, thyroid and pituitary glands, and changes in serum levels of progesterone and 17β-estradiol (EFSA, 2011c). Effects have been observed in male laboratory animals (adverse effects on testosterone concentrations, sexual behaviour, testis and secondary sex organ weight, testicular histology and spermatogenesis), but at much higher levels of exposure than those that cause adverse effects in females.

There is limited evidence for the carcinogenicity of ZEA, but evidence that it is clastogenic (cause chromosome breakages) due to metabolism to quinones (EFSA, 2011c).

6.2.3 Toxicological assessment

JECFA have not updated the PMTDI for ZEA of 0.5 µg/kg body weight/day (500 ng/kg body weight/day), based on a dose that had no observed hormonal effects in pigs, the most sensitive species (JECFA, 2000). Similarly, there has been no update of the IARC assessment of ZEA as Group 3 (not classifiable as to their carcinogenicity to humans) because of inadequate evidence in humans and limited evidence in experimental animals (IARC, 1993).

EFSA have reviewed ZEA and amended the previous temporary Tolerable Daily Intake (t-TDI) of 0.2 μg/kg body weight/day to a full TDI of 0.25 μg/kg body weight/day (250 ng/kg body weight/day) (EFSA, 2011c). The TDI was derived from a NOEL for estrogenic effects in pigs of 10 μg/kg body weight/day.

The EFSA assessment also included derivation of a benchmark dose, based on pituitary adenoma occurrence in mice. A lower $BMDL_{10}$ of 6.39 mg/kg body weight/day was derived.

6.2.4 Metabolites and their relative toxicity

In mammals and avian species, ZEA is metabolised to the stereoisomers, α- and β-ZOL and α- and β-ZAL. These metabolites can also be produced directly by *Fusarium* species and have been detected in foods of plant origin, but at much lower concentrations than ZEA (Zinedine *et al.*, 2007).

There is evidence that different animal species vary in the relative proportions of α- and β-ZOL that are produced during metabolism of ZEA and that this may explain, in part, the sensitivities of those species to ZEA estrogenicity (Kolf-Clauw *et al.*, 2008). For example, pigs primarily metabolise ZEA to α–ZOL (Dänicke *et al.*, 2005), while cows are primarily β-ZOL producers (Mirocha *et al.*, 1981). While poultry primarily produce α-ZOL, significant inter-species variation has been reported (Kolf-Clauw *et al.*, 2008).

A series of cereal product composites were analysed for a wide range of ZEA metabolites, including ZEA, α-ZOL, β-ZOL, ZEA-4-glucopyranoside (Z4G), ZEA-4-sulphate (Z4S), α-ZOL-glucopyranoside (α-ZG) and β-ZOL-glucopyranoside (β-ZG) (Vendl *et al.*, 2010). Only parent ZEA and Z4S were detected, with ZEA present at approximately 10% of the concentration of Z4S when both were quantified.

More recently glucose and sulphate conjugates of ZEA and its primary metabolites have been detected in plant foods (Berthiller *et al.*, 2013; De Boevre *et al.*, 2013). These conjugates can be cleaved in the intestines of mammals to produce the parent compounds (Dall'Erta *et al.*, 2013; EFSA, 2011c). In general, concentrations of metabolites in foods were found to be correlated to the concentration of parent ZEA (De Boevre *et al.*, 2012).

Studies in experimental animals suggest that α-ZOL and α-ZAL are as estrogenic or more estrogenic than ZEA, while β-ZOL is less estrogenic than ZEA (EFSA, 2011c; Metzler *et al.*, 2010).

6.3 Exposure Assessment

6.3.1 ZEA in New Zealand cereals

A study in the Waikato took maize samples from receipt at a feed mill and then samples of rejected and accepted maize (Lauren *et al.*, 2006). Samples at mill intake contained ZEA in the range not detected (LOD = 100 μg/kg) to 1140 μg/kg. Rejected maize samples were in the range 460-5800 μg/kg, while accepted bulk maize samples were in the range 100-670 μg/kg. Samples were split into good quality maize, poor quality maize (small, shrivelled kernels), split maize and pieces of cob and plant material. The poor quality maize, split maize

and cob pieces made up 3-24%, 4-27% and 0-0.4% of total sample weight, respectively, but accounted for a disproportionate amount of the ZEA contamination. For example, in 1 sample poor quality and split maize accounted for 11% of the sample weight, but 78% of the ZEA content.

Trials in a maize drying plant tended to show a decrease in ZEA content as the samples progressed through the plant, mainly due to the removal of small or broken material (Lauren *et al.*, 2006). For 5 samples received at the drying plant, 5-21% of the initial ZEA loading remained in the finished, dried maize (concentration range 100-200 µg/kg). The highest proportion of the ZEA ended up in the poor maize (58-95%), while the highest ZEA concentrations were seen in the cob and stalk material (maximum = 84,600 µg/kg). It should be noted that, although this study was published in 2006, the samples were taken in 1995.

6.3.2 ZEA in the New Zealand food supply

Since the previous version of this risk profile, no new information on ZEA in the New Zealand food supply has become available.

6.3.3 ZEA in Australian cereals

An investigation was carried out of an occurrence of *Fusarium* head blight in Western Australia in 2003 (Tan *et al.*, 2012). The pathogens responsible were identified as *F. graminearum, F. acuminatum* and *F. tricinctum*. ZEA was detected in infected grain, along with DON, 3-ADON, enniatins and chlamydosporol.

6.3.4 ZEA in the Australian food supply

The 23rd Australian Total Diet Survey analysed bread (white and multigrain), savoury biscuits, breakfast cereals, rolled oats, pasta and meat pies for ZEA (Food Standards Australia New Zealand, 2011). ZEA was not detected in any samples. However, the method used for analyses and the LOD for the method were not reported.

6.3.5 Overseas context

Internationally, there have been many reports of the occurrence of ZEA in food and feeds from a wide range of countries with the highest prevalence of the toxin occurring in cereals, namely, barley, corn or maize, oats, rice, sorghum and wheat. Table 15 summarises studies on ZEA in other foods. Studies on ZEA metabolites in cereal foods are also presented.

Table 15: Worldwide data on occurrence of ZEA in food

Country	Food	Incidence positive/total samples (%)	Concentration (µg/kg)	Reference
Belgium	Home-produced eggs - ZEA - α-ZOL - β-ZOL	 7/20 (35) 11/20 (55) 9/20 (45)	 3-10[1] 1.5-5 6-20	(Tangni *et al.*, 2009)

Country	Food	Incidence positive/total samples (%)	Concentration (µg/kg)	Reference
Belgium	Fibre-enriched bread		Mean (Maximum)	(De Boevre *et al.*, 2012; De Boevre *et al.*, 2013)
	- ZEA	23/52 (44)	29 (230)	
	- Z4S	4/52 (8)	4 (176)	
	- Z4G	15/52 (29)	15 (154)	
	- α-ZOL	16/52 (31)	6 (110)	
	- α-ZOL-4G	5/52 (10)	3 (63)	
	- β-ZOL	12/52 (23)	7 (86)	
	- β-ZOL-4G	10/52 (19)	7 (153)	
	Bran-enriched bread			
	- ZEA	14/36 (39)	38 (157)	
	- Z4S	2/36 (6)	4 (143)	
	- Z4G	2/36 (6)	18 (155)	
	- α-ZOL	3/36(8)	6 (60)	
	- α-ZOL-4G	1/36 (3)	0.3 (12)	
	- β-ZOL	6/36 (17)	13 (96)	
	- β-ZOL-4G	2/36 (6)	6 (153)	
	Breakfast cereals			
	- ZEA	32/62 (52)	76 (450)	
	- Z4S	17/62 (27)	23 (417)	
	- Z4G	25/62 (40)	39 (369)	
	- α-ZOL	32/62 (52)	43 (515)	
	- α-ZOL-4G	16/62 (26)	11 (192)	
	- β-ZOL	26/62 (42)	17 (147)	
	- β-ZOL-4G	18/62 (29)	11 (206)	
	Popcorn			
	- ZEA	7/12 (58)	9 (51)	
	- Z4S	1/12 (8)	1 (12)	
	- Z4G	0/12 (0)	-	
	- α-ZOL	2/12 (17)	3 (32)	
	- α-ZOL-4G	0/12 (0)	-	
	- β-ZOL	2/12 (17)	5 (47)	
	- β-ZOL-4G	1/12 (8)	1 (10)	
	Oatmeal			
	- ZEA	8/13 (62)	41 (85)	
	- Z4S	2/13 (15)	4 (36)	
	- Z4G	5/13 (38)	12 (91)	
	- α-ZOL	5/13 (38)	10 (68)	
	- α-ZOL-4G	1/13 (8)	1 (10)	
	- β-ZOL	4/13 (31)	8 (46)	
	- β-ZOL-4G	2/13 (15)	2 (10)	
Benin	Cassava flour	3/4 (75)	6-12	(Njumbe Ediage *et al.*, 2011)
Brazil	Rice	49/165 (30)	4-4900	(Almeida *et al.*, 2012)
	Rice husk	27/27 (100)	28-15,700	
	Rice bran	19/19 (100)	14-2700	
	Broken rice	8/18 (44)	4-31	

Country	Food	Incidence positive/total samples (%)	Concentration (µg/kg)	Reference
Cameroon	Maize Peanuts Beans Soybeans	31/40 (78) 10/16 (63) 5/15 (33) 0/5 (0)	28-273 31-186 27-157 -	(Njobeh *et al.*, 2010)
China	Pork Pig liver Eggs Milk	1/10 (10) 3/10 (30) 2/5 (40) 2/5 (40)	1.11 (α-ZOL) 1.05-2.23 (α-ZOL) 0.86-2.51 (β-ZOL) 0.69-1.25 (β-ZOL)	(Chen *et al.*, 2013)
Côte d'Ivoire	Maize Rice Peanuts	10/10 (100) 10/10 (100) 10/10 (100)	20-50 50-200 50-200	(Sangare-Tigori *et al.*, 2006)
Egypt	Peanuts	1/60 (2)	9.8	(Youssef *et al.*, 2008)
European Union	 Sweet corn Vegetable oils Beer Foods for infants/small children	 10/94 (11) 190/221 (86) 2/35 (6) 17/420 (4)	Mean (95th percentile) 1.4-4.8 (7.1-12) 70-72 (200) 0.1-1.0 (1.8-2.2) 0.3-7.0 (0.0-15)	(EFSA, 2011c)
Germany	Soy products - ZEA - α-ZOL - β-ZOL	 7/45 (16) 5/45 (11) 2/45 (4)	 2-214 2-11 5,5	(Schollenberger *et al.*, 2007b)
Germany	Edible oils - ZEA - α-ZOL	 12/110 (11) 1/110 (1)	 5-1730 8	(Schollenberger *et al.*, 2008)
Greece	Beer	0/15 (ZEA, α-ZOL, β-ZOL)	-	(Maragou *et al.*, 2008)
Italy	Cows' milk infant formula - ZEA - α-ZOL - β-ZOL - α-ZAL - β-ZAL Meat-based infant foods - ZEA - α-ZOL - β-ZOL - α-ZAL - β-ZAL	 17/185 (9) 49/185 (26) 53/185 (29) 0/185 (0) 0/185 (0) 0/44 (0) 12/44 (27) 0/44 (0) 1/44 (2) 0/44 (0)	Maximum (µg/L) 0.76 12.91 73.24 - - Maximum (µg/kg) - 30.5 - 950 -	(Meucci *et al.*, 2011)
Ireland	Beer - ZEA - α-ZOL	 1/25 (4) 0/25 (0)	 37.8 µg/L -	(Rubert *et al.*, 2011)
Malawi	Beer	0/9 (0)	-	(Matumba *et al.*, 2014)
South Korea	Polished rice	3/88 (3)	22-47	(Park *et al.*, 2005)

Country	Food	Incidence positive/total samples (%)	Concentration (µg/kg)	Reference
Spain			Maximum	(Cano-Sancho *et al.*, 2012a)
	Pasta	10/70 (14)	5.9	
	Corn flakes	0/71 (0)	-	
	Wheat flakes	4/29 (14)	12.1	
	Corn snacks	17/72 (24)	22.8	
	Sweet corn	13/72 (18)	5.9	
	Sliced bread	31/71 (44)	20.9	
	Beer	8/71 (11)	5.1	
	Baby food	7/30 (23)	5.4	
Spain			Maximum	(Escobar *et al.*, 2013)
	Maize germ, wet milled	3/12 (25)	34	
	Maize germ, dry milled	0/12 (0)	-	
	Corn oil	8/25 (32)	67	
	Corn oil margarine	6/25 (24)	86	
Spain			Maximum	(Santos *et al.*, 2010)
	Paprika	25/64 (39)	131	
	Chilli powder	16/35 (46)	129	
Spain			Maximum	(Santos *et al.*, 2011)
	Paprika	4/21 (19)	114	
	Chilli powder	4/11 (36)	78	
United States	White wine[2]	0/71 (0)	-	(Al-Taher *et al.*, 2012)
	Red wine	0/72 (0)	-	
	Beer	0/76 (0)	-	

NR = no result available ZEA = zearalenone α-ZOL = α-zearalenol
β-ZOL = β-zearalenol Z4S = ZEA-4-sulphate Z4G = ZEA-4-glucoside
α-ZOL-4G = α-ZOL-4-glucoside β-ZOL-4G = β-ZOL-4-glucoside

[1] All results in this study were reported as 'trace' values. The figures given here for the concentration range are the LOD and LOQ values

[2] Wines were from USA, Europe, South America and Australia

Although ZEA is not usually associated with fruit, analysis of 52 dried figs from a rejected lot detected ZEA in 7 figs (Şenyuva and Gilbert, 2008). Concentrations of mycotoxins were not quantified in this study.

A review of mycotoxin carryover to milk concluded that 0.06-0.08% of ingested ZEA would be transferred to bovine milk, mainly in the form of α-ZOL, which has similar or greater estrogenic potency than ZEA (Fink-Gremmels, 2008).

A predictive model was used to estimate the ZEA concentration of bovine milk given the level of contamination in feed products (Signorini *et al.*, 2012). The model estimated a mean ZEA concentration of 0.125 µg/kg (95th percentile confidence interval 0.016-0.469 µg/kg). The model did not include any consideration of the metabolism of ZEA to more (α-ZOL) or less (β-ZOL) estrogenic forms. The model used the carryover rate from the study summarised in the previous paragraph.

There appears to be little carryover of ZEA or its metabolites to edible animal tissues. Neither ZEA or its metabolites were detectable in liver or breast meat of male turkeys fed a diet containing up to 0.04 mg/kg ZEA from 21 to 56 days of age (Dänicke *et al.*, 2007). ZEA and metabolites were not detected in any of 300 bovine muscle samples (Kaklamanos *et al.*, 2009). However, this study gave no information on the ZEA content of animal diets. Of 1256

'meat and meat product' samples for which data were submitted to EFSA, ZEA was not detected in any sample (EFSA, 2011c).

6.3.6 New Zealand estimates of dietary exposure

No updated estimates of the dietary exposure of New Zealanders to ZEA have been conducted since the previous version of this risk profile.

6.3.7 Overseas estimates of dietary exposure

A summary of overseas exposure estimates for ZEA is given in Table 16.

Table 16: Overseas estimates of dietary exposure to ZEA

Country	Population group	Mean (95th percentile) exposure, ng/kg body weight/day	Reference
PMTDI (JECFA) = 500 ng/kg body weight/day TDI (EFSA) = 250 ng/kg body weight/day			
Belgium[1]	Adults -ZEA only -ZEA + metabolites[2]	 37-45 (85-102) 107-122 (243-277)	(De Boevre *et al.*, 2013)
European Union	Infants Toddlers Other children Adolescents Adults Elderly Very elderly	3.3-88 (33-217) 9.3-100 (24-277) 5.7-75 (9.9-124) 3.6-42 (7.5-76) 2.4-29 (4.7-54) 2.0-26 (3.5-42) 2.3-29 (7.0-47)	(EFSA, 2011c)
France	Children Adults	12-46 (23-88) 5.9-26 (11-43)	(Sirot *et al.*, 2013)
France	Women (18-45 years) - Before pregnancy (*n* = 1861) - In third trimester (*n* = 1775)	 3.7-18.8 (7.7-36.3) 3.0-14.6 (6.1-28.2)	(Chan-Hon-Tong *et al.*, 2013)
Iran[3]	Adults (from consumption of rice, bread, wheat flour and puffed corn snack)	12	(Yazdanpanah *et al.*, 2012)
Italy	Formula-fed infants - ZEA - α-ZOL - β-ZOL	 21-78[4] 87-170 760-2900	(Meucci *et al.*, 2011)
Serbia	Consumption of wheat products Children Adults	 20 20	(Škrbić *et al.*, 2012)
Spain (Catalonia)	Infants and toddlers (0-3 years) Children (4-12 years) Adolescents (13-18 years) Adults (20-65 years) Elderly (>65 years)	12.2-17.9 (35.4-51.9) 2.3-6.2 (5.7-16.5) 1.5-2.2 (4.5-6.8) 0.9-1.5 (2.5-4.2) 0.3-0.5 (0.9-2.0)	(Cano-Sancho *et al.*, 2012a)
Spain	Consumption of cereals (wheat, rice, maize) Infants Children Adults	 17.1 11.5 2.2	(Rodríguez-Carrasco *et al.*, 2013)

ZEA = zearalenone α-ZOL = α-zearalenol β-ZOL = β-zearalenol

[1] Based on consumption of cereal-based foods (fibre-enriched bread, bran-enriched bread, breakfast cereals, popcorn and oatmeal)
[2] Includes ZEA, α-ZOL, β-ZOL, ZEA-4-glucoside, ZEA-4-sulphate, α-zearalenol-4-glucoside and β-zearalenol-4-glucoside
[3] ZEA was not detected in any of the foods used as a basis for this exposure assessment and all concentration data were assigned values of half the LOQ
[4] The ranges of exposure estimate represent the range of estimate derived for different classes of infant formula (ready-to-use pre-term, ready-to-use starter, powdered starter)

In the EFSA exposure assessments bakery products and vegetable oils were consistently significant contributors to ZEA exposure, across all age groups (EFSA, 2011c).

6.3.8 Biomarkers of exposure

Methods have been developed for analysing ZEA and metabolites (α-ZOL, β-ZOL and ZEA-glucuronide) in human urinary samples (Njumbe Ediage *et al.*, 2012; Warth *et al.*, 2012b). In validating one of these methods, ZEA and/or β-ZOL were detected in 5 of 40 urine samples from volunteers, with β-ZOL present at higher concentrations than ZEA (Njumbe Ediage *et al.*, 2012).

One of these methods was then applied to a cross-sectional study of 220 children in Cameroon (Njumbe Ediage *et al.*, 2013). β-ZOL was detected in urine from 8% of study participants, with concentrations in the range 0.02-12.5 ng/ml. ZEA and α-ZOL were each detected in 4% of samples, with concentrations in the range 0.65-5.0 and 0.26-1.3 ng/ml, respectively. α-ZOL and β-ZOL did not co-occur in any urine samples, suggesting distinct inter-individual differences in the manner in which ZEA is metabolised. Urinary levels of ZEA and metabolites were highest in children from regions with a high frequency of maize consumption.

In a study of adults from Cameroon (n = 175) urinary total ZEA (ZEA + α-ZOL + β-ZOL + ZEA-14-Glucuronide) was detected in 7 samples (4%), with a maximum concentration of 21.4 μg/L ZEA equivalents (Abia *et al.*, 2013a). ZEA and ZEA-14-Glucuronide were detected with equal frequency, but the glucuronic acid conjugate was present at substantially higher levels.

A further urinary method was developed, including analysis for α-ZOL and β-ZOL, but not parent ZEA (Solfrizzo *et al.*, 2011). However, neither of these metabolites were detected in urine from healthy volunteers (n = 10). Similarly, a method which screened for ZEA, α–ZOL, β–ZOL, α-ZAL, β-ZAL and zearalanone (ZAN) in urine recovered spiked amount of these toxins from 2 human urines, but did not report detection of any endogenous toxins (de Andrés *et al.*, 2008).

A mass balance study on a 27-year old healthy volunteer ingesting foods naturally contaminated with ZEA concluded that about 10% of ingested ZEA was excreted in urine (Warth *et al.*, 2013). Excreted levels of ZEA metabolites were too low to quantify individual metabolites and measurements were made of total ZEA, following enzymatic hydrolysis. However, ZEA-14-glucuronide was detected in spot urine samples following the most heavily ZEA-contaminated meals.

Serum concentrations of ZEA have also been used as biomarkers of exposure (Massart *et al.*, 2008).

6.4 Risk Characterisation

6.4.1 Adverse health effects in New Zealand

No cases of human adverse health effects attributable to ZEA exposure have been reported in New Zealand.

6.4.2 Adverse health effects overseas

6.4.2.1 Epidemiological studies

ZEA or zearalanol have previous been implicated as a causative agent of precocious female puberty (Saenz de Rodriguez *et al.*, 1985; Szuets *et al.*, 1997). However, more recent studies have been equivocal.

Italy

An Italian study examined serum levels of ZEA and α-ZOL in 32 girls with central precocious puberty (CPP) and 31 healthy controls (Massart *et al.*, 2008). Estrogenic mycotoxins were detected in serum of 6 CPP cases and none of the controls. Height, weight and height velocity over a 12 month period were higher in ZEA/α-ZOL-positive girls than CPP, but negative, or control girls.

USA

A cross-sectional study of 9 and 10 year old girls (n = 163) was carried out in New Jersey, measuring urinary ZEA and zeranol (α-ZAL), anthropometric parameters, puberty staging (breast and pubic hair development) and dietary intake (Bandera *et al.*, 2011). ZEA and zeranol were detected in 78% of urine samples, with reported beef and popcorn consumption showing associations with urinary mycotoxin levels. Girls with urinary analyses negative for ZEA and zeranol were significantly taller, had higher adiposity and were more likely to have reached the onset of breast development than girls with urinary positivity for these compounds.

6.4.2.2 Risk assessment

Muri *et al*. (2009b) used stochastic methods to produce individual margins of exposure (iMOEs) for a range of fungicides and mycotoxins, including ZEA. The technique involved sampling from a population distribution of ZEA exposure estimates and from a distribution of 'critical effect doses' (CEDs) for particular endpoints (e.g. 20% decrease in foetal body weight). The CEDs were extrapolated from animal studies to humans. For ZEA, iMOE distributions had medians of approximately 10^7 in most cases, with iMOEs greater than 10^4 at the 1st percentile. These MOEs indicate a low level of risk due to ZEA exposure. Distributions of iMOEs for tebuconazole, a fungicide used for control of ZEA-producing

fungi, were similar to those for ZEA, suggesting that the use or non-use of fungicide to control ZEA content of crops carry approximately equal risks.

6.5 Risk Management Information

6.5.1 Relevant food controls: New Zealand

6.5.1.1 Establishment of regulatory limits

ZEA is not currently regulated in New Zealand.

6.5.2 Relevant food controls: overseas

6.5.2.1 Establishment of regulatory limits

A consolidation of regulatory limits for ZEA (Van Egmond and Jonker, 2004) was summarised in the previous version of this risk profile. Table 17 summarises regulatory positions on ZEA for different foods in different countries that have been reported since 2005.

Table 17: Regulatory limits for ZEA in various countries (food regulations only)

Country	Commodity description	Regulatory limit (µg/kg)
EU[1]	Unprocessed cereals, other than maize	100
	Unprocessed maize with the exception of unprocessed maize intended to be processed by wet milling	350
	Cereals intended for direct human consumption, cereal flour, bran as end product marketed for direct human consumption and germ	75
	Refined maize oil	400
	Bread, pastries, biscuits, cereal snacks and breakfast cereals, excluding maize snacks and maize based breakfast cereals	50
	Maize intended for direct human consumption, maize flour, maize-based snacks and maize based breakfast cereals	100
	Processed cereal-based (excluding processed maize-based foods) and baby foods for infants and young children	20
	Processed maize-based foods for infants and young children	20
	Milling fractions of maize with particle size > 500 micron falling within CN code 1103 13 or 1103 20 40 and other maize milling products with particle size > 500 micron not used for direct human consumption falling within CN code 1904 10 10	200
	Milling fractions of maize with particle size ≤ 500 micron falling within CN code 1102 20 and other maize milling products with particle size ≤ 500 micron not used for direct human consumption falling within CN code 1904 10 10	300
South Korea[2]	Grains and processed grain foods	200
	Confectioneries	50
	Baby foods	20
Thailand[2]	All foods	30-1000

[1] (European Commission, 2007)
[2] From (Anukul *et al.*, 2013)

6.5.2.2 Codes of practice and related initiatives

The European Commission published recommendations on the prevention and reduction of *Fusarium* toxins in cereals and cereal products (European Commission, 2006a). An outline of the EC recommendations is given in the chapter on trichothecene mycotoxins.

6.5.2.3 Management of ZEA formation in crops

A study conducted across the 3 major maize growing regions of New Zealand (Waikato, Bay of Plenty, Manawatu) during 1995-1997 demonstrated that the major determinants of mycotoxin contamination were; the hybrid grown and harvest date (Lauren *et al.*, 2007). Hybrids bred for resistance to mycotoxin contamination showed lower incidence and concentrations of mycotoxin, while the longer the period between the grain reaching 28% moisture and harvest, the higher the mycotoxin content.

A model has been developed for predicting mycotoxin (DON and ZEA) formation in maize in the Netherlands (van Asselt *et al.*, 2012). The model includes fungal infection during silking (dependent on wind speed and rainfall) and germination, growth and toxin formation (depending on temperature and water availability). In addition to weather factors, crop management factors can also be defined as inputs to the model (hybrid type, planting date, flowering period and harvest date).

The potential for genetic modification to reduce or mitigate mycotoxin contamination of crops has been reviewed (Cary *et al.*, 2009). Potential approaches are outlined in section 2.5.2.3. An enzyme (alkaline lactonohydrolase), capable of degrading ZEA to a non-toxic product, was cloned from the fungus *Clonostachys rosea* and inserted into maize (Igawa *et al.*, 2007). Maize seeds were immersed in a solution containing ZEA for 48 hours. Transgenic seeds were found to contain approximately 10% of the ZEA present in unmodified seeds.

6.5.3 Influence of processing on ZEA levels

6.5.3.1 Milling

Milling of soft Japanese wheats resulted in approximately 50% of the ZEA present in the cleaned grain being partitioned into the bran fraction (Zheng *et al.*, 2014). The premium flour stream retained approximately one-quarter of the ZEA present in the wheat.

6.5.3.2 Cooking and baking

During pilot plant breadmaking with naturally ZEA-contaminated flour, the initial fermentation step results in a marked decrease in ZEA levels, but subsequent fermentation and baking did not impact on ZEA levels (Cano-Sancho *et al.*, 2013b).

Degradation of ZEA during baking of traditional Turkish maize bread was shown to follow first order kinetics (Numanoglu *et al.*, 2012). Baking at 100ºC did not result in any loss of ZEA, even after heating for 6 hours. Baking at 250ºC for 70 minutes resulted in a maximum temperature in the crust of 180ºC and a 13% decrease in ZEA content, while the crumb reached a maximum of 92ºC, with no significant reduction in ZEA content.

The impact of biscuit (semi-sweet or cracker) making on ZEA content of wheat flour was examined (Scudamore *et al.*, 2009a). Neither biscuit manufacture type resulted in a significant decrease in ZEA content. Production of semi-sweet biscuits involves a higher ingredient fat content and a longer baking time at lower temperatures (5 minutes at 245ºC) than for crackers (3 minutes at 280ºC).

Extrusion of ZEA-containing maize flour resulted in unexpectedly large decreases in ZEA content (Scudamore *et al.*, 2008b). Losses were in the range 6-54%, depending on maize meal moisture content (greater losses at higher moisture content) and extruder barrel temperature (greater losses at lower barrel temperatures). Addition of salt (2%) or dextrose (5 or 10%) decreased ZEA losses during extrusion. It should be noted that the ZEA contamination level in the maize flour used for these experiments was quite low (22 μg/kg).

In contrast, there was little evidence of ZEA losses during extrusion of wholemeal wheat flour (Scudamore *et al.*, 2008a). The wholemeal wheat flour contained markedly higher concentrations of ZEA (approximately 300 μg/kg) than the maize flour used in the extrusion studies reported in the previous paragraph.

6.5.3.2 Brewing

Beer wort was spiked with ZEA and subjected to a laboratory scale micro-fermentation process (Mizutani *et al.*, 2011). After 18 days of fermentation, most (85.9%) of the ZEA had been converted to the less estrogenic β-ZOL.

ZEA was spiked into the malt used for beer making (Inoue *et al.*, 2013). ZEA was undetectable by the unhopped wort stage (malt was mixed with water, added to a starch-water 'mash', incubated and filtered). This appears to be due to a mixture of degradation and insolubility (approximately 50% of ZEA was recovered from the spent grain). When ZEA was added to the cool wort, just prior to fermentation, it had largely disappeared from the fermentation mix after 18 days.

6.6 Conclusions

6.6.1 Description of risks to New Zealand consumers

The link between ZEA exposure and human health effects is currently speculative. Although ZEA has been clearly demonstrated to have significant estrogenic activity, the significance of this activity at dietary concentrations in uncertain.

There is clear evidence of the presence of *Fusarium* fungi that are known to produce the mycotoxin ZEA, occurring in both the North and South Islands of New Zealand. There is also continuing evidence that ZEA may be present in maize grown in New Zealand, at concentrations that may exceed regulatory limits in other countries (Lauren *et al.*, 2006). However, New Zealanders consume relatively small amounts of maize. There is less information available on ZEA in New Zealand wheat and wheat products. There is potential for these products to be significantly greater contributors to ZEA exposure than maize products.

6.6.2 Commentary on risk management options

New Zealand does not currently exercise direct risk management measures to control the entry of ZEA into the human food chain. Control of ZEA is likely to occur as a consequence of GAP and GMP practices, designed to achieve other quality and safety objectives.

6.6.3 Data gaps

The major data gap at present is the establishment of a definitive link between ZEA exposure and adverse human health effects, although expert bodies such as JECFA and EFSA feel that there is sufficient evidence to recommend that exposure be kept as low as possible and further work be undertaken to elucidate the toxicity to humans.

In New Zealand information on ZEA contamination in wheat, wheat-based products and infant cereals is currently limited.

7 ERGOT ALKALOIDS

7.1 Hazard Identification

Ergot refers to fungal structures from *Claviceps* species replacing grain kernels with large discoloured sclerotia. *Claviceps* spp. produce a number of alkaloids, however 'ergot alkaloids' refers specifically to those containing the clavine or ergoline ring system. Ergot alkaloids (EAs) are mainly produced by *C. purpurea* and, to a lesser extent, *C. fusiformis* (Council for Agriculture and Technology, 2003).

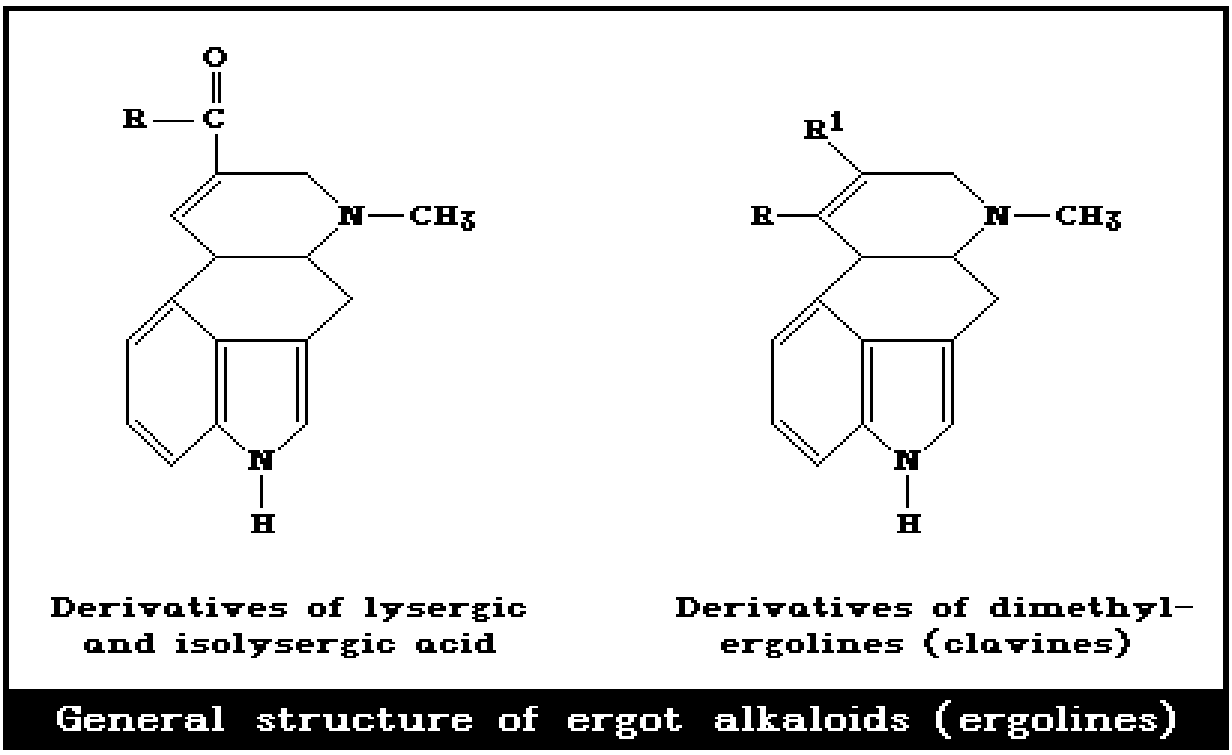
7.1.1 Structure and nomenclature

EAs are derivatives of lysergic acid and can be divided into 3 main groups:

- Group I: Derivatives of lysergic acid (ergotamine, α-ergocryptinine, ergocristine, ergosine, ergocornine, ergometrine);
- Group II: Derivatives of isolysergic acid (ergocristinine, ergometrinine, ergosinine, ergocorninine, α-ergocryptinine, ergotaminine);
- Group III: Derivatives of dimethylergolin (clavines; agrocalvine, elymoclavine, chanoclavine, penniclavine, setoclavine)

The basic skeletal structures for the ergoline and clavine EAs are shown in Figure 8.

Figure 7: Structure of EAs



Reproduced from WHO (1990)

The group I and II EAs are epimeric forms, due to asymmetry at the C8 position (EFSA, 2012a). The 8*R* epimers (Group I) are conventionally named with an -ine ending (e.g. ergotamine), while the 8*S* epimers (Group II) are named with an –inine ending (e.g. ergotaminine). Bidirectional epimerisation may occur and both epimeric forms usually exist in foods. The ratio between the epimers may depend on EA structure, storage conditions, light exposure, extraction and analytical method applied (EFSA, 2012a).

7.1.2 Occurrence

Sclerotia are compact hyphal structures that develop in the colonies of many fungal genera (WHO, 1990). Sclerotia formed by *Claviceps* spp. are unique in terms of size (up to several centimetres in length), colouration, and content of highly biologically active alkaloids.

Host plants for *Claviceps* species mainly belong to the grass family. *C. purpurea* has a particularly wide host range. The cereals most commonly colonised by *C. purpurea* are rye, wheat, triticale, barley, oats and sorghum. The ergot of *C. purpurea* contains group I and II ergolines. *C. fusiformis* is a parasite of pearl millet in Africa and East Asia and its ergot contains mainly group III ergolines (WHO, 1990).

EAs have been isolated from *Aspergillus, Rhizopus* and *Penicillium* fungi and from some higher plants (WHO, 1990). However, it is not known whether these sources represent human exposure routes.

Incidence of *C. purpurea* appears to be related to high humidity and low maximum temperatures in midsummer (Webster, 1980). These conditions probably cause an extension of the period during which cereals are susceptible to infection.

In New Zealand, *C. purpurea* has been reported on barley, rye and wheat, as well as a large number of non-food crops (Pennycook, 1989). In the middle of the last century in New Zealand, ergot was reported to be rarely found on wheat, oats or 2-row malting barley (Neill, 1941). Six-row barley was reported to be heavily ergotised in some areas, while rye was little grown in New Zealand. Two- and six-row barley refer to the number of rows of barley grains that make up the plant head.

7.2 Hazard Characterisation: Adverse Health Effects

7.2.1 Conditions

Ergotism has been known to man for centuries and numerous epidemics occurred in Europe between the 9th and 18th centuries, where it was known as St. Anthony's fire (WHO, 1990). Two types of disease may occur:

- Gangrenous ergotism. The affected part (arm or leg) shrinks, becoming mummified and dry, with the gangrene gradually spreading. The gangrenous form of ergotism is probably caused by the vasoconstrictive properties of Group I and II EAs (ergotamine-like). Symptoms include edema, pruritis, necrotic extremities, prickling sensations and severe muscular pain (Council for Agriculture and Technology, 2003).
- Convulsive ergotism. The whole body is attacked by general convulsions, returning at intervals of a few days. The convulsive form of ergotism appears to be caused by

Group III EAs produced by *C. fusiformis*. Symptoms include tingling under the skin, pruritis, numbness of extremities, muscle cramps, convulsions and hallucinations (Council for Agriculture and Technology, 2003).

7.2.2 Toxicity

7.2.2.1 Acute toxicity

The limited information available suggests that EAs are of low acute toxicity, with oral toxicity lower than following intravenous administration (EFSA, 2012a). Oral LD_{50}s for ergotamine, ergometrine and ergostine for rats, mice and rabbits are in the range 28 (rabbit, ergometrine) to 3200 (mouse, ergotamine) mg/kg body weight. Intravenous LD_{50}s are in the range 1.2 (rabbit, ergostine) to 265 (mouse, ergotamine) mg/kg body weight.

7.2.2.2 Chronic toxicity

EFSA has reviewed the available toxicity data from animal studies (EFSA, 2012a). EAs act on a number of neurotransmitter receptors. Repeated dose treatments result in ischaemia (insufficient blood supply), particularly in the extremities. This is consistent with the vasoconstriction seen in human gangrenous ergotism. Animal studies have demonstrated no major differences in the toxicity of ergotamine, ergometrine and α-ergocryptine.

EAs have exhibited a number of impacts on reproduction in animal studies, including prevention of implantation, embryotoxicity and inhibition of lactation. However, these impact occur at higher dose levels than those at which maternal toxicity would occur.

Studies on genotoxicity are limited, with the exception of studies on ergotamine. EAs are not considered to be mutagenic or genotoxic.

Several EAs (ergotamine, ergometrine, ergocornine and whole ergot) are also employed for human therapeutic uses and adverse effects information is available from this source. Adverse effects are generally due to impact of EAs on the central nervous system or due to vasoconstriction of blood vessels. In cases of chronic overdosing, these impacts may exhibit as permanent headaches and severe circulatory disturbance, including the extremities (particularly legs and feet) becoming numb, cold, tingling and pale or cyanotic. Gangrene of the toes or fingers can occur in extreme cases.

7.2.3 Toxicological assessment

EAs have been recently assessed by EFSA's Panel on Contaminants in the Food Chain (CONTAM) (EFSA, 2012a). The panel concluded that EAs could cause acute, as well as longer term, effects and proposed an acute reference dose (ARfD) in addition to a tolerable daily intake (TDI).

The CONTAM Panel concluded that vasoconstriction, resulting in tail muscular atrophy in rodents was the critical effect for hazard characterisation. Three health-based exposure guideline values were derived:

- $BMDL_{10}$ = 0.33 mg/kg body weight/day

- ARfD = 1 µg/kg body weight (applying a safety factor of 300 to the $BMDL_{10}$)
- TDI = 0.6 µg/kg body weight/day (applying a safety factor of 600 to the $BMDL_{10}$)

In the absence of relative potency data for different EAs, they were assumed to have equal potency and the ARfD and TDI are group guideline values for the sum of EAs.

These health-based exposure guideline values were considered to be consistent with known human dose-effect relationships for EAs from their therapeutic use.

7.2.4 Metabolites and their relative toxicity

While not strictly metabolites, the primary EAs may exist in 2 epimeric forms, due to asymmetry at the C8 position (EFSA, 2012a). While the 8*S* epimers are considered to be less toxic than the 8*R* epimers (Merkel *et al.*, 2012; Pierri *et al.*, 1982), the ease of epimerisation between the 2 forms means that the sum of both is usually considered when assessing risk (EFSA, 2012a).

An *in vitro* simulated human digestion model was used to examine the impact of digestion on the stability and epimerisation of EAs in baked cookies (Merkel *et al.*, 2012). Simulated intestinal digestion resulted in minimal epimerisation of ergometrine, but an marked shift to the 8*S* form for the ergotoxine EAs (ergocornine, ergocryptine, ergocristine), while ergosine and ergotamine showed a shift to the 8*R* form.

7.3 Exposure Assessment

7.3.1 Ergot in the New Zealand food supply

No information was identified on the prevalence or concentrations of ergot or EAs in New Zealand foods.

During 2013, it was reported that the biggest outbreak of ergot in more than a generation had forced New Zealand's largest malting plant to reject some barley crops.[13] The outbreak was confined to the lower North Island.

7.3.2 Ergot in the Australian food supply

No information was identified on the incidence or concentrations of ergot or EAs in Australian cereals. However, it is known that ergot may occur in Australian rye grasses and that the sclerotia from rye grass can contaminate grain crops (Blaney *et al.*, 2009). Samples of rye grass ergot sclerotia (n = 30) from rye grasses and grain screenings were collected in South Australia. Total alkaloids in sclerotia range from 0.10-0.33%, with ergotamine being the dominant alkaloid in all samples.

[13] http://www.stuff.co.nz/manawatu-standard/your-manawatu/rangitikei-mail/8426255/Disease-hits-farmers-hard Accessed 14 November 2013

7.3.3 Overseas context

Information on the incidence and levels of EAs in foods is summarised in Table 18.

Table 18: Worldwide data on occurrence of ergot or EAs in foods

Country	Year	Food	What measured	Incidence, positive/total samples (%)	Concentration (µg/kg)	Reference
Belgium	NS	Rye foods Wheat foods Mixed rye/ wheat foods	Total alkaloids[2]	33/40 (83) 44/61 (72) 45/61 (74)	1-95 1-533 1-58	(Diana Di Mavungu *et al.*, 2011)
Belgium	NS	Various food and feed products	Total alkaloids[2]	104/122 (85)	1-1145[3]	(Diana Di Mavungu *et al.*, 2012)
Canada	NS	Winter wheat Spring wheat Maize, oats, barley, rye	Ergotamine Ergocornine Ergotamine Ergocornine Ergotamine, Ergocornine	1/25 (4) 1/25 (4) 3/15 (20) 3/15 (20) 0/60 (0)	638 76 88-146 89-354 -	(Martos *et al.*, 2010)
Denmark	2000-2005	Rye flour	Sum of alkaloids[1]	32/34 (94)	Max = 230	(Storm *et al.*, 2008)
Estonia	2010-2011	Rye foods Wheat foods	Sum of alkaloids[2]	33/34 (97) 13/14 (93)	12-862 5-18	(Diana Di Mavungu *et al.*, 2011)
Finland	2010-2011	Rye foods Wheat foods	Sum of alkaloids[2]	27/28 (96) 7/13 (54)	2-335 1-4	(Diana Di Mavungu *et al.*, 2011)
France	2010-2011	Rye foods Wheat foods	Sum of alkaloids[2]	12/12 (100) 25/25 (100)	29-928 3-605	(Diana Di Mavungu *et al.*, 2011)
Germany	NS	Rye bread Pumpernickel Rye crispbread Rye bread rolls	Sum of alkaloids[1]	14/23 (61) 3/20 (15) 1/14 (7) 3/9 (33)	Max = 258 Max = 47 28 11, 31, 91	(Bürk *et al.*, 2006)
Germany	NS	 Rye flour Rye Rye coarse meal Rye flakes	Sum of alkaloids[2]	 22/22 (100) 6/7 (86) 6/7 (86) 2/3 (67)	Max 715 197 740 66	(Müller *et al.*, 2009)
Germany	2009	Rye flour and wholemeal rye flour	Sum of alkaloids[2]	16/31 (62)	Mean = 213, Max = 1063	(Reinhold and Reinhardt, 2011)
Germany	2010-2011	Rye foods Wheat foods	Sum of alkaloids[2]	28/30 (93) 13/17 (76)	1-425 2-88	(Diana Di Mavungu *et al.*, 2011)
Italy	2010-2011	Wheat foods	Sum of alkaloids[2]	12/12 (100)	4-64	(Diana Di Mavungu *et al.*, 2011)
Poland	2010-2011	Rye foods Wheat foods	Sum of alkaloids[2]	30/30 (100) 12/15 (80)	14-305 1-28	(Diana Di Mavungu *et al.*, 2011)

Country	Year	Food	What measured	Incidence, positive/total samples (%)	Concentration (µg/kg)	Reference
Sweden	2010-2011	Rye foods Wheat foods	Sum of alkaloids[2]	20/26 (77) 11/16 (69)	1-151 1-8	(Diana Di Mavungu *et al.*, 2011)
United Kingdom	NS	Rye bread Rye crispbread Other rye products	Total and individual alkaloids[2]	8/8 (100) 11/11 (100) 6/9 (67)	1-121 2-340 3-19	(Crews *et al.*, 2009)
United Kingdom	2010-2011	Rye foods Wheat foods	Sum of alkaloids[2]	19/22 (86) 14/15 (93)	1-1122 1-44	(Diana Di Mavungu *et al.*, 2011)
United States	2011-2012	Rice Wheat - Wheat flour - Pasta Corn Peanuts Pistachios Almonds	Sum of alkaloids[4]	0/6 (0) 1/7 (14) 1/9 (11) 0/18 (0) 0/11 (0) 0/10 (0) 0/9 (0)	 29.3 30.4	(Liao *et al.*, 2013)

NS = not stated Max = maximum

[1] Includes ergometrine, ergotamine, ergocornine, α-ergocryptine and ergocristine

[2] Includes ergocryptine, ergocryptinine, ergotamine, ergotaminine, ergocristine, ergocristinine, ergometrine, ergometrinine, ergosine, ergosinine, ergocornine and ergocorninine

[3] The presentation of this paper made summarisation of information on particular food and feed types difficult. The food with the highest median concentration of total alkaloids (160 µg/kg) was wheat bran

[4] Includes ergocornine, ergocristine, ergocryptine, ergometrine, ergosine and ergotamine

There have been no reports of carryover of EAs to foods of animal origin.

Holstein Friesian cows were fed diets containing 2.25% ergot (505-620 µg/kg alkaloid on a dry matter basis), equating to a daily exposure between 4.1 and 16.3 µg/kg body weight (Schumann *et al.*, 2009). No alkaloid residues were detected in milk or blood during a 4 week feeding period.

In a related study, Holstein Friesian bulls (n = 38) received feed containing 0, 0.45 or 2.25 g/kg of ergot (0, 69 or 421 µg/kg EAs on a dry weight basis) for approximately 230 days (Schumann *et al.*, 2007). No significant differences in growth performance or body composition was found between the dose groups. No carryover of EAs into tissues (liver, muscle, kidneys) was detected.

7.3.3.1 Alkaloid content of ergot

The study of Crews *et al.* (2009) showed few consistent patterns in the occurrence of individual EAs in rye bread, crispbread and other products. The ratio of the –ine (8*R*) form of the alkaloids to the –inine (8*S*) form varied in the range 0.1-6.0 across different products. Ergosine, ergocrystine and ergotamine were the alkaloids present at the highest concentrations in rye bread. Amongst highly contaminated crispbreads, ergotamine, ergotaminine, ergocristinine, ergometrine, ergometrinine and ergocorninine were the main alkaloids present.

7.3.1 New Zealand estimates of dietary exposure

No estimates of dietary exposure to ergot or EAs have been reported for the New Zealand population. Exposure of New Zealanders to ergot is likely to be largely due to its presence in rye or wheat.

According to Food Balance Sheets for 2009, rye is not a highly consumed food in New Zealand (<1 g/person/day).[14] However, in a 24 hour dietary recall study of 4,721 adult New Zealanders, 81 (1.7%) reported consumption of rye-containing bread during the previous 24 hour period (University of Otago and Ministry of Health, 2011).

In 2011, New Zealand imported less than 20 tonnes of rye flour, mainly from Germany.[15] While information on rye grown in New Zealand could not be found, it was noted that seed supply companies advertise rye seed.[16]

7.3.4 Overseas estimates of dietary exposure

EFSA used dietary consumption survey data from European countries and EA concentration data from consumer foods (not unprocessed commodities), for which 'at least 6' EAs were measured, to estimate acute and chronic EA exposure for European populations (EFSA, 2012a). Due to the high proportion of left-censored data (not detected) summary statistics were expressed as upper and lower bounds (UB and LB).

Across different surveys and age classes, mean chronic EA dietary exposure ranged from 0.007 μg/kg body weight/day (minimum LB) to 0.173 μg/kg body weight/day (maximum UB). High level exposures (95th percentile) ranged from 0.014 μg/kg body weight/day (minimum LB) to 0.335 μg/kg body weight/day (maximum UB). Highest exposures were in the toddler and other children age group. On average, the major contributors to dietary exposure were bread and bread rolls and particularly rye bread and rye bread rolls, followed by wheat bread and wheat bread rolls.

Acute exposure estimates were calculated at a daily level, rather than a meal level, due to limitations in the food consumption data. Across different surveys and age classes, mean acute EA dietary exposure ranged from 0.02 μg/kg body weight/day (minimum LB) to 0.42 μg/kg body weight/day (maximum UB). High level exposures (95th percentile) ranged from 0.06 μg/kg body weight/day (minimum LB) to 1.03 μg/kg body weight/day (maximum UB). As for chronic exposure, the highest acute exposures were in the toddlers and other children age group. The major food group contributing to acute EA exposure was rye bread and rolls.

[14] http://faostat3.fao.org/faostat-gateway/go/to/download/FB/*/E Accessed 19 February 2014

[15] http://www.stats.govt.nz/ Accessed 19 February 2014

[16] http://pggwrightsongrain.co.nz/media/4513/amilo%20dossier%202011%20nv1.pdf Accessed 19 February 2014

7.4 Risk Characterisation

7.4.1 Adverse health effects in New Zealand

No cases of human adverse health effects attributable to EA exposure have been reported in New Zealand.

7.4.2 Adverse health effects overseas

While outbreaks of ergotism occurred on a regular basis during the middle ages, such outbreaks have been reasonably rare in recent times. Few documented outbreaks of ergotism occurred during the second half of the twentieth century.

7.4.2.1 Ethiopia

The previous version of this risk profile summarised an outbreak of ergotism occurred in the Wollo region of Ethiopia in 1978, caused by locally grown barley heavily contaminated with wild oats (70%). A further outbreak of gangrenous ergotism occurred in the Arsi region of Ethiopia during February to June 2001 (Urga *et al.*, 2002). Field studies identified 18 cases, aged 5-30 years, with 3 reported deaths. Barley from the 2000-2001 outbreak was reported to have a peculiar odour and 7 samples were collected for analysis. All analysed barley samples contained ergotamine (2100-25,000 μg/kg) and ergometrine (1900-12,000 μg/kg).

Feeding of contaminated barley to laboratory mice resulted in debilitation, progressing to loss of movement and gangrene. Mortality rates were up to 55% with the most contaminated barley samples.

7.5 Risk Management Information

7.5.1 Relevant food controls: New Zealand

7.5.1.1 Establishment of regulatory limits

Standard 1.4.1 of the Joint Australia New Zealand Food Standards Code defines a maximum limit (ML) for ergot in cereal grains of 500 mg/kg (0.05%). However, the Standard does not extend to a limit for the EAs.

7.5.1.2 Guidelines

The Foundation for Arable Research (FAR®) has produced a guidance document entitled 'Managing ergot in cereal crops' (Foundation for Arable Research, 2013). Control measured described include:

- Ploughing, to bury sclerotia sufficiently deep that they cannot germinate;
- Rotation cropping;
- Controlling grass weeds around the crop;
- Separation of infected grain at harvest; and
- Seed cleaning.

7.5.2 Relevant food controls: overseas

7.5.2.1 Establishment of regulatory limits

In 2003, only 3 countries (Canada, Australia and New Zealand) reported having regulatory limits for ergot in food (Van Egmond and Jonker, 2004). The joint New Zealand and Australian regulatory limit is summarised in section 7.5.1.1. In Canada the ergot content of grains is regulated by the Canadian Grain Commission, with limits for various grades of wheat in the range 0.01-0.10%, rye (0.05-0.33%) and barley (0.05% to no limit) (http://www.grainscanada.gc.ca/views/ergot/ergot99-e.htm).

7.5.3 Influence of processing on EA levels

7.5.3.2 Breadbaking and cooking

Consistent results showing a reduction in naturally-occurring EA concentrations in food products produced by baking or other cooking processes have been achieved.

A decrease of 25% in the EA content was reported during baking of a single rye bread roll (Bürk *et al.*, 2006).

Baking of cookies from a rye flour containing ground sclerotia resulted in both degradation and epimerisation of EAs (Merkel *et al.*, 2012). The most heat resistant EA was ergocornine/ergocorninine for which concentrations decreased by 2, 3 and 8% after baking for 9, 13 or 17 minutes. Ergotamine/ergotaminine was the most susceptible, decreasing by 11, 20 and 30% after the same cooking times. Cookie baking consistently resulted in conversion of the 8*R* epimers (toxic) to the 8*S* form (lower toxicity). After baking for 17 minutes, 21-45% epimerisation had occurred, depending on the individual EA.

7.5.3.1 Malting and brewing

Sclerotia from barley and wheat were micro-malted, including steeping, germination and kilning (Schwarz *et al.*, 2007). Total EA content (ergosine, ergotamine, ergocornine, ergocryptine and ergocristine) decreased by 78% and 47% for barley and wheat sclerotia, respectively. Decreases were seen in concentrations of all individual toxins. Brewing of beer from EA-containing malt resulted in an even greater percentage decrease in alkaloid content. On average, 32, 10 and 2% of the alkaloids present in the malt were detected in the spent grain, wort and beer, respectively.

7.6 Conclusions

7.6.1 Description of risks to New Zealand consumers

Ergot is known to cause serious human disease. However, outbreaks of ergotism have become increasingly rare in modern times. There have been no documented cases of human ergotism in New Zealand.

Infection of cereals by *Claviceps purpurea* has been reported in New Zealand (Pennycook, 1989) and there have been recent reports of infections being sufficiently serious that grain

(barley) was diverted from processing. While no information was located on domestic production of rye, declining imports, availability of seed from New Zealand sources and the frequency of consumption of rye containing breads suggests that cultivation of rye may be increasing in New Zealand. Prevalence of infection of wheat is unknown.

Harvesting and cleaning of grain prior to milling will remove the majority of the ergot present in the crop and further processing (e.g. breadbaking) will tend to decrease ergot levels further.

Exposure of New Zealanders to ergot and the alkaloids contained within the ergot sclerotia is probably low, however, the lack of objective information to support this supposition is a concern. Good Agricultural Practice and modern grain handling practices are likely to provide a high level of risk management.

7.6.2 Commentary on risk management options

Under the Australia New Zealand Food Standards Code the maximum limit for ergot in cereal grains is set at 500 mg/kg (0.05%). While this standard would provide a high level of consumer protection, there is no evidence to suggest that the Standard is being actively enforced.

7.6.3 Data gaps

Data on the occurrence of ergot and EAs in New Zealand and Australian cereals are not available.

8 PATULIN

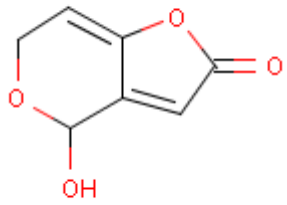
8.1 Hazard Identification

Patulin (PAT), 4-hydroxy-4H-furo[3,2c]pyran-2(6H)-one, is a bicyclic lactone metabolite of several species of *Penicillium, Byssochlamys* and *Aspergillus* moulds. Of the fungi producing PAT, *Penicillium expansum* is probably the most commonly encountered species and is often isolated from decaying apples.

8.1.1 Structure and nomenclature

The chemical structure of PAT is shown in Figure 9.

Figure 8: Structure of PAT



8.1.2 Occurrence

PAT in commercial apple products is principally due to soft rot caused by *Penicillium expansum* (Pitt and Hocking, 1997). The toxin is produced over the temperature range 0-25ºC, with optimum production at 25ºC. Production of PAT by *P. expansum* requires a minimum water activity of 0.95 and an acidic environment (pH 3.2-3.8). PAT is also relatively heat stable.

Production of PAT by other *Penicillium* species, including *P. griseofulvum, P. roqueforti*, and *P. funiculosum* has been reported (Pitt and Hocking, 1997), as well as *P. claviforme, P. urticae* and *P. patulum* (Drusch and Ragab, 2003).

Isolates of *Byssochlamys nivea* and *B. fulva* have been shown to produce PAT under experimental conditions, but there are no reports of production of PAT in commercial fruit juices due to *Byssochlamys* infection (Pitt and Hocking, 1997).

PAT has been shown to be produced by isolates of *Aspergillus clavatus* (Pitt and Hocking, 1997) and *A. giganteus* (Drusch and Ragab, 2003).

8.2 Hazard Characterisation: Adverse Health Effects

No reports were located of adverse health effects in humans due to PAT exposure. PAT was trialled as an antibiotic for use against the common cold in the 1940s. The authors of the study reported that no ill effects were observed, but the report is unclear as to the clinical tests applied (Hopkins, 1993).

8.2.1 Toxicity

No significant new information on the toxicity of PAT has been published since the previous version of this risk profile. The available animal and *in vitro* toxicity data have been recently reviewed (Puel *et al.*, 2010).

Although experimental data are variable, JECFA assessed PAT to be genotoxic, but not carcinogenic. Studies in V79 cell (Chinese hamster fibroblasts) lines suggested that PAT may cause structural DNA damage through its ability to cross-link DNA, forming nucleoplasmic bridges (Glaser and Stopper, 2012).

8.2.2 Toxicological assessment

No new toxicological assessments of PAT have been carried out since the previous version of this risk profile. The JECFA PMTDI of 0.4 µg/kg body weight/day (400 ng/kg body weight/day) is still the sole health-based exposure limit for PAT (JECFA, 1995).

Similarly, IARC have not updated their assessment of the carcinogenicity of PAT, that no evaluation could be made of the carcinogenicity of PAT to humans (Group 3) (IARC, 1986).

8.2.3 Metabolites and their relative toxicity

No metabolites of PAT have been reported.

8.3 Exposure Assessment

8.3.1 PAT in New Zealand apple-based foods

No surveys of PAT in the New Zealand food supply have been conducted since the previous version of this risk profile.

New Zealand production of apple juice is dominated by 1 manufacturer (Enzafoods New Zealand Limited[17]). However, apple juice available to the consumer will include product from a number of other smaller manufacturers. New Zealand also imports significant quantities of apple juice (approximately 3000 tonnes in the 2012 year[18]), with over 80% of imports from China and approximately 10% from each of Australia and South Africa. Routine regulatory testing of imported apple juice for PAT is not carried out.

[17] http://www.enzafoods.co.nz/
[18] http://www.stats.govt.nz/infoshare/TradeVariables.aspx?DataType=TIM

While no surveys of PAT in apple juice in New Zealand have been carried out since the previous version of this risk profile, a survey was carried out of apple juice concentrates from China, the main source of apple juice imported into New Zealand (Guo *et al.*, 2013c). From 2006-2010, PAT was detected in 1941 of 1987 apple juice concentrates, with an average PAT content of 6.7 µg/kg and a maximum of 78 µg/kg. Another Chinese study reported a mean PAT content for 20 apple juice concentrates of 28.6 µg/kg, with a maximum of 94.7 µg/kg (Yuan *et al.*, 2010). These concentrations are similar or slightly lower than those found in a survey of apple juice concentrates available in New Zealand (range 12-95 µg/kg) (Stanton, 1998).

8.3.2 PAT in Australian apple-based foods

The 23rd Australian Total Diet Study included analysis of fruit juices for PAT (Food Standards Australia New Zealand, 2011). PAT were not detected in any food sample analysed. However, the analytical method and the LOD were not reported. It is also not clear whether apple-containing juices were included.

8.3.3 Overseas context

The majority of monitoring studies on PAT examine the presence of the toxin in apples or pears or their products. However, there have been several reports of PAT prevalence in other fruit and non-fruit foods. These are summarised in the following sections. These reports include a report of PAT in an animal product (cheese), although it appears likely that the contamination was the result of deposition of fungal spores onto the cheese during maturation, rather than carryover from contamination of animal feed. A review of mycotoxin carryover into bovine milk concluded that this did not occur for PAT (Fink-Gremmels, 2008).

8.3.3.1 Plant-based foods

Quince

A Portuguese study examined PAT in quince and quince products (Cunha *et al.*, 2009). PAT concentrations as high as 118 µg/kg were detected in quince fruit with 75% 'brown areas', while quince jams were found to contain PAT at concentrations up to 29 µg/kg. It should be noted that quince, like apple and pear, is classified as a pome fruit.

Dried figs

Turkish figs are graded as palatable (premium), fluorescent (second grade) or cull (used for further processing). A study of figs from the Aegean region of Turkey found mean PAT concentrations in dried figs from the 3 grades of 11.4, 35.5 and 80.8 µg/kg, respectively (Karaca and Nas, 2006). The maximum concentration detected in cull dried figs was 152 µg/kg.

Peach

PAT was detected in 4 of 15 peach juice concentrates, with concentrations in the range 9.4-21.3 µg/kg (Marín *et al.*, 2011). Another study detected PAT in both of 2 peach juice samples

at concentrations of 12.2 and 15.3 μg/kg (Moukas *et al.*, 2008). An Italian study detected PAT in 2 of 30 peach juice samples, with a maximum concentration of 5 μg/kg (Spadaro *et al.*, 2008)

Other fruits

PAT was detected in a single sample of pineapple juice at a concentration of 7.7 μg/kg and in 3 samples of orange juice, with concentrations in the range 3.1-10.8 μg/kg (Moukas *et al.*, 2008). A Malaysian study detected PAT in 1 of 6 pineapple juice samples (33.1 μg/L) and 1 of 6 lychee juice samples (13.1 μg/L), but not in samples of mango, guava, tamarind or soursop juice (Lee *et al.*, 2014).

A South Korean study also detected PAT in orange juice and grape juice (Cho *et al.*, 2010). PAT was detected in 7 of 27 apricots juices, with a maximum concentration of 32.4 μg/kg (Spadaro *et al.*, 2008).

Tree nuts

PAT was detected in mouldy hazelnuts (mean concentration 56.3 μg/kg) and hazelnuts with 'hidden' mould (mean concentration 36.5 μg/kg), but not in sound hazelnuts from the Black Sea region of Turkey (Ekinci *et al.*, 2014).

8.3.3.2 Foods of animal origin

Cheese

An Italian study examined the interior and rind of handmade cheeses (n = 32) for PAT (Pattono *et al.*, 2013). PAT was detected in the interior of 1 cheese at a concentration of 26.6 μg/kg and in the rind of 8 cheeses, with concentrations in the range 15.4-460.8 μg/kg.

8.3.1 New Zealand estimates of dietary exposure

No new estimates of dietary PAT exposure in New Zealand have been carried out since the previous version of this risk profile.

New Zealand imports 2000-3000 tonnes per annum of apple juice and apple juice concentrate from China.[19] An exposure estimate has been determined, based on the PAT content of Chinese apple juice concentrates, for the WHO GEMS/Food cluster diets[20] (Guo *et al.*, 2013c). The estimate for cluster M, which includes New Zealand, was 0.8 ng/kg body weight/day.

[19] http://www.stats.govt.nz/infoshare/TradeVariables.aspx?DataType=TIM
[20] http://www.who.int/foodsafety/chem/gems/en/index1.html

8.3.2 Overseas estimates of dietary exposure

Table 19 summarises a number of estimates of dietary exposure to PAT that have been derived overseas.

Table 19: Overseas estimates of dietary exposure to PAT

Country	Foods included	Population group	Mean (95th percentile) exposure, ng/kg body weight/day	Reference
PMTDI (JECFA) = 400 ng/kg body weight/day				
France	NS	Children Adults	1.2-39 (6.9-97) 0.6-21 (3.2-51)	(Sirot *et al.*, 2013)
France	NS	Adult females - Pre-pregnancy - Third trimester	 0.22-25.7 (0.66-69.2) 0.20-20.8 (0.58-57.4)	(Chan-Hon-Tong *et al.*, 2013)
Greece	Fruit juice, fruit-based baby foods	Child, 20 kg Adolescent, 55 kg Adult, 70 kg	40-150 8-80 10-30	(Moukas *et al.*, 2008)
India	Apple juice	5-10 years, 27 kg 10-15 years, 35 kg 15-40 years, 58 kg 0-60 years, 62 kg	240 (700)[1] 220 (760) 110 (430) 150 (510)	(Saxena *et al.*, 2008)
Netherlands	Apple juice	Child, 2.5-6.5 years	19 (68)	(Baert *et al.*, 2007a)
South Korea	Fruit juices	General population	0.17	(Cho *et al.*, 2010)
Spain	Apple juice, apple-based products	Infants (0-3 years) Children (4-18 years) Adults (19-66 years)	40 (130)[2] 8 5	(Cano-Sancho *et al.*, 2009)
Spain	Apple juice, apple-based products	Population average (68 kg)	0.42	(González-Osnaya *et al.*, 2007)
Spain	Apple juice	Babies Children Adults	252 155 55	(Murillo-Arbizu *et al.*, 2009)
Spain (Catalonia)	Apple juice	 Infants/young children (0-3 years) Children (4-18 years) Adults (19-66 years)	Conventional Organic 4 (26) 16 (103) 4 15 2 8	(Piqué *et al.*, 2013)

[1] High exposures were calculated at the 90th percentile in this study

[2] Exposure was calculated for consumers only and does not contain consideration of those who did not consume apple products on the survey day

8.4 Risk Characterisation

Human intoxication due to PAT ingestion has not been reported and PAT exposure has not been implicated in any human disease states. PAT was trialled as an antibiotic for use against the common cold in the 1940s. The authors of the study reported that no ill effects were observed, but the report is unclear as to the clinical tests applied (Hopkins, 1993).

8.5 Risk Management Information

8.5.1 Relevant food controls: New Zealand

8.5.1.1 Establishment of regulatory limits

PAT is not currently regulated in New Zealand.

8.5.1.2 Industry quality assurance procedures

The majority of New Zealand's domestically produced apple juice is processed by ENZAfoods New Zealand Ltd (http://www.enzafoods.co.nz/). ENZAfoods process have been covered by ISO9001 accreditation and HACCP plans since 1993, including daily monitoring of product for PAT.

8.5.2 Relevant food controls: overseas

8.5.2.1 Establishment of regulatory limits

The previous version of this risk profile summarised international regulations for PAT, as published by Van Egmond and Jonkers (2004). The most commonly adopted regulatory limit for PAT was in apple juice with a limit of 50 µg/kg. This is also the maximum level proposed by Codex (Standard 235-2003).

In 2006, the European Commission established maximum limits for PAT, in µg/kg (European Commission, 2006b):

Fruit juices, concentrated fruit juices as reconstituted and fruit nectars	50
Spirit drinks, cider and other fermented drinks derived from apples or containing apple juice	50
Solid apple products, including apple compote, apple puree intended for direct consumption with the exception of foodstuffs listed in other categories	25
Apple juice and solid apple products, including apple compote and apple puree, for infants and young children and labelled and sold as such	10
Baby foods other than processed cereal-based foods for infants and young children	10

8.5.2.2 Codes of Practice

In addition to the Codex Code of Practice (CoP) for the prevention and reduction of PAT in apple juice and apple juice ingredients, summarised in the previous version of this risk profile, the European Commission have also issued recommendation on the prevention and reduction of PAT in these products (European Commission, 2003). Recommendation based on Good Agricultural Practice (GAP) and Good Manufacturing Practice (GMP) are included.

8.5.3 Influence of storage and processing on PAT levels

Two extensive reviews of the impact of processing on PAT in apples (Morales *et al.*, 2010) and apple juice (Sant'Ana *et al.*, 2008).

A farm-to-fork quantitative risk assessment model (QRAM) was established to examine the impact of various factors and combinations of factors on the PAT content of apple juice (Baert *et al.*, 2012). Sorting to exclude visibly infected apples was found to decrease the PAT content of apple juice, while long-term storage under controlled atmosphere increased PAT content, compared to short-term cold storage or immediate processing. Minimising 'deck storage' (the period between picking and cold or controlled atmosphere storage) was also found to be important for producing apple juice with low concentrations of PAT.

Factors that increase stress on the producing organism (*P. expansum*) during storage were shown to stimulate PAT production (Baert *et al.*, 2007b). Stress factors included lowering of the temperature below 25ºC and decreasing the oxygen content of the atmosphere. However, at extremes (decreasing temperature from 4 to 1ºC, decreasing oxygen content from 3 to 1%) caused decreases in PAT production. These general observations were very strain dependent.

The impact of biocontrol agents (*Candida sake, Pantoea agglomerans*) on blue rot formation, *P. expansum* growth and PAT production was studied during cold storage followed by ambient (20ºC) storage of apples (Morales *et al.*, 2008). Both organisms were able to inhibit fungal growth and decrease PAT production during cold storage, but during ambient storage PAT production increased to equal or exceed that in control apples. It was suggested that the increased stress on *P. expansum* may have stimulated PAT production.

Yeasts of the *Metschnikowia* species were assessed as potential biocontrol agents on apples stored at 22ºC or 1ºC (Spadaro *et al.*, 2013). All strains were shown to control *P. expansum* growth and decrease PAT production at both temperatures. The best yeast strain was shown to be as effective as chemical fungicides.

Pulsed light was shown to be effective in reducing the PAT concentration in buffer, apple juice and apple purée (Funes *et al.*, 2013). After application of pulsed light for 30 seconds PAT was reduced in buffer (85-95% reduction) and apple juice (78% reduction). In apple purée, PAT was not detectable after 20 seconds of pulsed light irradiation.

Ultraviolet (UV) radiation was shown to be effective in reducing the PAT content of apple cider and apple juice (Tikekar *et al.*, 2013). However, the radiation dose required for 50% PAT reduction in apple juice was greater than that required to achieve a 5-log reduction in *Escherichia coli* O157:H7 and care may be required to achieve useful PAT reductions without impacting on juice quality. The kinetics of PAT reduction by UV light have been examined (Zhu *et al.*, 2013).

A study was carried out to examine the effectiveness of treated waste cider yeast and calcium alginate as biosorption substrates for removing PAT from apple juice (Guo *et al.*, 2013a). Caustic treated waste cider yeast gave the best results, with approximately 60% of PAT (100 µg/L) removed at optimal pH (4.5-5.5). The percentage removal of PAT increased with decreasing apple juice PAT concentration. Calcium alginate was also found to be an effective biosorbant for PAT, removing approximately 70% of PAT. Inclusion of immobilised caustic waste cider yeast particle into the calcium alginate matrix increased PAT removal to 100%.

The influence of processing apple homogenate into apple purée was examined for homogenates containing 23, 140 or 537 µg/kg PAT (Janotová *et al.*, 2011). Pulping (blanching followed by sieving) reduced PAT concentrations by 29-80%, with the final product containing 15-51% of the PAT present in the homogenate.

The production of apple juice concentrate requires sequential steps of milling, pasteurisation, enzymatic treatment, microfiltration and evaporation (Welke *et al.*, 2009). These processes were shown to decrease the PAT content from 433 µg/kg to 107 µg/kg. The greatest step decrease was effected by pasteurisation. A Chinese study found a lower overall reduction in PAT (46%), with pasteurisation only making a small contribution to overall reduction (Yuan *et al.*, 2010).

8.6 Conclusions

8.6.1 Description of risks to New Zealand consumers

PAT has not been linked to actual cases of adverse health effects in human. It has been administered to humans as a potential antibiotic for use against the common cold.

No new surveillance or exposure information on PAT in the New Zealand food supply has been generated since the previous version of this risk profile.

The major apple juice manufacturer in New Zealand (ENZAfoods) have quality assurance systems in place to control PAT contamination. Surveys of PAT in apple juice in China, the source of 80% of apple juice concentrate imported into New Zealand, found concentrations of PAT (Guo *et al.*, 2013c; Yuan *et al.*, 2010) similar to those reported for apple juices available in New Zealand (Stanton, 1998). It is probable that New Zealanders' exposure to PAT is well below the PMTDI.

While PAT in apple juice may indicate poor manufacturing practice (e.g. use of ground harvested apples for juice manufacture), there is little evidence to indicate that it constitutes a human health risk.

8.6.2 Commentary on risk management options

PAT contamination of apple juice is largely controllable by good manufacturing practice (GMP) and there is good evidence that GMP is employed by the major New Zealand manufacturer. However, there is currently no risk management applied to the large amount of imported apple juice. Application of a regulatory limit is the most obvious management measure for this product, although this is probably not justified on the basis of risk.

9 CITRININ

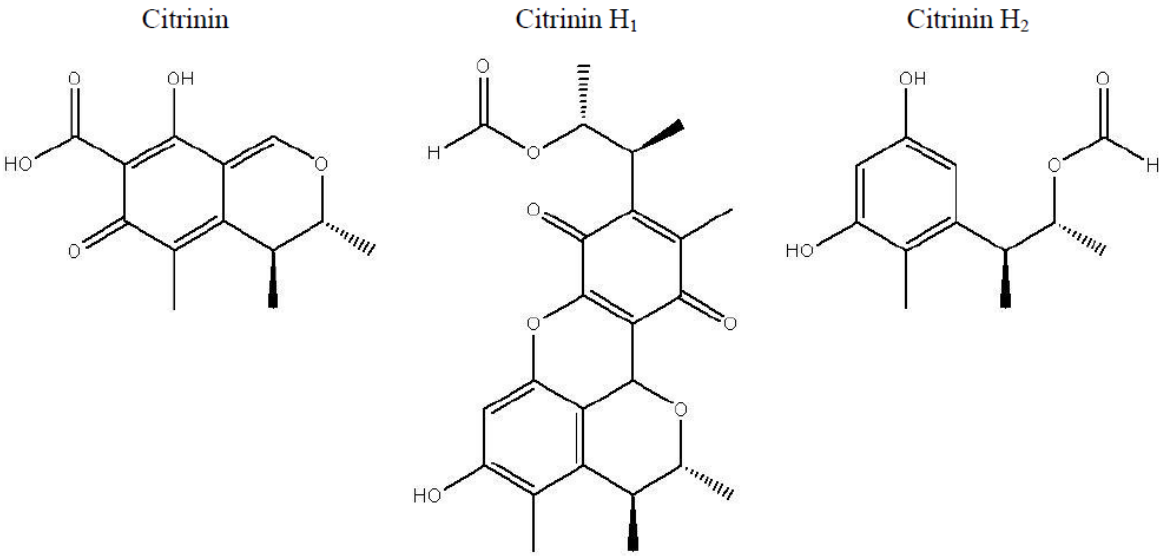
9.1 Hazard Identification

Citrinin (CIT), (3*R*, 4*S*)-4,6-dihydro-8-hydroxy-3,4,5-trimethyl-6-oxo-3*H*-2-benzopyran-7-carboxylic acid, is a polyketide mycotoxin produced by several species of the genera *Aspergillus*, *Penicillium* and *Monascus* (EFSA, 2012c). *Monascus* fermentation products (generally described as red mould rice) have been used in Asia for centuries for meat preservation and food colouring. CIT production is mainly associated with the *Penicillium* species; *P. citrinum*, *P. verrucosum* and *P. expansum.*

9.1.1 Structure and nomenclature

The chemical structures of CIT and its decomposition products CIT H_1 and CIT H_2, are shown in Figure 9.

Figure 9: Structure of CIT and its decomposition products



Reproduced from (EFSA, 2012c)

9.1.2 Occurrence

The *Penicillium* species associated with CIT production occur over a wide geographical range, including temperate regions. *Penicillium* species, including *P. expansum* have been reported in New Zealand cereal crops (Sayer and Lauren, 1991).

P. citrinum grows optimally at 26-30ºC, but will not grow at temperatures below 5ºC (Pitt and Hocking, 1997). The minimum water activity for *P. citrinum* growth is 0.80-0.84 and it will grow across the pH range 2-10.

P. expansum will grow at sub-zero temperatures, but has a growth optimum about 25ºC, with minimum water activity for growth of 0.82-0.83 (Pitt and Hocking, 1997).

P. verrucosum will grow at temperatures in the range 0-31ºC, with an optimum of 20ºC, a minimum water activity of 0.80 and a pH range of 2.1-10.0 (Pitt and Hocking, 1997).

It should be noted that *P. expansum* is the main species producing PAT, while *P. verrucosum* strains are capable of producing OTA.

CIT is generally formed after harvest and occurs mainly in stored grains, but also in other plant products such as beans, fruits, fruit and vegetable juices, herbs and spices, and also in spoiled dairy products (EFSA, 2012c).

9.2 Hazard Characterisation: Adverse Health Effects

No reports were located of adverse health effects in humans due to dietary CIT exposure.

9.2.1 Toxicity

9.2.1.1 Acute toxicity

CIT is moderately toxic in laboratory animals, with subcutaneous LD_{50} in the range 35-73 mg/kg body weight (mouse, rat, guinea pig), intraperitoneal LD_{50} in the range 35-89 mg/kg body weight (mouse, rat, rabbit) and oral LD_{50} in the range 105-134 mg/kg body weight (mouse, rabbit) (EFSA, 2012c).

9.2.1.2 Chronic toxicity

There is some evidence from laboratory animal and other animal studies that CIT displays nephrotoxicity, immunotoxicity, hepatotoxicity, reproductive and developmental toxicity and carcinogenicity (EFSA, 2012c). However, the EFSA CONTAM panel concluded that the kidney was the principal target organ in all relevant studies. The longest study conducted on CIT (80 week, F344 rats) demonstrated high incidence of nephrotoxicity and renal adenomas, but not renal carcinomas, in rats receiving a diet containing 1000 mg/kg of CIT (Arai and Hibino, 1983).

9.2.2 Toxicological assessment

EFSA's Panel on Contaminants in the Food Chain (CONTAM) reviewed information on CIT and concluded that, due to limitations and uncertainties in the toxicity data, derivation of a health-based exposure limit, such as a TDI, was not appropriate (EFSA, 2012c). However, the panel further commented that "In order to give risk managers a tool to evaluate the risk of citrinin in food and feed, the Panel decided to characterise the risk of citrinin on the available data on nephrotoxicity, and determined therefore a level of no concern for nephrotoxicity. Applying a default uncertainty factor of 100 to the NOAEL of 20 µg/kg b.w. per day, accounting for inter-species variation (extrapolation from animals to humans) and for inter-individual variation (within the human population), the CONTAM Panel concluded that there would be no concern for nephrotoxicity in humans at an exposure level of 0.2 µg/kg b.w. per day. Based on the available data, a concern for genotoxicity and carcinogenicity could not be excluded at the level of no concern for nephrotoxicity".

IARC have reviewed information on the carcinogenicity of CIT and concluded that there was limited evidence for the carcinogenicity of CIT in experimental animals and that no evaluation could be made of the carcinogenicity of CIT to humans (Group 3) (IARC, 1986).

9.2.3 Metabolites and their relative toxicity

CIT degrades at 175ºC in dry conditions and at 140ºC in semi-moist conditions (EFSA, 2012c; Flajs and Peraica, 2009; Kitabatake *et al.*, 1991). Known degradation products are CIT H_1 and CIT H_2. In cytotoxicity tests, CIT H_2 showed no significant toxicity, while CIT H_1 was more toxic than CIT.

9.3 Exposure Assessment

9.3.1 CIT in the Australasian food supply

No information was found on the occurrence of CIT in crops or foods in New Zealand or Australia.

9.3.2 Overseas context

Studies reporting on the prevalence and concentration of CIT in food items are summarised in Table 20. CIT is most commonly reported as a contaminant of cereal grains and products produced from them, although a range of other foods may occasionally be contaminated.

Table 20: Worldwide data on occurrence of CIT in food

Country	Year	Food	Incidence, positive/total samples (%)	Concentration (µg/kg)	Reference
Belgium	2006-2007	Home-produced eggs	0/20 (0)	-	(Tangni *et al.*, 2009)
Brazil	NS	Rice	1/38 (3)	120	(Hackbart *et al.*, 2012)
Bulgaria	1998	Wheat Maize Barley Oats	3/37 (8) 0/23 (0) 0/6 (0) 0/9 (0)	20, 83, 420 - - -	(Vrabcheva *et al.*, 2000)
Burkina Faso	2010	Maize Peanuts	3/26 (12) 0/9 (0)	531-5074 -	(Warth *et al.*, 2012a)
Canada	1968	Moisture damaged grains (wheat, oats, barley, rye)	13/29 (45)	70-80,000	(Scott *et al.*, 1972)
Croatia	NS	Apples	19/100 (19)	50-240	(Pepeljnjak *et al.*, 2002)
Croatia	NS	Game sausages Semi-dry sausages Dry meat products	1/15 (7) 1/25 (4) 3/50 (6)	1.0 1.0 1.0-1.3	(Markov *et al.*, 2013)
Czech Republic	2006-2008	Bread wheat Malting barley Feed barley Feed wheat	2/12 (17) 3/3 (100) 3/6 (50) 0/10 (0)	<LOQ (1.5) <LOQ,1.8, 93.6 <LOQ, 5.3, 13.2 -	(Polisenska *et al.*, 2010)
Denmark	NS	Apple, cherry fruit, juice and pulp	0/6 (0)	-	(Andersen *et al.*, 2004)

Country	Year	Food	Incidence, positive/total samples (%)	Concentration (µg/kg)	Reference
Egypt	NS	Hazelnut Walnut	0/20 (0) 0/20 (0)	- -	(Abdel-Hafez and Saber, 1993)
Egypt	1992	Dried figs Dried apricots Prunes Raisins	0/4 (0) 0/3 (0) 0/3 (0) 0/3 (0)	- - - -	(Zohri and Abdel-Gawad, 1993)
Egypt	NS	Spices, 24 types	Black cumin 2/5 (40) All other 0/115 (0)	8,12 -	(El-Kady *et al.*, 1995)
Egypt	1991-1993	White maize Yellow maize Wheat Barley Rice Coffee beans	0/27 (0) 3/36 (8) 0/26 (0) 15/27 (56) 13/33 (39) 0/20 (0)	- 71.2-211.3 - 53.2-100.0 6.4-27.9 -	(El-Sayed, 1996)
Egypt	NS	Strawberry Apricot Plum Peach Grape Date Fig Apple Pear Mulberry	0/10 (0) 0/10 (0) 0/10 (0) 0/10 (0) 2/10 (20) 0/10 (0) 1/10 (10) 0/10 (0) 1/10 (10) 0/10 (0)	- - - - 70 - 60 - 50 -	(Aziz and Moussa, 2002)
Egypt	2002	Rice, paddy	10/30 (33)	2.7-28.5	(Abd-Allah and Ezzat, 2005)
Egypt	NS	Maize Soybean Wheat Barley Rice Kidney beans Peanuts	1/20 (5) 2/10 (20) 1/10 (10) 1/10 (10) 0/20 (0) 1/10 (10) 0/10 (0)	300 130, 270 112 100 - 370 -	(Aziz *et al.*, 2006)
France	NS	Breakfast cereals	8/45 (18)	<LOQ-42	(Molinié *et al.*, 2005)
Germany	NS	Apple juice Tomato juice Cherry juice Blackcurrant juice Grape juice	1/35 (3) 1/11 (9) 1/5 (20) 1/2 (50) 0/2 (0)	0.13 0.12 0.10 0.20 -	(Dietrich *et al.*, 2001)
Germany	NS	Oats Rye Wheat, wholemeal Wheat, milling by-products Muesli Cocoa Raisins Sultanas Red-fermented rice	0/2 (0) 2/3 (67) 1/1 (100) 8/8 (100) 0/1 (0) 0/2 (0) 1/1 (100) 1/2 (50) 1/1 (100)	- 0.9,1.1 0.5 1.7-2.7 - - 0.5 Trace 2903	(Meister, 2004)
Ghana	NS	Fermented maize	20/20 (100)	1.4-585	(Kpodo *et al.*,

Country	Year	Food	Incidence, positive/total samples (%)	Concentration (µg/kg)	Reference
		products			1996)
India	1984-1986	Turmeric Coriander Fennel Cinnamon Black pepper Cardamom Greater cardamom Cassia Ammi Cumin Chili Yellow mustard Indian mustard Garlic Clove	2/9 (22) 1/9 (11) 2/9 (22) 0/6 (0) 1/8 13) 1/6 (17) 0/6 (0) 0/6 (0) 0/7 (0) 0/8 (0) 0/9 (0) 0/6 (0) 0/7 (0) 0/6 (0) 0/6 (0)	48,52 34 28,59 - 50 25 - - - - - - - - -	(Saxena and Mehrotra, 1989)
India (Karnataka)	1994-1997	Maize	1/197 (0.5)	12	(Janardhana *et al.*, 1999)
India	NS	Rice	4/30 (13)	49-92	(Tanaka *et al.*, 2007)
Japan	NS	Rice	2/2 (100)	700-1130	(Tanaka *et al.*, 2007)
Japan	NS	Wheat Barley Oats Rye Coix seed Rice Buckwheat Maize	1/12 (8) 0/3 (0) 0/3 (0) 0/1 (0) 0/2 (0) 0/5 (0) 2/2 (100) 0/3 (0)	0.19 - - - - - 0.55,0.62 -	(Tabata *et al.*, 2008)
Morocco	NS	Black olives	8/10 (80)	0.2-0.52	(El Adlouni *et al.*, 2006)
Mozambique	2010	Maize Peanuts	6/13 (46) 0/23 (0)	276-5074 -	(Warth *et al.*, 2012a)
Portugal	NS	Apples	14/351 (4)	Mean 320-920 depending on cultivar	(Martins *et al.*, 2002)
Romania	1997	Wheat (feed) Maize (feed)	0/25 (0) 1/30 (3)	- 580	(Curtui *et al.*, 1998)
Russia	2003-2006	Wheat (feed) Barley (feed) Maize (feed)	11/243 (5) 5/138 (4) 3/157 (2)	50-144 63-998 218-953	(Kononenko and Burkin, 2008)
Saudi Arabia	NS	Almond, cashew, chestnut, hazelnut, pistachio, walnut	0/30 (0)	-	(Abdel-Gawad and Zohri, 1993)
South Africa	NS	Beer, commercial Beer, home brewed	0/6 (0) 0/29 (0)	- -	(Odhav and Naicker, 2002)
Spain	1986-1987	Almonds, peanuts, hazelnuts, pistachios, sunflower seeds	0/168 (0)	-	(Jiménez *et al.*, 1991)
Sri Lanka	NS	Red chilli	0/10 (0)	-	(Yogendrarajah

Country	Year	Food	Incidence, positive/total samples (%)	Concentration (µg/kg)	Reference
		Black pepper White pepper	1/10 (10) 0/10 (0)	<LOQ (65) -	*et al.*, 2013)
Tunisia	NS	Wheat	100/200 (50)	1-170	(Zaied *et al.*, 2012)
Turkey	2000-2001	Black olives	53/69 (77)	Max = 350	(Heperkan *et al.*, 2006)
Turkey	2007-2008	Black table olives Green table olives	35/63 (56) 15/25 (60)	Mean = 3.44 Mean = 2.28	(Tokuşoğlu and Bozoğlu, 2010)
Vietnam	NS	Rice	13/100 (13)	Max = 0.42	(Nguyen *et al.*, 2007)

NS = not stated Max = maximum
LOQ = limit of quantification

CIT contamination has also been reported in 'red yeast rice' or 'red mould rice' (RMR). This product is produced in Asia by the fermentation of white rice with red yeast (*Monascus purpureus*) and is used as a food colouring and meat preservative (EFSA, 2012c). CIT concentrations in the part per million range have been reported in RMR formulations. Liao *et al*. (2014) detected CIT in 69.0, 35.1 and 5.7% of RMR, RMR-containing dietary supplements and RMR processed products, respectively. Mean concentrations were 13.3, 1.2 and 0.1 mg/kg, respectively.

9.3.3 Estimates of dietary exposure

No estimates of dietary exposure for CIT were located. EFSA concluded that the occurrence data available from the literature was inadequate to carry out a dietary exposure assessment (EFSA, 2012c). EFSA used a reverse approach, using the NOAEL for nephrotoxicity and cereal consumption data to calculate critical CIT concentrations in grains and grain-based products that would result in exposures of no concern for nephrotoxicity. For average consumers of grains and grain-based products, critical concentrations of CIT were in the range 19-111 µg/kg, while for high consumers (95th percentile) of grains and grain-based products critical concentrations were in the range 9-54 µg/kg, depending on the population group considered. Concentrations of CIT in excess of these critical concentrations have been reported in cereals (Table 18).

9.3.4 Biomarkers of exposure

A method has been developed to determine CIT and its metabolite dihydrocitrinone (HO-CIT) in blood and urine (Blaszkewicz *et al.*, 2013). CIT was detected in plasma samples from all of 8 German adults (0.11-0.26 ng/ml) and in 8/10 urine samples (0.16-0.79 ng/ml). HO-CIT was detected in 5/10 urine samples at similar concentrations to CIT.

CIT was also included in a multi-mycotoxin analytical method for the detection of mycotoxin biomarkers in urine (Njumbe Ediage *et al.*, 2012). A pilot study on a convenience cohort of 40 adults detected CIT in 1 urine sample at a concentration of 6.8 ng/ml (4.5 ng/mg creatinine). The sample methodology was used for a study of mycotoxin exposure in 220 children (1.5-4.5 years) from Cameroon (Njumbe Ediage *et al.*, 2013). CIT was not detected (LOD = 2.88 ng/ml) in any sample.

9.4 Risk Characterisation

Human intoxication due to CIT has not been reported. However, given that this mycotoxin has rarely been considered in investigations of human disease, this is not surprising. An EFSA study concluded that there was potential for exposure to exceed levels of no concern for nephrotoxicity due to consumption of grains and grain-based products, but that no conclusions can be reached concerning the likelihood of exceeding the level of no concern for nephrotoxicity.

9.5 Risk Management Information

9.5.1 Relevant food controls: New Zealand

9.5.1.1 Establishment of regulatory limits

CIT is not currently regulated in New Zealand.

9.5.2 Relevant food controls: overseas

9.5.2.1 Establishment of regulatory limits

A collation of worldwide regulatory limits for mycotoxins did not identify any country with regulatory limits for CIT (Van Egmond and Jonker, 2004). This collation is in the process of being updated, but is not yet available (Monique De Nijs, RIKILT, Netherlands, personal communication).

9.5.3 Influence of storage and processing on CIT levels

CIT was not detected in stored wheat (30ºC for 2 months), following inoculation with a toxin producing strain of *P. citrinum*, when the water activity was 0.80 or lower (Comerio *et al.*, 1998). As the water activity was increased above 0.80, CIT was detected sooner after the inoculation event and the maximum concentration detected increased markedly. A maximum CIT concentration of 22,000 µg/kg was reached at water activity of 0.885. After peak CIT concentrations were achieved (about 40 days), the concentration of CIT decreased rapidly. It was suggested this may be due to cellular release of lytic enzymes or reactions between the toxin and substrate.

Irradiation has been shown to prevent CIT formation in stored fruit (Aziz and Moussa, 2002). CIT was not detected on any fruit sample (n = 81) after 28 days of refrigerated storage, following irradiation at 3 kGy. CIT was detected in 8 of 81 unirradiated samples with concentrations in the range 280-400 µg/kg.

9.6 Conclusions

9.6.1 Description of risks to New Zealand consumers

CIT is nephrotoxic, but has not yet been epidemiologically linked to cases of human illness.

No information is available on CIT in the New Zealand food supply, but at least 1 of the CIT-producing fungal species (*Penicillium expansum*) has been reported in New Zealand cereals. CIT-producing species also produce OTA and PAT and these mycotoxins have been detected in the New Zealand food supply. It is likely that CIT will be present in New Zealand foods, but it is not possible to speculate on how frequently or at what concentration it may be present.

No estimates of dietary exposure are available, but work by EFSA suggests that there is, at least, the possibility of dietary exposure at levels above the no concern level for nephrotoxicity.

9.6.2 Commentary on risk management options

No risk management practice specific to CIT were identified. Given that CIT is produced primarily by organisms that may produce OTA or PAT, measures to control these mycotoxins are likely to contribute to control of CIT.

9.6.3 Data gaps

The major data gaps are; evidence for an association between CIT exposure and human disease, and information of the CIT content of the New Zealand food supply.

10 CYCLOPIAZONIC ACID

10.1 Hazard Identification

Cyclopiazonic acid (CPA), (6a*R*,11a*S*,11b*R*)-10-acetyl-11-hydroxy-7,7-dimethyl-2,6,6a,7, 11a,11b-hexahydro-9*H*-pyrrolo[1',2':2,3]isoindolo[4,5,6-*cd*]indol-9-one, is an indole-tetramic acid mycotoxin produced by several species of the genera *Aspergillus* and *Penicillium* (Burdock and Flamm, 2000). CPA production has been associated with *Aspergillus* species; *A. flavus, A. tamarii, A. oryzae* and *A.versicolor,* and the *Penicillium* species; *P. camemberti* and others (Antony *et al.*, 2003; Burdock and Flamm, 2000; Chang *et al.*, 2009).

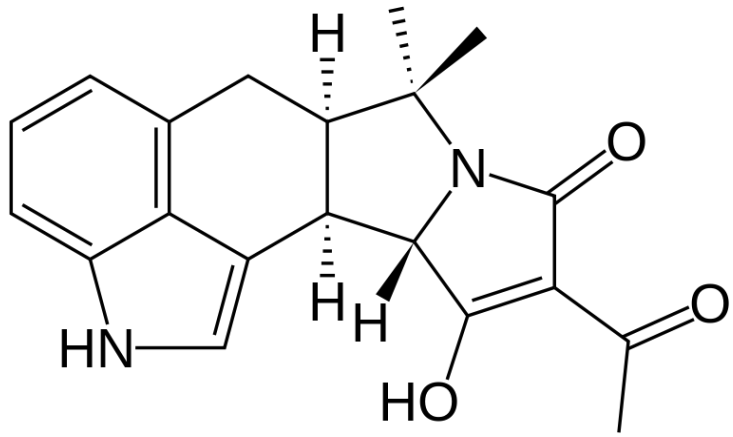
Although CPA was originally named after the *Penicillium* species, *P. cyclopium,* other strains of *P. cyclopium* were not found to produce CPA and the original CPA-producing strain was later found to be *P. griseofulvum* (Chang *et al.*, 2009).

It should be noted that *A. flavus* is important as a producer of aflatoxins and aflatoxins and CPA may often be present concurrently in foods. It has been suggested that some of the toxic effects of aflatoxins may be due to a combination of aflatoxins and CPA (Burdock and Flamm, 2000).

10.1.1 Structure and nomenclature

The chemical structures of CPA is shown in Figure 10.

Figure 10: Structure of CPA



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10.1.2 Occurrence

Aspergillus and *Penicillium* species infect food materials during storage, with *Aspergillus* species dominating spoilage in tropical regions, while *Penicillium* species dominate in temperate climates (Pitt and Hocking, 1997).

A. flavus has a growth minimum of 10-12ºC, an optimum of 33ºC, and a maximum of 43-48ºC (Pitt and Hocking, 1997). Growth occurs over the pH range 2.1-11.2 and minimum water activities for growth vary from 0.78 at 33ºC to 0.84 at 25ºC. There is less information on the physiology of *A. tamarii*, but its characteristics are believed to be similar to *A. flavus* (Pitt and Hocking, 1997). *A. versicolor* grows at lower temperatures than *A. flavus*, with a growth range of 9-39ºC and an optimum of 27ºC. Low pH (<3.1) prevents growth, while the minimum water activity for growth is 0.78-0.80.

P. cyclopium grows in the range -2-30ºC, with an optimum near 23ºC (Pitt and Hocking, 1997). The minimum water activity for growth is 0.81. *P. camemberti* is a domesticated species, derived from *P. commune.*

The fungi that produce CPA are generally considered to be storage fungi, rather than field fungi (Burdock and Flamm, 2000). CPA has been reported in cereals, ground and tree nuts, beans, and processed foods, such as cheese and processed meats (Burdock and Flamm, 2000).

10.2 Hazard Characterisation: Adverse Health Effects

10.2.1 Conditions

CPA has been implicated in a condition known as kodua poisoning, observed in the Utter Pradesh state of India (Rao and Husain, 1985). Symptoms included sleepiness, tremor and giddiness and lasted 1-3 days. Complete recovery was observed in all cases. Cases were linked to consumption of kodo millet infected with *A. flavus* and *A. tamarii*. Millet samples were shown to contain CPA.

10.2.2 Toxicity

10.2.2.1 Acute toxicity

CPA is acutely toxic in laboratory animals, with intraperitoneal LD_{50} in the range 2.3-13 mg/kg body weight (mouse, rat, catfish) and oral LD_{50} in the range 12-64 mg/kg body weight (mouse, rat, chicken) (Burdock and Flamm, 2000).

10.2.2.2 Chronic toxicity

CPA is a potent, specific, reversible inhibitor of the sarcoplasmic and endoplasmic reticulum Ca^{2+} activated ATPase (Burdock and Flamm, 2000). Inhibition of this enzyme and the resultant alteration of the normal intracellular calcium flux is believed to be responsible for the toxic effects seen on striated muscle and in the liver, kidneys and spleen (formation of lesions, necrosis).

The pig appears to be the most sensitive laboratory animal, with a NOEL of 1.0 mg/kg body weight/day. This is consistent with results from rodent studies (Burdock and Flamm, 2000)

10.2.3 Toxicological assessment

CPA has not been formally assessed by any international or national body. The most complete assessment found was the review article of Burdock and Flamm (2000). The

reviewers concluded that CPA was not carcinogenic or mutagenic, and was not immunotoxic. Reproductive toxicity was only seen at dose levels that were maternally toxic.

An NOEL of 1.0 mg/kg body weight/day and an associated ADI of 10 µg/kg body weight/day was proposed by these authors.

10.2.4 Metabolites and their relative toxicity

No CPA metabolites have been identified.

10.3 Exposure Assessment

10.3.1 CPA in the Australasian food supply

No information was found on the occurrence of CPA in crops or foods in New Zealand or Australia. However, a survey of *A. flavus* isolates (*n* = 38) from Queensland found that 34 (89%) produced CPA in culture (Blaney *et al.*, 1989).

10.3.2 Overseas context

Studies on the prevalence and concentrations of CPA in various foods are summarised in Table 21. As might be expected from the identity of the CPA-producing organisms, CPA has been reported in nuts (tree and ground), cereals and fruit.

Table 21: Worldwide data on occurrence of CPA in food

Country	Year	Food	Incidence, positive/total samples (%)	Concentration (µg/kg)	Reference
Argentina	NS	Peanuts	2/50 (40)	493-4300	(Fernández Pinto *et al.*, 2001)
Austria/ Turkey	2007	Almonds Hazelnuts Peanuts Pistachios	3/8 (38) 0/22 (0) 4/15 (27) 0/8 (0)	Max = 130 - Max = 310 -	(Varga *et al.*, 2013)
Botswana	2001-2002	Peanuts	18/83 (22)	1-10	(Mphande *et al.*, 2004)
Brazil	1994-1995	Tomato juice Tomato pulp Tomato purée Tomato paste Tomato, whole stewed	0/11 (0) 6/22 (27) 2/22 (9) 0/24 (0) 0/1 (0)	- 64-178 36,117 - -	(da Motta and Valente Soares, 2001)
Brazil	2004	Pasteurised milk UHT milk	2/36 (6) 0/12 (0)	6-10 -	(Oliveira *et al.*, 2006)
Brazil	2005-2006	Raw milk	3/50 (6)	6.4-9.1	(Oliveira *et al.*, 2008)
Brazil	2009	Brazil nuts, dehusked	11/200 (6)	98-161	(Reis *et al.*, 2012)
Burkina Faso	2010	Maize Peanuts	0/26 (0) 0/9 (0)	- -	(Warth *et al.*, 2012a)
Canada	NS	Wheat Maize Oats	0/40 (0) 0/15 (0) 0/10 (0)	- - -	(Martos *et al.*, 2010)

Country	Year	Food	Incidence, positive/total samples (%)	Concentration (µg/kg)	Reference
		Barley Rye	0/20 (0) 0/15 (0)	- -	
China	1998	Maize (corn)	7/20 (35)	42-1220	(Hayashi and Yoshizawa, 2005a)
Egypt	NS	Strawberry Apricot Plum Peach Grape Date Fig Apple Pear Mulberry	2/10 (20) 0/10 (0) 0/10 (0) 0/10 (0) 2/10 (20) 0/10 (0) 0/10 (0) 0/10 (0) 2/10 (20) 0/10 (0)	12-5 - - - 120 - - - 150 -	(Aziz and Moussa, 2002)
France	NS	Cheese - Crust - Interior	 11/20 (55) 0/4 (0)	 50-1500 -	(Le Bars, 1979)
Indonesia	NS	Maize	21/26 (81)	30-9000	(Widiastuti *et al.*, 1988)
Indonesia	1992	Maize (corn)	1/12 (8)	63	(Hayashi and Yoshizawa, 2005a)
Italy	NS	White-surface cheese	6/6 (100)	20-80	(Zambonin *et al.*, 2001)
Italy	NS	Cornflakes	1/1 (100)	72	(Aresta *et al.*, 2003)
Italy	NS	Milk, retail	3/20 (15)	4.5-8.3	(Losito *et al.*, 2002)
Japan	2004	Koji (mould-fermented rice)	1/38 (3)	480	(Hayashi *et al.*, 2005)
Mozambique	2010	Maize Peanuts	1/13 (8) 1/23 (4)	606 763	(Warth *et al.*, 2012a)
Philippines	1997-1998	Maize (corn)	6/39 (15)	27-1510	(Hayashi and Yoshizawa, 2005a)
Philippines	1997-1998	Maize	1/6 (17)	76	(Hayashi and Yoshizawa, 2005b)
Thailand	2002	Rice	0/10 (0)	-	(Hayashi and Yoshizawa, 2005b)
Thailand	1993	Maize (corn)	1/28 (4)	42	(Hayashi and Yoshizawa, 2005a)
Turkey	NS	Dried figs	28/115 (24)	25-187	(Heperkan *et al.*, 2011)
USA	1980	Peanuts -Loose-shell kernel - Sound mature kernel	 8/13 (62) 3/13 (23)	 130-1088 32-65	(Lansden and Davidson, 1983)
USA	NS	Maize	4/7 (57)	25-250	(Lee and Hagler, 1991)

Country	Year	Food	Incidence, positive/total samples (%)	Concentration (µg/kg)	Reference
USA	1990	Maize Peanuts	23/45 (51) 45/50 (90)	<25-2800 <50-2900	(Urano *et al.*, 1992)

NS = not stated
LOQ = limit of quantification

Lactating ewes (n = 3) were administered 5 mg/kg body weight of CPA for 2 days (Dorner *et al.*, 1994). CPA concentration in ewe's milk peaked at an average of 568 µg/kg the day after the second dose, but had returned to baseline by 7-10 days. CPA administration resulted in increased respiration and body temperatures in ewes and feed intake and milk production dropped substantially within 24 hours of the first dose.

Daily doses of CPA (0, 2.5, 5, and 10 mg/kg body weight) were administered to laying chickens for 9 days (Dorner *et al.*, 1994). High mortality occurred in the 10 mg/kg (100% mortality) and 5 mg/kg (80% mortality) dose groups. Where eggs were available, CPA was found to accumulate almost exclusively in the egg whites. Highest CPA concentrations were observed in the 5 mg/kg group on day 2 (381 µg/kg in pooled egg whites), but declined after that time, as feed intake, live weight and egg production declined. In the 2.5 mg/kg dose group, egg white CPA increased to 350 µg/kg over the 9 day trial. A chronic study was conducted at doses of 0, 1.25 and 2.5 mg/kg daily for 28 days. In both dose groups the average CPA concentration in egg whites over the course of the trial was approximately 100 µg/kg.

A single chicken received a dose of 10 mg/kg body weight of CPA by intubation (Norred *et al.*, 1987). After 48 hours, the bird was killed and CPA was measured in muscle at a concentration of 1450 µg/kg, accounting for 14.5% of the administered dose.

10.3.3 Estimates of dietary exposure

No estimates of dietary exposure for CPA were located.

10.3.4 Biomarkers of exposure

No studies utilising biomarkers of CPA exposure were located.

10.4 Risk Characterisation

One incident of human intoxication due to CPA has reported (Rao and Husain, 1985). Symptoms of intoxication were relatively mild and cases recovered completely.

10.5 Risk Management Information

10.5.1 Relevant food controls: New Zealand

10.5.1.1 Establishment of regulatory limits

CPA is not currently regulated in New Zealand.

10.5.2 Relevant food controls: overseas

10.5.2.1 Establishment of regulatory limits

A collation of worldwide regulatory limits for mycotoxins did not identify any country with regulatory limits for CPA (Van Egmond and Jonker, 2004). This collation is in the process of being updated, but is not yet available (Monique De Nijs, RIKILT, Netherlands, personal communication).

10.5.2.2 Management of CPA in crops

Competitive exclusion has been used as a means of controlling mycotoxin formation in maize. Various combinations of toxigenic and atoxigenic strains of *A. flavus* were inoculated onto crops (Abbas *et al.*, 2011). There were significant strain differences, but competitive exclusive resulted in reduction of CPA levels ranging from no reduction to 97% reduction.

This approach has also been used in peanuts, where inoculation with atoxigenic strains of *A. flavus* resulted in approximately 90% reductions in both CPA and aflatoxins (Cole and Dorner, 1999).

10.5.3 Influence of storage and processing on CPA levels

While a number of processing measures have been developed to control aflatoxins on peanuts, it is considered likely that these measures will also result in reduced levels of CPA contamination (Dorner, 2008). Measures include segregation of *A. flavus* infected lots, screening to remove immature or shrivelled pods, density segregation, kernel sizing and electronic colour sorting.

Irradiation has been shown to prevent CPA formation in stored fruit (Aziz and Moussa, 2002). CPA was not detected on any fruit sample (n = 81) after 28 days of refrigerated storage, following irradiation at 3 kGy. CPA was detected in 10 of 81 unirradiated samples with concentrations in the range 380-500 μg/kg.

CPA was found to have high stability on dry-cured ham, with 80% of added CPA remaining on the ham after incubation at 20ºC for 192 hours (Bailly *et al.*, 2005). Stability of CPA on dry-cured ham was marked greater than the stability of OTA, CIT or PAT.

Processing milk was found to have little impact on the CPA content of artificially contaminated milk (Prasongsidh *et al.*, 1997; 1998). Storage of milk at 4ºC for 21 days resulted in a 5.8% decrease in CPA, while frozen storage for 140 days decreased CPA levels by less than 12%. Processing milk into condensed milk resulted in an approximate 40% decrease in CPA, while processing into evaporated milk or dried milk powder resulted in virtually no decrease in CPA. Heating milk at 60, 80 or 100ºC for 2 hours resulted in CPA reductions of 9-17%, 20-34% and 49-50%, respectively.

10.6 Conclusions

10.6.1 Description of risks to New Zealand consumers

CPA is a potent inhibitor of a group of regulatory enzymes (Ca^{2+} ATPase) and has been implicated in cases of transient illness in humans.

No information is available on CPA in the New Zealand food supply. The main producing organisms (*Aspergillus flavus, A. tamarii, A. oryzae, A. versicolor*) have not been reported in New Zealand.

No estimates of dietary exposure are available.

10.6.2 Commentary on risk management options

CPA is known to co-occur with aflatoxins and current control measures for aflatoxins will be likely to have some impact on CPA in the food supply.

10.6.3 Data gaps

Information on the prevalence of CPA-producing organisms and the toxin itself in New Zealand foods would aid in risk assessment.

11 STERIGMATOCYSTIN

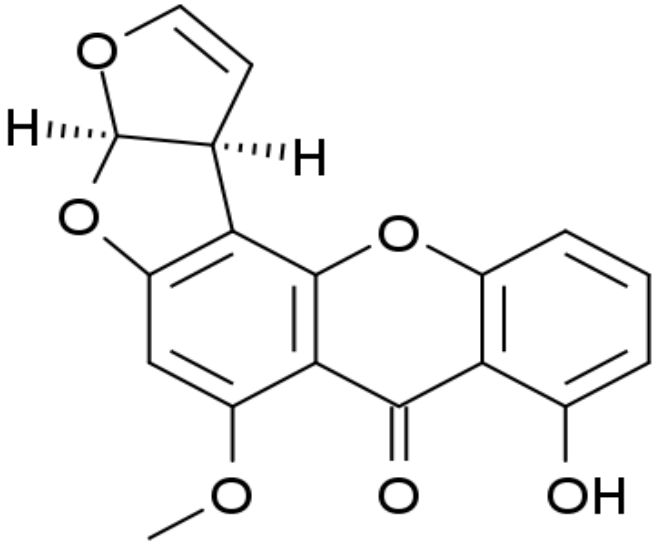
11.1 Hazard Identification

Sterigmatocystin (STC), (3a*R*,12c*S*)-8-hydroxy-6-methoxy-3a,12c-dihydro-7*H*-furo[3',2':4,5]furo[2,3-*c*]xanthen-7-one, is a polyketide mycotoxin that shares its biosynthetic pathway with aflatoxins and is structurally related to AFB_1 (EFSA, 2013a). STC is produced by several *Aspergillus* species, including *A. flavus, A. parasiticus, A.versicolor* and *A. nidulans*. Some strains of *A.versicolor* and *A. nidulans* are unable to biotransfom STC into the direct precursor to AFB_1 (O-methylSTC) and foods infected with these strains can contain high levels of STC, while foods infected with *A. flavus* and *A. parasiticus* contain only low concentrations of STC, as most of the STC is biotransformed to AFB_1 (Yu *et al.*, 2004).

11.1.1 Structure and nomenclature

The chemical structures of STC is shown in Figure 11.

Figure 11: Structure of STC



Reproduced from http://en.wikipedia.org/wiki/File:Sterigmatocystin.png

11.1.2 Occurrence

Aspergillus species dominate spoilage in tropical regions (Pitt and Hocking, 1997).

A. flavus has a growth minimum of 10-12ºC, an optimum of 33ºC, and a maximum of 43-48ºC (Pitt and Hocking, 1997). Growth occurs over the pH range 2.1-11.2 and minimum water activities for growth vary from 0.78 at 33ºC to 0.84 at 25ºC. The growth characteristics of *A. parasiticus* are very similar to *A. flavus* and there have been a number of instances of *A. parasiticus* being misidentified as *A. flavus* (Pitt and Hocking, 1997). *A. nidulans* is marginally thermophilic and has been reported to grow at temperatures up to 51ºC, with an

optimum of 35-37ºC. *A. versicolor* grows at lower temperatures than *A. flavus*, with a growth range of 9-39ºC and an optimum of 27ºC. Low pH (<3.1) prevents growth, while the minimum water activity for growth is 0.78-0.80.

STC has been reported in cereals and cereal products (including beer), nuts, green coffee beans, spices and cheese.

11.2 Hazard Characterisation: Adverse Health Effects

Due to its structural relatedness to AFB_1, STC exhibits a similar pattern of toxicity, although it is apparently less potent than AFB_1.

11.2.1 Conditions

No cases of adverse human health effects have been definitively linked to STC exposure. STC has been implicated in gastric cancer and liver disease, including cirrhosis and HCC (EFSA, 2013a).

11.2.2 Toxicity

11.2.2.1 Acute toxicity

STC is of moderate acute toxicity (LD_{50} range 120-166 mg/kg body weight) (EFSA, 2013a). The acute toxicity is about an order of magnitude less than that of AFB_1.

11.2.2.2 Chronic toxicity

STC is mutagenic (*in vitro* and *in vivo*) and carcinogenic in animal studies (EFSA, 2013a). The liver is the main target organ for STC toxicity. However, the cancer potency of STC appears to be about 3 orders of magnitude less than AFB_1.

11.2.3 Toxicological assessment

STC was evaluated by IARC most recently in 1976 (IARC, 1976). It was concluded that there was sufficient evidence for carcinogenicity in laboratory animals, but not adequate data to establish human carcinogenicity. STC was assigned to category 2B (probable human carcinogen).

Toxicological assessment of STC has been carried out by EFSA (EFSA, 2013a). Due to the mutagenicity and carcinogenicity of STC no tolerable daily intake (TDI) or similar health-based exposure limits were proposed for STC.

A BMD_{10} (a benchmark dose for a 10% extra risk), based on occurrence of haemangiosarcomas in rat liver, of 0.36 mg/kg body weight/day was calculated (EFSA, 2013a). The lower 95th percentile confidence limit for this benchmark dose ($BMDL_{10}$) was 0.16 mg/kg body weight/day. For AFB_1 $BMDL_{10}$ values in the range 0.16-0.30 μg/kg body weight/day have been reported, depending on the method used to model the dose-response curve (Dybing *et al.*, 2008).

11.2.4 Metabolites and their relative toxicity

There have been no reports of metabolites of dietary significance.

11.3 Exposure Assessment

11.3.1 STC in the Australasian food supply

No information was found on the occurrence of STC in crops or foods in New Zealand or Australia.

11.3.2 Overseas context

Studies of STC in foods are summarised in Table 22. Results across the various studies are not consistent, with a number of studies failing to detect STC. However, as might be expected there are similarities between STC and AFB_1 in the foods in which they are found.

Table 22: Worldwide data on occurrence of STC in food

Country	Year	Food	Incidence, positive/ total samples (%)	Concentration (µg/kg)	Reference
Austria/ Turkey	2007	Almonds Hazelnuts Peanuts Pistachios	0/8 (0) 21/22 (95) 5/15 (33) 0/8 (0)	- Max = 5.5 Max <2.4 -	(Varga *et al.*, 2013)
Belgium	2008	Cheese	3/13 (23)	<LOQ (0.1)-1.23	(Veršilovskis *et al.*, 2009)
Brazil	1985-1986	Maize and maize products Cassava flour Rice Dried beans	0/130 (0) 0/45 (0) 0/60 (0) 0/61 (0)	- - - -	(Valente Soares and Rodriguez-Amaya, 1989)
Canada	1968	Wheat Barley Oats Rye	1/20 (5) 0/2 (0) 0/3 (0) 0/2 (0)	300 - - -	(Scott *et al.*, 1972)
Canada	2008-2009	Wheat Maize Oats Barley Rye	0/40 (0) 0/15 (0) 0/10 (0) 0/20 (0) 0/15 (0)	- - - - -	(Martos *et al.*, 2010)
Egypt	NS	Hazelnuts Walnuts	0/20 (0) 0/20 (0)	- -	(Abdel-Hafez and Saber, 1993)
Egypt	NS	Spices (24 varieties) - Red pepper - Caraway - Cumin - Marjoram - All others	 3/5 (60) 3/5 (60) 3/5 (60) 1/5 (20) 0/100 (0)	 10-23 14-18 11 17 -	(El-Kady *et al.*, 1995)
Egypt	NS	Cheese	35/100 (35)	10-63	(Abd Alla *et al.*, 1996)
Egypt	2004	Peanuts - Raw	 0/20 (0)	 -	(Youssef *et al.*, 2008)

Country	Year	Food	Incidence, positive/ total samples (%)	Concentration (µg/kg)	Reference
		- Roasted - Roasted with salt	3/20 (15) 1/20 (5)	12.2-16.8 12.2	
India	NS	Maize	3/50 (6)	Trace-150	(Devi and Polasa, 1982)
India	1984-1986	Turmeric Coriander Fennel Cinnamon Black pepper Cardamom Greater cardamom Indian cassia Ammi Cumin Chili Yellow mustard Indian mustard Garlic Cloves	0/9 (0) 0/9 (0) 1/9 (11) 0/6 (0) 2/8 (25) 0/6 (0) 0/6 (0) 0/6 (0) 0/7 (0) 0/8 (0) 0/9 (0) 0/6 (0) 0/7 (0) 0/6 (0) 0/6 (0)	- - 142 - 105,125 - - - - - - - - - -	(Saxena and Mehrotra, 1989)
Italy	2002	Cereal-based products	0/85 (0)	-	(Stroka *et al.*, 2005)
Japan	2005	Rice, brown	0/48 (0)	-	(Tanaka *et al.*, 2007)
Latvia	2006-2007	Wheat Barley Oats Buckwheat Rye	17/70 (24) 13/35 (37) 6/40 (15) 11/35 (31) 8/35 (23)	Not able to be presented. All positive samples were less than 200 µg/kg	(Veršilovskis *et al.*, 2008a)
Latvia	NS	Beer	2/26 (8)	4.0,7.8	(Veršilovskis *et al.*, 2008b)
Latvia	NS	Bread	5/29 (17)	2.4-7.1	(Veršilovskis and Milkelsone, 2008; Veršilovskis and Bartkevičs, 2012)
Latvia	2008	Cheese	4/8 (50)	<LOQ (0.1)	(Veršilovskis *et al.*, 2009)
Netherlands	NS	Cheese, surface layer	9/39 (23)	5-600	(Van Egmond *et al.*, 1980)
Norway	2011 (very wet season)	 Barley Oats Wheat	 3/20 (15) 16/28 (57) 2/28 (7)	Median (maximum) 1.0 (1.2) 2.1 (20.1) 1.0 (1.0)	(Uhlig *et al.*, 2013)
Saudi Arabia	NS	Almonds Cashews Chestnuts Hazelnuts Pistachios Walnuts	0/5 (0) 0/5 (0) 0/5 (0) 0/5 (0) 0/5 (0) 0/5 (0)	- - - - - -	(Abdel-Gawad and Zohri, 1993)
Saudi Arabia	NS	Green coffee beans	3/30 (10)	5-13	(Bokhari and

Country	Year	Food	Incidence, positive/ total samples (%)	Concentration (µg/kg)	Reference
					Aly, 2009)
South Africa	NS	Green coffee beans (condemned)	1/2 (50)	1143	(Purchase and Pretorius, 1973)
Spain	1986-1987	Almonds Peanuts Hazelnuts Pistachios Sunflower seeds	0/34 (0) 0/38 (0) 0/29 (0) 0/32 (0) 0/35 (0)	- - - - -	(Jiménez *et al.*, 1991)
Spain	NS	Cheese, Manchego	0/12 (0)	-	(López-Díaz *et al.*, 1996)
Sri Lanka	NS	Red chilli Black pepper White pepper	4/10 (40) 5/10 (50) 4/10 (40)	<LOQ (11) <LOQ (8) <LOQ (16)-36	(Yogendrarajah *et al.*, 2013)
Turkey	1986	Maize	10/50 (20)	Approximately 20	(Özay and Heperkan, 1989)
UK	NS	Maize Maize flour Maize flakes Maize-based breakfast cereals Oat-based breakfast cereals Wheat-based breakfast cereals	2/29 (7) 0/13 (0) 1/2 (50) 0/6 (0) 0/6 (0) 1/14 (7)	NS - NS - - 7	(Jarvis, 1982)
UK	1997-1998	Breakfast cereals Corn oils Corn on the cob Corn-base ingredients Polenta Tacos Tinned sweetcorn Popcorn Corn snacks Cheese Barley Wheat Oats Rice Rye	0/26 (0) 0/12 (0) 0/10 (0) 0/18 (0) 0/12 (0) 0/5 (0) 0/12 (0) 0/12 (0) 0/21 (0) 0/33 (0) 0/20 (0) 0/20 (0) 0/21 (0) 0/21 (0) 0/20 (0)	- - - - - - - - - - - - - - -	(MAFF, 1998)
UK	2000	Rice	0/100 (0)	-	(Food Standards Agency, 2002b)
UK	2000	Peanuts	0/20 (0)	-	(Food Standards Agency, 2002a)

NS = not stated
LOQ = limit of quantification

11.3.3 Estimates of dietary exposure

No estimates of dietary exposure for STC were located. In their recent consideration of STC, EFSA concluded that the available concentration data were too limited to carry out a dietary exposure assessment (EFSA, 2013a).

11.3.4 Biomarkers of exposure

Blood and urinary STC have been used as biomarkers of STC exposure (Huţanaşu *et al.*, 2011; Tian *et al.*, 1995).

STC has been shown to form N7-guanyl DNA-adducts in a dose-dependent manner (Olson and Chu, 1993).

11.4 Risk Characterisation

11.4.1 Adverse health effects overseas

11.4.1.1 Epidemiological studies

China

The STC prevalence and concentrations in grain were reported to be higher in regions of high incidence of gastric cancer than in regions with low incidence (Lou *et al.*, 1995).

The same research group studied the presence of STC and STC-adducts in patients with gastric or liver cancer (Tian *et al.*, 1995). STC was found in blood of 4 of 13 patients (range 65-113 μg/kg), but only in the blood of 1 of 14 healthy controls (68 μg/kg). STC-DNA adducts were detected in 14 of 28 tissue samples, collected from 12 cancer patients. STC was only present at very low concentrations in urine from patients or controls.

Romania

STC was measured in blood and urine of controls (n = 55), liver cirrhosis (LC) cases (n = 58) and HCC cases (n = 53) (Huţanaşu *et al.*, 2011). STC was detected more frequently in the LC and HCC groups than the control group. Mean STC concentrations in blood and urine respectively were; 0.014 and 0.005 ng/ml for controls, 0.626 and 1.053 ng/ml in LC cases, and 2.02 and 9.39 in HCC cases. A strong correlation was seen between STC concentration and α-fetoprotein (a tumour marker) in HCC cases.

11.5 Risk Management Information

11.5.1 Relevant food controls: New Zealand

11.5.1.1 Establishment of regulatory limits

STC is not currently regulated in New Zealand.

11.5.2 Relevant food controls: overseas

11.5.2.1 Establishment of regulatory limits

A collation of worldwide regulatory limits for mycotoxins identified regulatory limits for STC in the Czech Republic and in Slovakia (Van Egmond and Jonker, 2004). Limits were; 5 µg/kg in milk, meat, poultry, flour and its products, rice, vegetables and potatoes, and 20 µg/kg in all other foods. These 2 countries joined the EU in 2004 and it is not known whether they have maintained these independent regulatory limits. This collation is in the process of being updated, but is not yet available (Monique De Nijs, RIKILT, Netherlands, personal communication).

11.5.3 Influence of storage and processing on STC levels

The influence of milling on the STC content of brown rice was examined (Takahashi *et al.*, 1984). STC was concentrated in the bran layer and STC content of the milled rice and the bran was strongly influenced by milling yield. At a low yield (56.4%) the milled rice contained only 7.7% of that in the intact grain, with the remaining 92.3% in the bran. At a yield of 91.7%, 71.6% of the STC was in the milled rice.

STC was found to be stable during the breadmaking process, with the STC content of the baked bread not significantly different to that in the intact grain (Veršilovskis and Bartkevičs, 2012).

During production of cheese from STC-contaminated milk, 80% of the toxin was retained in the curd, with only 20% in the whey (Abd Alla *et al.*, 1996). Cheese ripening at 6ºC had virtually no effect on STC content, while ripening at 20ºC reduced the toxin content by 16% after 90 days.

Roasting of naturally-contaminated coffee beans at 200ºC resulted in a 70% reduction in STC content after 15 minutes (Bokhari and Aly, 2009).

11.6 Conclusions

11.6.1 Description of risks to New Zealand consumers

STC is mutagenic and carcinogenic. STC has been implicated in causation of gastric and liver cancer in China and Eastern Europe, although few studies have been carried out and the study designs used do not provide strong evidence of causation.

No information is available on STC in the New Zealand food supply. The main producing organisms (*Aspergillus versicolor, A. nidulans*) have not been reported in New Zealand.

No estimates of dietary exposure are available.

11.6.2 Commentary on risk management options

STC is known to co-occur with aflatoxins and current control measures for aflatoxins will be likely to have some impact on STC in the food supply.

11.6.3 Data gaps

Information on the prevalence of STC-producing organisms and the toxin itself in New Zealand foods would aid in risk assessment.

12 *ALTERNARIA* TOXINS

12.1 Hazard Identification

Alternaria toxins are produced by species of *Alternaria* fungi. Approximately 70 toxins have been reported, but only a small proportion of them have been characterised (EFSA, 2011a). *Alternaria alternata* is considered to be the most important species with respect to toxin production, although *A. solani*, *A. tenuissima* and *A. alternata* f. sp. *lycopersici* have also been reported to produce *Alternaria* toxins.

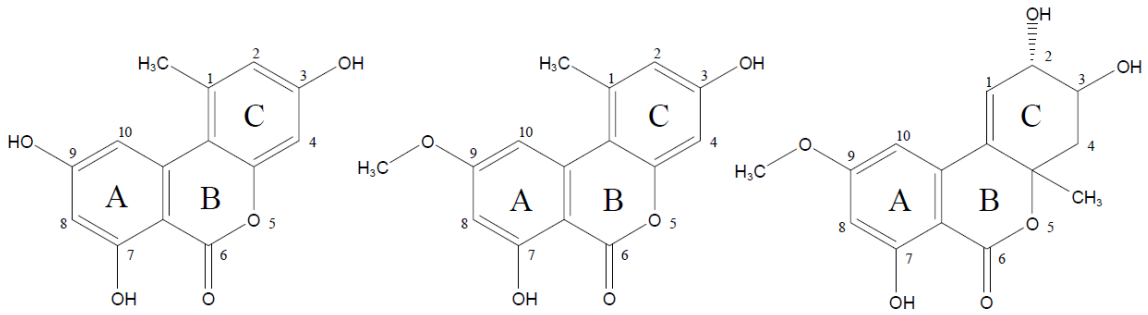
12.1.1 Structure and nomenclature

Alternaria toxins may be divided into 5 structural classes:

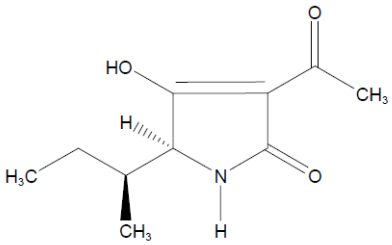
- Dibenzo-α-pyrones, including alternariol (AOH), alternariol monomethyl ether (AME) and altenuene (ALT);
- Tenuazonic acid (TeA) and iso-tenuazonic acid (iso-TeA);
- Perylene quinones, including altertoxin I, II and III (ATX-I, ATX-II and ATX-III) and stemphyltoxin III;
- *A. alternata* f. sp. *Lycopersici* toxins (AAL toxins), AAL-TA and AAL-TB; and
- Miscellaneous toxins, including the cyclic tetrapeptide, tentoxin (TEN).

The structures of these toxins are shown in Figure 12.

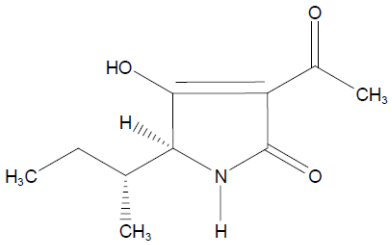
Figure 12: Structure of *Alternaria* toxins



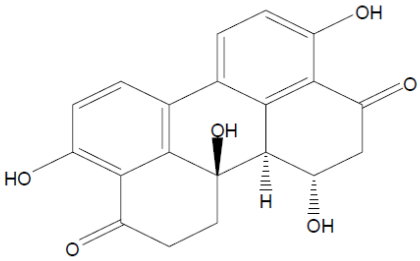
AOH **AME** **ALT**



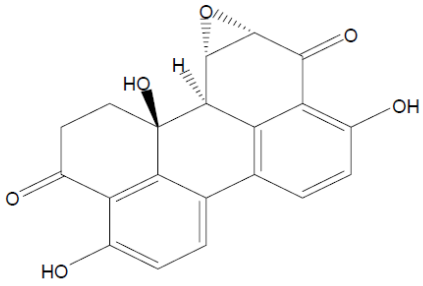
TeA



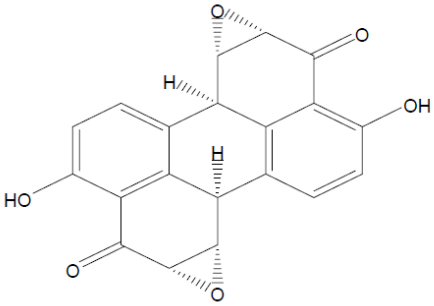
iso-TeA



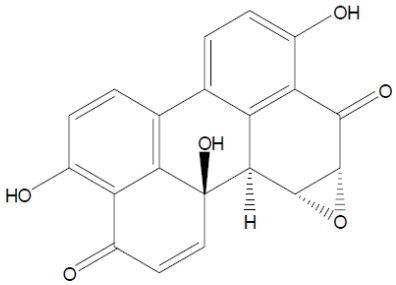
ATX-I



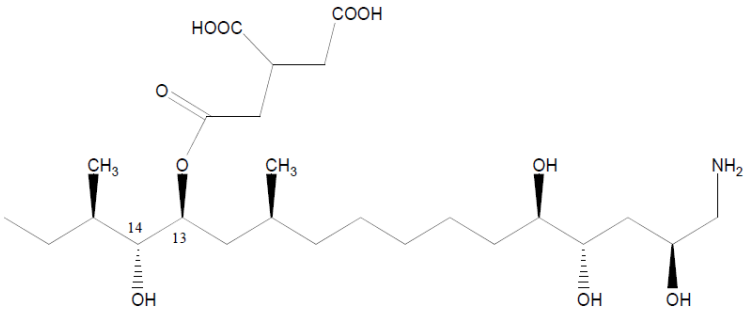
ATX-II



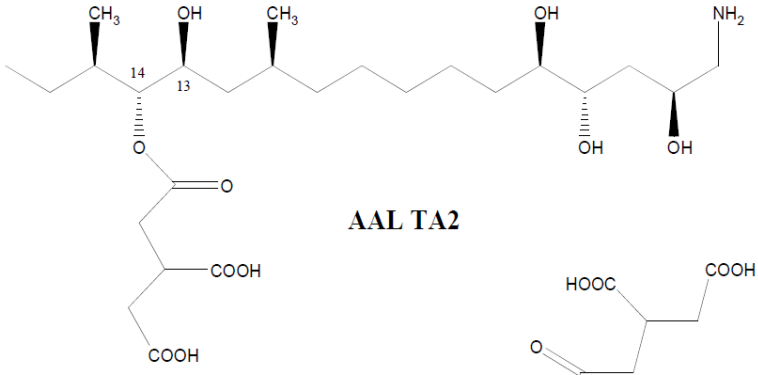
ATX-III



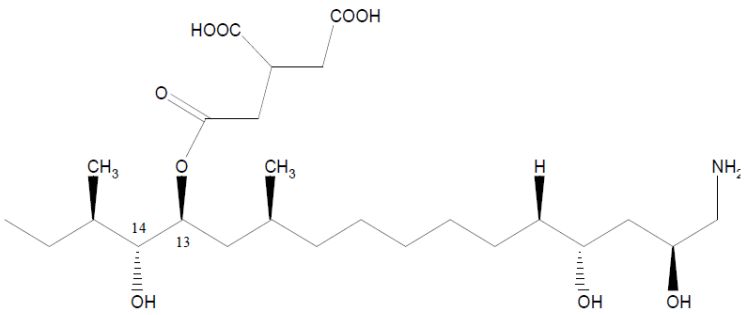
Stemphyltoxin III



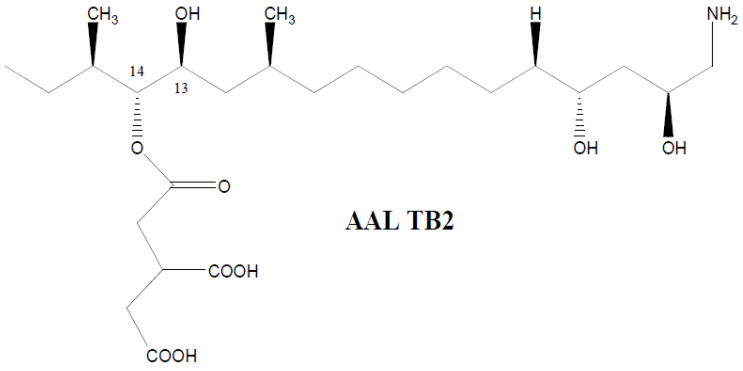
AAL TA1



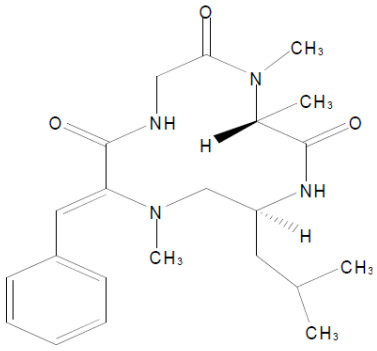
AAL TA2



AAL TB1



AAL TB2



TEN

Reproduced from (EFSA, 2011a)

12.1.2 Occurrence

Alternaria species are normal components of the microflora of many soils and are widespread in both humid and semi-arid environments (EFSA, 2011a). *Alternaria* are the principal fungi contaminating wheat, barley and sorghum. Fungi of this genus have also been reported on

oilseeds, tomatoes, apples, citrus fruit and other fruits and vegetables. Many *Alternaria* species are host specific and can be presumptively identified from their source (Pitt and Hocking, 1997).

Alternaria are able to grow even at very low temperatures, with *A. alternata* reported to have a growth minimum in the range -5 to 6.5ºC (Pitt and Hocking, 1997). This allows these species to cause spoilage even under conditions of refrigerated storage. Growth optima for *Alternaria* species are generally in the range 18-25ºC.

Some crops affected by *Alternaria* species can also be infected by strains of *Aspergillus*, *Penicillium* and *Fusarium*, and *Alternaria* toxins may co-occur with other mycotoxins (EFSA, 2011a).

12.2 Hazard Characterisation: Adverse Health Effects

No reports were located of adverse health effects in humans due to *Alternaria* toxin exposure. *Alternaria* toxins have been implicated in the aetiology of oesophageal cancer in areas of China (Dong *et al.*, 1987; Liu *et al.*, 1991; Liu *et al.*, 1992). TeA has also been implicated in onyalai, a haemorrhagic disease occurring in southern Africa (Steyn and Rabie, 1976)

12.2.1 Toxicity

12.2.1.1 Acute toxicity

Little toxicological information is available on pure single *Alternaria* toxins. The available information suggests that these toxins are of low acute toxicity (EFSA, 2011a; Pero *et al.*, 1973). Intraperitoneal administration in female mice resulted in less than 50% mortality at a dose of 400 mg/kg body weight for AOH and AME, while a dose of 50 mg/kg body weight of ALT resulted in mortality in 1/3 mice (Pero *et al.*, 1973). ATX-I and ATX-II doses of 200 mg/kg body weight resulted in mortality in all mice, while no or very low mortality rates were observed at 100 mg/kg body weight.

The toxicity of TeA appeared to be relative unaffected by the route of administration, with LD_{50} values in the range 81-225 mg/kg body weight for rats and mice (EFSA, 2011a).

A single dose of 100 mg/kg body weight of purified AAL toxins caused no toxic effects when administered to rats by intragastric tube (Mirocha *et al.*, 1992a).

12.2.1.2 Chronic toxicity

There is some evidence that AOH, AME and the ATX toxins are mutagenic in *in vitro* tests (EFSA, 2011a), with ATX-II reported to be 50 times more potent as a mutagen than AOH or AME (Fleck *et al.*, 2012). An extract of *Alternaria* infected rice, containing AOH, AME and TeA as the major mycotoxins, was shown to exhibit far greater DNA damaging potential in *in vitro* assays than equivalent concentrations of the single compounds (Schwarz *et al.*, 2012). However, this has not been confirmed in *in vivo* tests and evidence for the carcinogenicity of *Alternaria* toxins in animal studies is unconvincing, due to unconventional experimental designs in relevant studies.

There is some evidence of developmental toxicity due to AOH and AME following subcutaneous or intraperitoneal administration in mice and hamsters (EFSA, 2011a). However, no effects were seen following oral administration.

12.2.2 Toxicological assessment

Toxicological assessment of *Alternaria* toxins has been carried out by EFSA (2011a). It was concluded that there were no relevant toxicity data for estimation of reference points for different toxicological effects.

The EFSA CONTAM panel concluded that there were sufficient occurrence data for AOH, AME, TeA and TEN to apply the threshold of toxicological concern (TTC) method. This method assigns an exposure limit based on chemical structural characteristics of the compound (Barlow, 2005). The estimated dietary exposure for AOH and AME exceeded the relevant TTC value (2.5 ng/kg body weight/day), suggesting a need for additional compound specific toxicity data. Estimated dietary exposures to TeA and TEN were lower than the relevant TTC value (1500 ng/kg body weight/day) and are unlikely to be of public health concern.

12.2.3 Metabolites and their relative toxicity

The biosynthesis of TeA includes 1 molecule of L-isoleucine (Asam *et al.*, 2013b). Methods were developed for analysis of TeA analogues from other amino acids. Analogues from valine and leucine were detected in foods contaminated by high concentrations (>100 μg/kg) of TeA (Asam *et al.*, 2013b). Analogues were found at concentrations 1-16% of the associated TeA concentration. However, little is known about the toxicity of these analogues.

12.3 Exposure Assessment

12.3.1 *Alternaria* toxins in the Australasian food supply

No information was found on the occurrence of *Alternaria* toxins in crops or foods in New Zealand.

A study of weather damaged wheat and sorghum from the 1995-1996 harvest in Northern New South Wales detected low concentration of AOH, AME and TeA in weather damaged wheat, but only low levels of TeA in weather damaged sorghum and undamaged wheat (Webley *et al.*, 1997). These toxins were not found in weather damaged wheat from other regions of Australia, where infection was principally by *A. infectoria*, rather than *A. alternata.*

12.3.2 Overseas context

Studies on the prevalence and concentrations of *Alternaria* toxins in specific foods are summarised in Table 23.

Table 23: Worldwide data on occurrence of *Alternaria* toxins in food

Country	Year	Food	Toxin	Incidence, positive/ total samples (%)	Concentration (µg/kg)	Reference
Argentina	NS	Tomato purée	AOH AME TeA	5/80 (6) 21/80 (26) 23/80 (29)	187-8760 84-1730 39-4020	(Terminiello *et al.*, 2006)
Argentina	2011	White wine Red wine Rosé wine Apple juice Other juice	AOH AME AOH AME AOH AME AOH, AME AOH AME	4/53 (8) 3/53 (6) 6/56 (11) 1/56 (2) 1/4 (25) 0/4 (0) 0/37 (0) 3/35 (9) 0/35 (0)	<LOQ (2.0)-18 <LOQ (1.4)-225 <LOQ (7.5)-13 <LOQ (0.2) <LOQ (7.5) - - <LOQ (10) -	(Broggi *et al.*, 2013)
Austria/ Turkey	2007	Almonds Hazelnuts Peanuts Pistachios	AOH AME ATX-I TEN AOH AME ATX-I TEN AOH AME ATX-I TEN AOH, AME, ATX-I, TEN	1/8 (13) 3/8 (38) 0/8 (0) 1/8 (13) 20/22 (91) 19/22 (86) 2/22 (9) 17/22 (77) 3/15 (20) 5/15 (33) 1/15 (7) 4/15 (27) 0/8 (0)	Max <LOQ (3.0) 0.84 - <LOQ (1.2) 650 220 <LOQ (14) 21 <LOQ (8.8) <LOQ (2.7) <LOQ (14) 11 -	(Varga *et al.*, 2013)
Argentina	2004-2005	Wheat	AOH AME TeA	4/64 (6) 15/64 (23) 12/64 (19)	645-1388 566-7451 1001-8814	(Azcarate *et al.*, 2008)
Argentina	2006-2008	Soya beans	AOH AME	23/50 (46) 22/50 (44)	25-211 62-1153	(Oviedo *et al.*, 2012)
Belgium	NS	Tomato concentrate Tomato purée Other tomato products	AOH AME AOH AME AOH, AME	4/18 (22) 2/18 (11) 2/15 (13) 2/15 (13) 0/86 (0)	NS NS NS NS -	(Van de Perre *et al.*, 2014)
Brazil	1994-1995	Tomato juice Tomato pulp Tomato purée Tomato paste Tomato, whole stewed	AOH, AME, TeA (only TeA was detected)	0/11 (0) 7/22 (32) 4/22 (18) 0/24 (0) 0/1 (0)	- 39-111 31-76 - -	(da Motta and Valente Soares, 2001)
Canada	NS	Apple juice	AOH AME	3/8 (38) 0/8 (0)	0.8-5.0 -	(Scott *et al.*, 1997)
Canada	NS	Wine (ice)	TeA	0/26 (0)	-	(Abramson *et al.*, 2007)
Canada	NS	Apple juice	AOH	11/11 (100)	<LOQ (0.04)-2.4	(Lau *et al.*,

Country	Year	Food	Toxin	Incidence, positive/ total samples (%)	Concentration (µg/kg)	Reference
			AME	10/11 (91)	<LOQ (0.03)-0.43	2003)
		Other fruit beverages	AOH	5/9 (56)	0.84-5.6	
			AME	3/9 (33)	0.23-1.4	
Canada	NS	Wine, red	AOH	20/24 (83)	0.03-19.4	(Scott *et al.*, 2006)
			AME	19/24 (79)	0.01-0.23	
		Wine, white	AOH	2/23 (9)	0.67-1.48	
			AME	2/23 (9)	0.02-0.06	
		Grape juice, red	AOH	3/10 (30)	0.03-0.46	
			AME	5/10 (50)	0.01-39.5	
		Grape juice, white	AOH	0/4 (0)	-	
			AME	0/4 (0)	-	
		Cranberry juice	AOH	1/5 (20)	0.04	
			AME	1/5 (20)	0.003	
Canada	NS	Wheat flour, bran	AOH	6/15 (40)	0.5-63	(Scott *et al.*, 2012)
			AME	5/15 (33)	0.5-8.9	
		Breakfast cereals	AOH	10/10 (100)	0.4-35	
			AME	10/10 (100)	0.4-12	
		Bread	AOH	29/29 (100)	0.4-6.7	
			AME	22/29 (76)	0.2-3.0	
		Infant foods	AOH	25/29 (86)	0.5-4.4	
			AME	27/29 (93)	0.5-9.0	
Czech Republic	NS	Lentils	AOH	3/3 (100)	Max = 290	(EFSA, 2011a)
			AME	0/3 (0)	-	
			ALT	0/3 (0)	-	
			TeA	0/3 (0)	-	
Czech Republic	2002-2003	Peas	AOH	0/84 (0)	-	(Králová *et al.*, 2006)
			AME	0/84 (0)	-	
			ALT	0/84 (0)	-	
		Linseed/flax seed	AOH	4/122 (3)	14-104	
			AME	20/122 (16)	6-30	
			ALT	2/122 (2)	4-9	
Czech Republic	2004	Fresh grape juice	AOH, AME, ALT, TeA	0/13 (0)	-	(Ostrý *et al.*, 2007)
		Must		0/13 (0)	-	
		Wine		0/13 (0)	-	
Germany	NS				Max	(Ackermann *et al.*, 2011)
		Apple sauce	AOH	6/10 (60)	2.0	
		Apple juice		9/44 (20)	3.5	
		Tomato ketchup		18/18 (100)	5.0	
		Tomato paste		10/10 (100)	13.0	
		Tomato juice		9/16 (56)	3.1	
		White wine		2/11 (18)	2.0	
Germany	NS	Cereals	AOH	1/13 (8)	4.1	(Asam *et al.*, 2011a)
			AME	1/13 (8)	0.6	
		Wine	AOH	4/6 (67)	1.2-4.9	
			AME	4/6 (67)	0.1-0.3	
		Juice (red grape, carrot, vegetable)	AOH	0/4 (0)	-	
			AME	1/4 (25)	0.1	
		Tomato juice	AOH	1/1 (100)	5.4	
			AME	1/1 (100)	0.9	
		Tomato products	AOH	4/6 (67)	2.6-25	

Country	Year	Food	Toxin	Incidence, positive/ total samples (%)	Concentration (µg/kg)	Reference
		(Ketchup, purée, paste)	AME	4/6 (67)	0.4-5.3	
Germany	NS	White (white, red, mulled) Fruit punch Juice (grape, apple, orange, tomato, vegetable)	AOH AME AOH AME AOH AME	13/13 (100) 4/13 (31) 1/1 (100) 1/1 (100) 13/13 (100) 5/13 (38)	Max = 7.6 Max = 0.15 0.27 0.04 Max = 7.8 Max = 0.79	(Asam *et al.*, 2009)
Germany	NS	Cereal flours Crispbread	TeA	6/18 (33) 7/9 (78)	<LOQ (50) – 851 <LOQ (50) - 61	(Siegel *et al.*, 2009)
Germany	NS	Beer	TeA	37/43 (86)	<LOQ (8) - 175	(Siegel *et al.*, 2010b)
Germany	NS	Apple juice Tomato juice Tomato ketchup Tomato paste	TeA	1/7 (14) 3/15 (20) 2/18 (11) 0/10 (0)	58 61-227 55, 67 -	(Gross *et al.*, 2011)
Germany	NS	Tomato ketchup Tomato paste Tomato sauces and purées	TeA	9/9 (100) 2/2 (100)	15-195 363-909 8-247	(Asam *et al.*, 2011b)
Germany	NS	Tomato ketchup Tomato paste Tomato, minced or puréed Other tomato products (sauce, soup, salsa, juice) Tomato powder Bell pepper products	TeA	8/8 (100) 3/3 (100) 4/4 (100) 9/9 (100) 1/1 (100) 4/4 (100)	11-105 38-541 23-98 7-508 2330 3-712	(Lohrey *et al.*, 2012)
Germany	NS	*Fruit juices* Orange juice Cherry juice Apple juice Blackcurrant juice Grape juice Pear juice Banana juice Grapefruit juice Apricot juice Strawberry juice Pomegranate juice Pineapple juice Other juice *Cereals* Oat flakes Wheat flour Rye flour Maize grit *Spices*	TeA	 6/6 (100) 6/6 (100) 5/5 (100) 5/5 (100) 4/4 (100) 3/3 (100) 2/3 (67) 0/3 (0) 2/2 (100) 2/2 (100) 2/2 (100) 0/2 (0) 7/7 (100) 3/4 (75) 4/4 (100) 2/2 (100) 2/2 (100)	 1.0-1.9 0.8-54 0.6-6 0.5-2.3 1.7-7 0.5-23 0.5-0.7 - 25-27 5-6 8-13 - 0.5-10 7-14 5-36 42-57 16-16	(Asam *et al.*, 2012)

Country	Year	Food	Toxin	Incidence, positive/ total samples (%)	Concentration (µg/kg)	Reference
		Paprika		9/9 (100)	880-37,300	
		Pepper		6/6 (100)	60-1000	
		Curry		5/5 (100)	190-2100	
		Dill		0/3 (0)	-	
		Curcumin		2/2 (100)	60-100	
		Ginger		2/2 (100)	50-70	
		Cumin		2/2 (100)	530-1350	
		Coriander		2/2 (100)	1500-1700	
		Other spices		5/7 (71)	60-420	
Germany	2001-2010	Wheat (winter)	AOH	86/1064 (8)	<LOQ (10)-832	(Müller and Korn, 2013)
			AME	33/1064 (3)	<LOQ (10)-905	
			ALT	7/267 (3)	62-197	
			TeA	322/1064 (30)	<LOQ (60)-4224	
Germany	NS	Fruit tea	TeA	5/5 (100)	1.0-2.4	(Asam and Rychlik, 2013)
		Herbal tea		3/3 (100)	0.7-3.8	
		Fennel tea		10/10 (100)	0.8-17.5	
		Purée infant foods		12/12 (100)	1.0-78	
		Infant cereals, various		4/4 (100)	1.3-30	
		Infant cereals, sorghum-based		12/12 (100)	130-1200	
		Sorghum		20/20 (100)	8-670	
Italy	NS	Olives, undamaged	AOH, AME, ALT, TeA, ATX-I	0/9 (0)	-	(Visconti *et al.*, 1986)
		Olive husks		0/3 (0)	-	
		Olive oil, from undamaged		0/4 (0)	-	
		Olives, damaged	AOH	4/4 (100)	109-2320	
			AME	4/4 (100)	30-2870	
			ALT	1/4 (25)	1400	
			TeA	2/4 (50)	110-263	
			ATX-I	0/4 (0)	-	
		Olive oil, from damaged	AOH	1/3 (33)	286	
			AME	1/3 (33)	794	
			ALT	0/3 (0)	-	
			TeA	0/3 (0)	-	
			ATX-I	0/3 (0)	-	
Italy	NS	Cornflakes	TeA	1/1 (100)	25	(Aresta *et al.*, 2003)
Italy	NS	Apple juice	AOH, AME, TEN	0/10 (0)	-	(Prelle *et al.*, 2013)
			ALT	1/10 (10)	46	
			TeA	2/10 (20)	24-45	
		Beer	AME, TeA	0/30 (0)	-	
			AOH	9/30 (30)	6-23	
			ALT	1/30 (3)	15	
			TEN	1/30 (3)	11	
		Tomato products	AME, TeA	0/10 (0)	-	
			AOH	5/10 (50)	4.0-6.8	
			ALT	8/10 (80)	3.8-4.8	
			TEN	1/10 (10)	4.7	

Country	Year	Food	Toxin	Incidence, positive/ total samples (%)	Concentration (µg/kg)	Reference
		Olives	AOH, AME, ALT, TeA, TEN	0/10 (0)	-	
		Dried basil	AOH, AME, ALT, TeA, TEN	0/10 (0)	-	
Netherlands, France, Denmark	NS	Carrots	AOH, AME, TeA, ATX-I	0/266 (0)	-	(Solfrizzo *et al.*, 2004)
Netherlands	NS	Wine (red, white, rosé)	AOH	33/54 (61)	0.6-13.2	(Scussel *et al.*, 2013)
			AME	8/54 (15)	0.2-0.53	
		Cider	AOH, AME	0/24 (0)	-	
Nigeria	2011	Fonio millet	AOH	13/16 (81)	0.3-10	(Ezekiel *et al.*, 2012)
			AME	13/16 (81)	0.3-16	
			TeA	16/16 (100)	14-1049	
		Sesame	AOH	15/17 (88)	0.3-14	
			AME	16/17 (94)	0.2-4	
			TeA	16/17 (94)	2-40	
Norway	2011 (very wet season)				Median (maximum)	(Uhlig *et al.*, 2013)
		Barley	AOH	16/20 (80)	10.4 (37.7)	
			AME	19/20 (95)	0.5 (5.2)	
			TeA	3/20 (15)	59 (247)	
			ATX-I	19/20 (95)	2.7 (5.6)	
			TEN	5/20 (25)	0.2 (0.4)	
		Oats	AOH	26/28 (93)	53.6 (449)	
			AME	28/28 (100)	21.6 (177)	
			TeA	25/28 (89)	21 (82)	
			ATX-I	27/28 (96)	7.3 (36.1)	
			TEN	26/28 (93)	1.3 (3.6)	
		Wheat	AOH	28/28 (100)	116 (305)	
			AME	28/28 (100)	0.8 (2.5)	
			TeA	6/28 (21)	18 (35)	
			ATX-I	27/28 (96)	4.5 (15.7)	
			TEN	0/28 (0)	-	
Spain	NS	Apple Juice	AOH	0/7 (0)	-	(Delgado *et al.*, 1996)
			AME	1/7 (14)	0.85	
Spain	1993-1994	Apple juice concentrate	AOH	17/32 (53)	<LOQ (0.8)-5.4	(Delgado and Gómez-Cordovés, 1998)
			AME	17/32 (53)	<LOQ (0.8)-1.7	
Switzerland	2010	Ketchup	AOH	3/19 (16)	4-5	(Noser *et al.*, 2011)
			AME	3/19 (16)	1	
			TeA	19/19 (100)	3-141	
			ALT,TEN	0/19 (0)	-	
		Dried tomatoes	AOH	1/8 (13)	4	
			AME	3/8 (38)	2-7	
			ALT	2/8 (25)	2	
			TEN	2/8 (25)	2	
			TeA	7/8 (88)	2-166	
		Fresh and whole tomatoes	TeA	1/4 (25)	37	
			AOH, AME,	0/4 (0)	-	

Country	Year	Food	Toxin	Incidence, positive/ total samples (%)	Concentration (µg/kg)	Reference
			ALT, TEN			
		Tomato purée/concentrates	AOH	11/17 (65)	4-33	
			AME	12/17 (71)	1-9	
			TEN	6/17 (35)	1-3	
			TeA	17/17 (100)	2-790	
		Tomatoes, peeled, minced	ALT	0/17 (0)	-	
			AOH	3/13 (23)	4-7	
			AME	1/13 (8)	1	
			TEN	1/13 (8)	2	
			TeA	13/13 (100)	25-200	
		Tomato sauces and soups	ALT	0/13 (0)	-	
			AOH	8/24 (33)	4-10	
			AME	7/24 (29)	1-4	
			TeA	24/24 (100)	4-144	
			ALT, TEN	0/24 (0)	-	

NS = not stated
LOQ = limit of quantification
AOH = alternariol
AME = alternariol methyl ester
ALT = altenuene
TeA = tenuazonic acid
TEN = tentoxin
ATX-I = altertoxin-I

Analysis of moulded tomatoes from several countries found that *Alternaria* mycotoxins appear to be the major contaminants in fruit from temperate countries (Belgium, Spain, South Africa), but not in fruit from tropical regions (Brazil, India) (Van de Perre *et al.*, 2014).

As part of their assessment of *Alternaria* toxins, EFSA made a call for data from European countries (EFSA, 2011a). The final cleaned dataset included almost 12,000 observations covering 7 *Alternaria* toxins. The results are summarised in Table 24. While data were submitted for ALT, ATX-I and AAL, ALT and AAL were not detected in any samples analysed. ATX-I was detected in 1 sample of sesame seed (80 µg/kg) and 1 sesame seed paste (41 µg/kg).

Table 24: Summary of European data on *Alternaria* toxins in food, by food group

Food group	*Alternaria* toxin Prevalence (total samples (%positive)), mean (lower bound-upper bound), maximum							
	AOH		**AME**		**TeA**		**TEN**	
Grains and grain products	911 (3),	1.8-7.3, 256	911 (2),	0.37-1.99, 86	810 (6),	6.7-32, 851	676 (3),	0.29-41, 38
Vegetables and vegetable products	392 (8),	1.1-5.8, 100	382 (8),	1.4-8.7, 280	364 (12),	15-34, 520	108 (1),	0.09-3.9, 9.2
Starchy roots and tubers	37 (0)		37 (0)		37 (0)		-	
Legumes, nuts and oilseeds	254 (13),	22-26, 1200	254 (27),	11-12, 440	168 (45),	333-349, 5400	170 (26),	47-50, 880
Fruit and fruit products	106 (11),	2.7-7.3, 151	86 (7),	1.4-2.4, 42	86 (24),	158-176, 8700	86 (0)	
Sugar and confectionary	5 (0)		5 (20),	1.3-2.3, 6.7	5 (20),	68-88, 340	5 (0)	
Vegetable oils	100 (7),	0.9-5.6, 18	100 (16),	3.4-6.1, 85	100 (36),	35-42, 390	99 (20),	3.4-5.1, 67
Fruit and vegetable juices	299 (13),	0.4-2.7, 13	276 (3),	0.02-1.3, 3.0	194 (2),	2.4-14, 286	158 (0)	
Non-alcoholic beverages	15 (0)		15 (0)		3 (0)		3 (0)	
Alcoholic beverages	54 (17),	0.4-1.7, 4.9	49 (10),	0.02-0.9, 1.5	76 (20),	4.7-10, 175	7 (0)	
Herbs, spices and condiments	33 (58),	1.5-2.7, 5.0	15 (7),	0.03-0.9, 1.0	31 (35),	30-54, 163	13 (0)	
Foods for infants and small children	49 (0)		49 (0)		49 (4),	3.7-30, 110	49 (0)	
Products for special nutritional uses	21 (0)		21 (5),	0.16-1.1, 3.3	21 (5),	20-45, 424	12 (0)	
Composite foods	3 (0)		3 (0)		3 (0)		2 (0)	
Snacks, desserts and other foods	12 (0)		12 (0)		-		-	

AOH = alternariol AME = alternariol methyl ester TeA = tenuazonic acid TEN - tentoxin

12.3.3 Estimates of dietary exposure

Table 25 summarises estimates of dietary exposure to *Alternaria* mycotoxins that have been derived overseas.

Table 25: Overseas estimates of dietary exposure to *Alternaria* mycotoxins

Country	Foods included	Population group*	Toxin	Mean (95th percentile) estimated dietary exposure (ng/kg body weight/day)	Reference
Belgium	Tomato products	Adult	TeA	2900-4230 (7430-10,820)	(Van de Perre *et al.*, 2014)
EU[1]	Various	Adult (18-65)	AOH -Lowest -Highest AME -Lowest -Highest TeA -Lowest -Highest TEN -Lowest -Highest	 1.9-17 (5.9-42) (Ireland) 5.7-37 (17-77) (Spain) 0.9-2.1 (3.6-6.1) (Ireland) 3.0-4.7 (12-15) (Spain) 36-78 (89-169) (France) 64-125 (219-362) (Czech Republic) 0.01-0.02 (-) (Denmark) 1.2-5.1 (4.2-12.1) (Finland)	(EFSA, 2011a)

[1] Suitable dietary surveys for exposure assessment were only available for Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Netherlands, Spain, Sweden, United Kingdom

The maximum exposure to TeA by German consumers, due to consumption of contaminated tomato products, was reported to be less than 1 µg/kg body weight/day (1000 ng/kg body weight/day) (Asam *et al.*, 2011b).

The exposure assessments carried out by EFSA demonstrated that the major food types contributing to *Alternaria* toxin exposure were:

- AOH; grains and grain products > fruit and vegetable juices > fruit and fruit products > alcoholic beverages
- AME; fruit and fruit products > grain and grain products > fruit and vegetable juices > vegetable oils
- TeA; vegetables and vegetable products > alcoholic beverages > grain and grain products
- TEN; vegetable oils > oilseeds

12.3.4 Biomarkers of exposure

An assay for TeA in urine has been developed (Asam *et al.*, 2013a). TeA was detected in 24-hour urine samples from 6 German volunteers, with concentrations in the range 1.3-17.3 µg/L. Two volunteers consumed 30 µg TeA from contaminated sorghum infant cereal and tomato juice. After 24 hours, 87-93% of TeA ingested dose was recovered in urine. However, the fate of the remaining 10% was not identified.

12.4 Risk Characterisation

Human intoxication due to *Alternaria* toxins has not been reported.

12.5 Risk Management Information

12.5.1 Relevant food controls: New Zealand

12.5.1.1 Establishment of regulatory limits

Alternaria toxins are not currently regulated in New Zealand.

12.5.2 Relevant food controls: overseas

12.5.2.1 Establishment of regulatory limits

A collation of worldwide regulatory limits for mycotoxins did not identify any country with regulatory limits for *Alternaria* toxins (Van Egmond and Jonker, 2004). This collation is in the process of being updated, but is not yet available (Monique De Nijs, RIKILT, Netherlands, personal communication).

12.5.2.2 Management of Alternaria toxins in crops

Accumulation of TeA in winter wheat has been shown to be greater in years of high rainfall, when the preceding crop was maize or wheat, rather than rape, and when minimum tillage techniques were used, rather than conventional ploughing (Müller and Korn, 2013).

12.5.3 Influence of storage and processing on *Alternaria* toxin levels

The stability of AOH, AME and TeA in heated sunflower meal was examined (Combina *et al.*, 1999). AOH and AME were stable following humid heat treatment at 100ºC for up to 90 minutes. Under the same conditions, the TeA content of the meal decreased to 83% after 30 minutes, 67% after 60 minutes and 50% after 90 minutes. Humid heat and pressure (115ºC at 0.075 MPa or 121ºC at 0.1 MPa) were also assessed. At the lower temperature/pressure combination AOH and AME were stable after 30 minutes, but degraded to about two-thirds of their initial concentration after 60 minutes. TeA decreased to 37% of its initial concentration after 30 minutes and then decreased further, to 30%, after 60 minutes. At the higher temperature/pressure, AME was completely degraded after 60 minutes, while AOH and TeA were reduced to 25 and 33% of their initial concentrations.

The stability of AOH, AME and ATX-I in acid media was assessed by adding these toxins to apple juice or wine (10-100 μg/L) and storing at room temperature or heating at 80ºC (Scott and Kanhere, 2001). AOH and AME were stable in apple juice at room temperature for the duration of the study (27 days in apple juice with or without added vitamin C, 8 days in white wine) and for 20 minutes in apple juice at 80ºC. ATX-I was stable in apple juice for up to 27 days.

The stability of AOH, AME and ALT was studied in wheat flour during wet baking (mixing with water and baking) and dry baking (heating of dry flour) (Siegel *et al.*, 2010a). During

wet baking, all *Alternaria* toxins studied were stable for up to 60 minutes at 170 and 200ºC and up to 45 minutes at 230ºC. AOH and ALT, but not AME, contents of doughs decreased by approximately 20% after heating for 60 minutes at 230ºC. Degradation during dry baking was much more pronounced, with ALT being the most sensitive to the effects of heat and AME the least sensitive. ALT was almost completely degraded after dry baking for 60 minutes at 230ºC, while AME content was reduced by 50% under the same circumstances. However, it should be noted that the wet baking experiments have more relevance to food processing situations, such as bread, cake or biscuit making.

12.6 Conclusions

12.6.1 Description of risks to New Zealand consumers

There is little evidence linking *Alternaria* toxin exposure to adverse health effects in human.

Alternaria spp. capable of producing toxins have been reported in New Zealand crops and non-crop plants (Biswas *et al.*, 2014; Everett and Neilson, 1996; Takahashi *et al.*, 1997), which is consistent with their optimum growth temperatures. *Alternaria* toxins are almost certainly present in the New Zealand food supply. However, concentrations in foods and levels of dietary exposure are currently unknown.

12.6.2 Commentary on risk management options

Specific risk management options for *Alternaria* toxins were not identified. Control of *Alternaria* fungi and toxin production is likely to be achieved through Good Agricultural Practice.

12.6.3 Data gaps

Internationally there is a need for better information on the toxicity of *Alternaria* toxins. In New Zealand, information on the prevalence of the causative organisms and the toxins is needed for a more accurate risk assessment.

13 PENICILLIC ACID

13.1 Hazard Identification

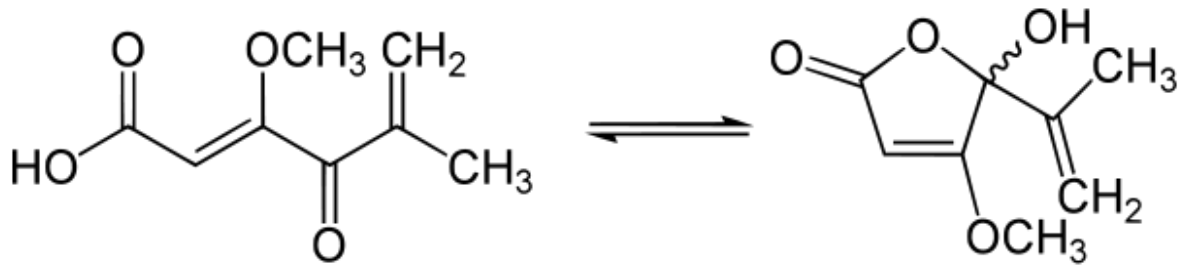
Penicillic acid (PEN), 5-hydroxy-5-isopropenyl-4-methoxy-furan-2-one, is a polyketide mycotoxin produced by several *Aspergillus* and *Penicillium* species, including *A. ochraceus, P. roqueforti,* and *P. aurantiogriseum* (IARC, 1976; Pitt and Hocking, 1997; Sorenson and Simpson, 1986).

Penicillic acid was the earliest described mycotoxin, discovered in 1913 (Alsberg and Black, 1913).

13.1.1 Structure and nomenclature

The chemical structures of PEN is shown in Figure 13. PEN exists as an equilibrium form between γ-keto acid form and γ-hydroxy lactone form (IARC, 1976). Most of the chemical reactions involving PEN occur through the lactone form.

Figure 13: Structure of penicillic acid



Reproduced from http://en.wikipedia.org/wiki/File:Penicillic_acid.svg

13.1.2 Occurrence

A. ochraceus grows at moderate temperatures (8-37˚C, optimum 24-31˚C) and at water activities above 0.8 (optimum 0.95-0.99) (Pitt and Hocking, 1997).

P. aurantiogriseum also grows at moderate temperatures, but can also grow at refrigeration temperatures (range -2-30˚C, optimum 23˚C) (Pitt and Hocking, 1997). A minimum water activity of 0.81 is required for growth.

P. roqueforti species includes a diverse range of varieties, including the strain used for cheese manufacture (variety *roqueforti*) and a spoilage organism (variety *carneum*) (Pitt and Hocking, 1997). *P. roqueforti* is a psychrophile, growing vigorously at refrigeration temperatures, but not above 35˚C. It is alkaline-tolerant, growing in the pH range 3-10.

PEN has been reported in maize, where it is associated with a disease called 'blue eye', caused by *P. aurantiogriseum* (Pitt and Hocking, 1997). It has also been detected in mould-ripened cheeses, beans and apple juice (IARC, 1976).

13.2 Hazard Characterisation: Adverse Health Effects

13.2.1 Conditions

No cases of adverse human health effects have been definitively linked to PEN exposure. Investigations into the causes of Balkan Endemic Nephropathy (BEN) have noted that a range of mycotoxins may be present in the food supply, including OTA, CIT, FB_1 and PEN (Stoev *et al.*, 2009). A combination of OTA and PEN has been shown to cause a nephropathy, with similar characteristics to BEN, in pigs and chickens.

13.2.2 Toxicity

13.2.2.1 Acute toxicity

PEN has moderate to low acute toxicity, with an oral LD_{50} of 600 mg/kg body weight and an intravenous LD_{50} of 200 mg/kg body weight in mice (IARC, 1976). A LD_{50} for oral administration of the sodium salt of PEN to broiler chickens was 92 mg/kg body weight (Huff *et al.*, 1980).

13.2.2.2 Chronic toxicity

PEN has been reported to be hepatotoxic (Chan *et al.*, 1980; Chan and Hayes, 1981), although feeding chickens diets containing up to 400 mg/kg PEN for 3 weeks did not result in measurable toxicity (Huff *et al.*, 1980).

PEN has been reported to increase the nephrotoxicity of OTA in mice and chickens (Kubena *et al.*, 1984; Shepherd *et al.*, 1981). It has been suggested that this may be due to the ability of PEN to inhibit the enzyme carboxypeptidase, which is involved in the detoxification of OTA (Parker *et al.*, 1982).

13.2.3 Toxicological assessment

PEN was evaluated by IARC most recently in 1976 (IARC, 1976). While there was some evidence of mutagenicity from animal studies (sarcoma development) and *in vitro* studies (DNA strand breaks), IARC concluded that there was insufficient evidence that PEN was carcinogenic (group 3).

PEN has not been evaluated by JECFA or EFSA.

13.2.4 Metabolites and their relative toxicity

There have been no reports of metabolites of dietary significance.

13.3 Exposure Assessment

13.3.1 PEN in the Australasian food supply

No information was found on the occurrence of PEN in crops or foods in New Zealand or Australia.

13.3.2 Overseas context

Studies of PEN in foods are summarised in Table 26.

An early study on production of PEN following inoculation of food materials noted that commodities with high protein contents did not support toxin production (Ciegler and Kurtzman, 1970). The results in Table 26 tend to support this conclusions, with commodities found to contain PEN (fruit, maize, dried beans) containing less than 10% protein.

Table 26: Worldwide data on occurrence of PEN in food

Country	Year	Food	Incidence, positive/ total samples (%)	Concentration (µg/kg)	Reference
Benin	NS			LOD	(Njumbe Ediage *et al.*, 2011)
		Maize	0/4 (0)	12	
		Cassava	0/4 (0)	8	
		Peanut cake	0/15 (0)	8	
Egypt	NS	Strawberry	3/10 (30)	160-180	(Aziz and Moussa, 2002)
		Apricot	1/10 (10)	135	
		Plum	3/10 (30)	125-130	
		Peach	6/10 (60)	100-170	
		Grape	0/10 (0)	-	
		Date	0/10 (0)	-	
		Fig	0/10 (0)	-	
		Apple	6/10 (60)	140-180	
		Pear	1/10 (10)	135	
		Mulberry	1/10 (10)	100	
Finland	2003	Cheese, white or blue mould ripened	0/21 (0)	LOD = 2.0	(Kokkonen *et al.*, 2005)
Netherlands	NS	Wine	0/54 (0)	LOD = 0.8 µg/L	(Scussel *et al.*, 2013)
		Cider	0/24 (0)		
		Corks/stoppers	2/72 (3)	10.8, 19.4	
Spain	NS	Cheese (Manchego)	0/12 (0)	LOD = 30	(López-Díaz *et al.*, 1996)
USA	1973	Maize	7/20 (35)	5-231	(Thorpe and Johnson, 1974)
		Dried beans	5/20 (25)	11-179	
		Apple juice	0/19 (0)	-	

NS = not stated LOD = limit of detection

PEN was detected in 90% of pig and chicken feed samples (n = 50) with mean concentrations of about 880 µg/kg (Stoev *et al.*, 2009). PEN was also detected in serum from 85% and urine of 60% of 20 pigs receiving the feed, with mean concentrations of 23 µg/L and 1.7 µg/L in serum and urine, respectively.

Chickens were administered oral doses of PEN in the range 50-400 mg/kg body weight (Hanna *et al.*, 1981). Four hours after dosing, PEN was detectable in kidney, heart, gizzard and liver samples from birds in the highest dose group. Concentrations were highest in

kidneys and this was the only tissue with detectable PEN concentrations in the lowest dose group. PEN was not detected in blood and muscle at any dose level.

13.3.3 Estimates of dietary exposure

No estimates of dietary exposure for PEN were located.

13.3.4 Biomarkers of exposure

While measurement of PEN in serum and urine have been reported for pigs (Stoev *et al.*, 2009), the use of biomarkers of human exposure has not been reported in the scientific literature.

13.4 Risk Characterisation

13.4.1 Adverse health effects overseas

No human disease surveillance, epidemiological studies or risk assessments related to PEN were identified.

13.5 Risk Management Information

13.5.1 Relevant food controls: New Zealand

13.5.1.1 Establishment of regulatory limits

PEN is not currently regulated in New Zealand.

13.5.2 Relevant food controls: overseas

13.5.2.1 Establishment of regulatory limits

A collation of worldwide regulatory limits for mycotoxins did not identify regulatory limits for PEN in any country (Van Egmond and Jonker, 2004). This collation is in the process of being updated, but is not yet available (Monique De Nijs, RIKILT, Netherlands, personal communication).

13.5.3 Influence of storage and processing on PEN levels

PEN was not formed in wheat stored at 15ºC for 4 months when the wheat was suitably dry (15% moisture) (Chelkowski *et al.*, 1987). However, at 18% grain moisture PEN concentration reached 6-8 mg/kg in 16 weeks. At 24% grain moisture similar PEN concentrations were observed after 2 weeks.

PEN was added to Swiss cheese, bologna and cooked cornmeal (Lieu and Bullerman, 1977). Foods were stored at 5ºC for up to 1 week, with periodic testing to determine how much PEN remained. PEN was undetectable in bologna after 48 hours. After 1 week, 8 and 80% of the original PEN was detected in Swiss cheese and cooked cornmeal, respectively.

Toxigenic *Penicillium* spp. strains were inoculated onto Swiss cheese, Mozzarella cheese, bologna, bacon, cooked cornmeal and English muffins and incubated at 5, 12 or 25ºC for up to 6 weeks. PEN was only produced in cooked cornmeal (at all temperatures) and at very low levels in English muffins incubated at 5ºC.

Ciegler *et al*. (1972) reported similar results following inoculation of salami with toxigenic *Penicillium* strains. No PEN was detected up to 70 days of ripening. The authors ascribed this observation to the ready reaction of PEN with components present in meat, including primary amino acids (cysteine, arginine, histidine and lysine) and glutathione.

Irradiation of fruit (3.5 kGy) prior to storage (28 days) was shown to prevent in decrease production of PEN (Aziz and Moussa, 2002). PEN production was not completely prevented in strawberries, but the concentrations in irradiated product (10-50 μg/kg) was substantially less than in non-irradiated product (380-700 μg/kg). Similar results were reported for mulberry, while no PEN was detected in irradiated samples of any other fruit type.

13.6 Conclusions

13.6.1 Description of risks to New Zealand consumers

PEN may occasionally contaminate foods infected with some strains of *Aspergillus* and *Penicillium*, although PEN appears to undergo rapid reactions in high protein foods.

Some animal studies have suggested that PEN may be hepatotoxic and carcinogenic, although IARC concluded that there was insufficient evidence of its carcinogenicity. Of more importance may be the apparent ability of PEN to increase the toxicity of co-ingested OTA. There is no direct evidence linking PEN exposure to human disease.

No information is available on PEN in the New Zealand food supply. The main producing organisms are active in temperature climates and are probably present in New Zealand.

No estimates of dietary exposure are available.

13.6.2 Commentary on risk management options

No specific risk management measures for control of PEN were identified.

13.6.3 Data gaps

Information on the prevalence of PEN-producing organisms and the toxin itself in New Zealand foods would aid in risk assessment.

14 RANKING RISKS ASSOCIATED WITH DIETARY MYCOTOXIN EXPOSURE IN NEW ZEALAND

While it is not possible to attribute individual cases of human disease in New Zealand, information is available from which to consider the relative importance of risks due to various mycotoxins in New Zealand. Such a ranking exercise needs to consider:

- The likely adverse health effects due to exposure to each mycotoxin, and the seriousness of those effects.
- The weight of evidence for a causative role of the mycotoxin in the adverse health effect observed.
- The exposure level or dose at which the mycotoxin can exert its toxic effects. A surrogate for this exposure level is the tolerable daily intake or equivalent for each mycotoxin.
- The proximity of New Zealand exposure estimates to tolerable limits and the need for sufficient data to make those estimates realistic. This would include information on imported foods.

Table 27 summarises information reviewed in this risk profile relevant to risk ranking.

While the information in Table 27 contains considerable uncertainties the following general comments can be made:

- There is consistent evidence to support a causal link between chronic aflatoxin exposure and serious human disease (primary liver cancer). Exposure levels in New Zealand are low and represent a very low level of risk. Improved information on aflatoxin contamination of spices would assist further characterisation of the risks associated with aflatoxins in New Zealand.
- There is some evidence to support a link between human kidney disease and exposure to OTA, although little has happened in the last decade to strengthen the evidence base. Further work is required to establish a causal relationship. Dietary exposure to OTA in New Zealand is low.
- While there is good evidence for T2/HT2 toxins causing human disease, there is little evidence that these toxins occur in New Zealand or Australian cereal crops. Information from a recently completed surveillance project supports this observation.
- There is very good evidence that the trichothecene mycotoxins, DON, is able to cause outbreaks of gastrointestinal disease in humans. A recent assessment concluded that New Zealanders' exposure to DON is low.
- While there is a body of information linking fumonisin exposure to serious human diseases, there is virtually no information on the exposure of New Zealanders to these mycotoxins. The *Fusarium* fungal species that produce fumonisins have only rarely been reported in New Zealand and New Zealanders only consume relatively small quantities of the food most commonly contaminated (maize). However, the emergence of wheat and fruit products as potential sources of fumonisins and the discovery of *Aspergillus niger* as a potential fumonisin-producer means there is previously unrecognised potential for New Zealanders to be exposed to fumonisins.
- Evidence linking ZEA exposure to human disease states is fragmentary and inconsistent. However, the exposure of New Zealanders to ZEA may be significant when compared to tolerable daily intakes. Further investigation of the role of wheat-based foods in ZEA dietary exposure in New Zealand would help to clarify this issue.

The emergence of analytical techniques capable of measuring metabolites of ZEA has highlighted that earlier exposure assessments may have significantly underestimated dietary ZEA exposure.

- Ergotism represents a serious and real human health risk. Recent events have highlighted that ergot may occur in New Zealand cereals at levels high enough to result in shipment rejections. Ergot in cereals is regulated in New Zealand and there is currently a complete lack of information on EAs in our food supply.
- While toxicological experiments have raised concerns about PAT exposure, there is no evidence linking PAT exposure to human disease. However, high levels of PAT contamination are indicative of poor manufacturing practice and a level of ongoing monitoring is probably justified.
- For the remaining mycotoxins considered in this risk profile (CIT, CPA, STC, *Alternaria* toxins, PEN) there is little evidence linking their presence in the food supply to human disease. The co-occurrence of these toxins in foods with better characterised toxins (e.g. CPA and STC co-occurring with aflatoxins) suggests that some level of control on exposure to these toxins will occur through existing mycotoxin control measures.

Ranking of risk across different mycotoxins will involve a degree of subjectivity, as there is no absolute measure for the relative seriousness of different health effects. The development of the benchmark dose approach is useful in this regard.

The MPI mycotoxin work programme since the previous version of this risk profile has better characterised risks associated with priority mycotoxin (aflatoxins, OTA, trichothecene mycotoxins) and risks associated with these toxins are currently low in New Zealand. Amongst toxins reviewed for the first time in this risk profile (CIT, CPA, STC, *Alternaria* toxins, PEN) no issues of immediate concern were identified. There is still a lack of New Zealand specific information on which to assess the potential risks associated with fumonisin, EA and ZEA exposure. These topics are the most obvious next tier candidates for mycotoxin surveillance projects.

Table 27: Risk ranking information for mycotoxins in the New Zealand food supply

Mycotoxin	Human health effects	Animal health effects	Weight of evidence[1]	Critical exposure limit (ng/kg body weight/day)	Mean New Zealand dietary exposure ng/kg body weight/day	Major contributing foods
Aflatoxins (AFB_1)	Primary liver cancer	Hepatocellular and/or cholangiocellular liver tumours	High	140-310 ($BMDL_{10}$)	0.09-0.36	Spices, peanuts
Ochratoxin A	Nephrotoxicity	Nephrotoxicity	Medium-low	14.3 (PMTDI)[2] 17.1 (TDI)[2] 15,000-25,000 ($BMDL_{10}$)	0.28-3.17	Bread, cereals, pasta/noodles
Deoxynivalenol	Gastrointestinal symptoms	General toxicity, haematotoxicity, immunotoxicity	High	1000 (TDI, PMTDI) 8000 (ARfD)	17-77	Bread, pasta/noodles, coffee, beer
Nivalenol	-	General toxicity, haematotoxicity, immunotoxicity	Medium	1200 (TDI) 350,000 ($BMDL_5$)	4-24	Bread, pasta/noodles
T2/HT2 toxin	Gastrointestinal symptoms, haematotoxicity	General toxicity, haematotoxicity, immunotoxicity	High	100 (TDI) 21,700 ($BMDL_{10}$)	<1	
Fumonisins	Gastrointestinal symptoms, oesophageal cancer, liver cancer, neural tube defects	Nephrotoxicity, carcinogenicity	Medium	2000 (PMTDI) 63,000 ($BMDL_5$)	2-720[3]	Maize
Zearalenone	Early puberty, hormone-dependent cancers	Hormonal effects	Low	500 (PMTDI) 250 (TDI) 6,390,000 ($BMDL_{10}$)	2-100[3]	Grains, bread and bakery products, vegetable oil
Ergot alkaloids	Ergotism (gangrenous or convulsive)		High	600 (TDI) 1000 (ARfD) 330,000 ($BMDL_{10}$)	7-173[3,4]	Rye, wheat, barley, triticale

Mycotoxin	Human health effects	Animal health effects	Weight of evidence[1]	Critical exposure limit (ng/kg body weight/day)	Mean New Zealand dietary exposure ng/kg body weight/day	Major contributing foods
Patulin	-	Reduced weight gain, immunotoxicity	Low	400 (PMTDI)	4-50	Apple juice and apple products
Citrinin	Nephrotoxicity	Nephrotoxicity	Low	200 (level of 'no concern')	NA	NA
Cyclopiazonic acid	Sleepiness, tremors, giddiness	Effects (lesions, necrosis) on striated muscle, liver, kidney and spleen	Low	10,000 (ADI)	NA	NA
Sterigmatocystin	Liver cancer	Liver cancer	Low	160,000 ($BMDL_{10}$)	NA	NA
Alternaria toxins	Unknown	Unknown	Low	AOH 2.5 (TTC) AME 2.5 (TTC) TeA 1500 (TTC) TEN 1500 (TTC)	1.9-37[3] 0.9-4.7 36-125 0.01-5.1	Grains and grain products Fruit and fruit products Vegetables and vegetable products Vegetable oils
Penicillic acid	Unknown	Unknown	Low	NA	NA	NA

[1] The weight of evidence assessment is subjective, but is based on the strength and consistency of associations between mycotoxin exposure and specified human disease. The consistency between human and animal disease associations is also considered. A definitive cause and effect relationship between the toxin and human disease (e.g. ergotism) is classified as a high weight of evidence, while failure to identify a human disease state (e.g. patulin) is classified as a low weight of evidence.
[2] The health-based exposure limits for ochratoxin A are weekly limits, but have been recalculated here as daily limits for consistency with limits for other toxins
[3] In the absence of New Zealand or Australian-specific exposure estimates the range of European-derived exposure estimates are included as a reference point.
[4] Based on the sum of at least six ergot alkaloids

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APPENDIX 1: FUNGAL SPECIES PRODUCING MYCOTOXINS DISCUSSED IN THIS DOCUMENT

Genus	Species	Major mycotoxin(s) produced	Other mycotoxin(s) reported
Aspergillus	*flavus*	AFB_1, AFB_2	CPA, STC
	parasiticus	AFB_1, AFB_2, AFG_1, AFG_2	STC
	nomius	AFB_1, AFB_2, AFG_1, AFG_2	
	tamarii	CPA	
	ochraceus	OTA	PEN
	carbonarius	OTA	
	niger	OTA	FB_2, FB_4
	oryzae	CPA	
	versicolor	CPA, STC	
	nidulans	STC	
Penicillium	*verrucosum*	OTA	CIT
	expansum	PAT	CIT
	citrinum	CIT, CPA	
	camemberti	CPA	
	roqueforti	PEN	
	aurantiogriseum	PEN	
Fusarium	*graminearum*	DON, NIV, ZEA	
	culmorum	DON, NIV, ZEA	
	crookwellense	NIV, ZEA	
	equiseti	ZEA, T2, HT2	
	cerealis	ZEA	
	semitectum	ZEA	T2
	poae	T2, HT2, NIV	
	sporotrichioides	T2, HT2	ZEA
	acuminatum	T2, HT2	ZEA
	verticillioides	FB_1, FB_2	FB_3
	proliferatum	FB_1, FB_2, FB_3	
Alternaria	*alternata*	*Alternaria* toxins	
Claviceps	*purpurea*	Ergot alkaloids (group I and II)	
	fusiformis	Ergot alkaloids (group III)	

AFB_1, AFB_2, AFG_1, AFG_2	aflatoxins B_1, B_2, G_1, G_2
OTA	ochratoxin A
PAT	patulin
DON	deoxynivalenol
NIV	nivalenol
T2	T-2 toxin
HT2	HT-2 toxin
ZEA	zearalenone
FB_1, FB_2, FB_3, FB_4	fumonisin B_1, B_2, B_3, B_4
CIT	citrinin

CPA	cyclopiazonic acid
STC	sterigmatocystin
PEN	penicillic acid

APPENDIX 2: ACRONYMS AND ABBREVIATIONS USED IN THIS REPORT

3ADON	3-acetyl-deoxynivalenol
15ADON	3-acetyl-deoxynivalenol
α-ZAL	α-zearalanol
β-ZAL	β-zearalanol
α-ZOL	α-zearalenol
β-ZOL	β-zearalenol
AAL toxins	*Alternaria alternata* f. sp. *Lycopersici* toxins
ADI	Acceptable Daily Intake
AFB_1, AFB_2, AFG_1, AFG_2, AFM_1, AFM_2	Aflatoxin B_1, aflatoxin B_2, aflatoxin G_1, aflatoxin G_2, aflatoxin M_1, aflatoxin M_2
ALT	Altenuene
AME	Alternariol methyl ester
AOH	Alternariol
ARF	Acute renal failure
ARfD	Acute reference dose
ATA	Alimentary toxic aleukia
ATX-I, ATX-II, ATX-III	Altertoxin I, altertoxin II, altertoxin III
BEN	Balkan endemic nephropathy
BMD_x	Benchmark dose producing a response x% above background
$BMDL_x$	The lower 95^{th} percentile confidence limit of BMD_x
CAST	Council for Agriculture and Technology
CCCF	Codex Committee on Contaminants in Food
CED	Critical effects dose
CER	Cost effectiveness ratio
CIN	Chronic interstitial nephropathy
CIT	Citrinin
CONTAM	EFSA Panel on Contaminants in the food chain
COP	Code of practice
CPA	Cyclopiazonic acid
CPP	Central precocious puberty
DAS	Diacetoxyscirpenol
DNA	Deoxyribonucleic acid
DON	Deoxynivalenol
DON-3-G	Deoxynivalenol-3-glucoside
EA	Ergot alkaloids
EFSA	European Food Safety Authority
EOW	Electrolysed oxidised water
ESRD	End-stage renal disease
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FAR	Foundation for Arable Research
FB_1, FB_2, FB_3, FB_4	Fumonisin B_1, fumonisin B_2, fumonisin B_3, fumonisin B_4
FFQ	Food frequency questionnaire
FHB	*Fusarium* head blight

FSA	United Kingdom Food Standards Agency
FSANZ	Food Standards Australia New Zealand
FSCJ	Food Safety Council of Japan
FX	Fusarenon X
GAP	Good agricultural practice
GEMS	Global Environmental Monitoring Systems
GMP	Good manufacturing practice
HACCP	Hazard Analysis Critical Control Point
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HFB	Hydrolysed fumonisin B
HPLC	High performance (or pressure) liquid chromatography
HT2	HT-2 toxin
IARC	International Agency for Cancer Research
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LB	Lower bound
LC-MS	Liquid chromatography-mass spectrometry
LOD, LOQ	Limit of detection, limit of quantification
LOEL	Lowest observed effect level
MAS	Monoacetoxyscirpenol
MeOTA	Methyl-ochratoxin A
ML	Maximum limit
MoE	Margin of exposure
MPI	New Zealand Ministry for Primary Industries
NACMA	Australian National Association of Commodity Marketing Agencies
NCCP	New Zealand dairy industry National Chemical Contaminants Programme
NEO	Neosolaniol
NIV	Nivalenol
NOAEL	No observed adverse effect level
NOEL	No observed effect level
OC	Oesophageal cancer
OIV	International Organization of Vine and Wine
OTA, OTB, OTC	Ochratoxin A, ochratoxin B, ochratoxin C
PAR	Population attributable risk
PAT	Patulin
PCR	Polymerase chain reaction
PEN	Penicillic acid
PLC	Primary liver cancer
PMTDI	Provisional Maximum Tolerable Daily Intake
PMTWI	Provisional Maximum Tolerable Weekly Intake
PTWI	Provisional Tolerable Weekly Intake
QRAM	Quantitative risk assessment model
RMF	Risk Management Framework
RMR	Red mould rice
RNA	Ribonucleic acid

SAR	Structure acitivity relationship
STC	Sterigmatocystin
T2	T-2 toxin
TDI	Tolerable Daily Intake
TeA	Tenuazonic acid
TEN	Tentoxin
TWI	Tolerable Weekly Intake
UB	Upper bound
WBC	White blood cell
WHO	World Health Organization
ZEA	Zearalenone