New Zealand Food Safety
Haumaru Kai Aotearoa

CONTAMINANTS IN ANIMAL FEED

New Zealand Food Safety Technical Paper No: 2020/21

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ISBN No: 978-1-99-002550-1 (online)
ISSN No: 2624-022X (online)

July 2020

New Zealand Government

Ministry for Primary Industries
Manatū Ahu Matua

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Scientific Interpretative Summary

This Scientific Interpretative Summary is prepared by New Zealand Food Safety (NZFS) risk assessors to provide context to the following report for MPI risk managers and external readers.

FW19009 Scoping document for risk of contaminants in animal feeds

New Zealand Food Safety (NZFS) contracted the Institute of Environmental Science and Research Ltd (ESR) to review the contemporary information on the presence, and potential risks to human and animal health, of chemical contaminants that are not otherwise regulated in fodder and forage.

Incidences of animal poisoning were identified as a result of consumption of plant and fungal toxins in feed material, and to a much lower extent from toxic element contamination in soil or non-feed sources. However, for many of the contaminants there was no evidence that toxicity would be a concern for New Zealand livestock.

The natural plant and fungal toxins were not expected to transfer to animal tissue to any great extent and consequently are unlikely to present a health risk to consumers of meat and milk. An exception was aflatoxin (aflatoxin B_1), where importation of contaminated supplementary feed could result in some transfer of its metabolite aflatoxin M_1 into milk. New Zealand Food Safety currently regularly monitor aflatoxin in milk as part of the National Chemical Contaminants Programme.

Animal tissue levels of contaminant elements will reflect those in the feed and also in grazing plot soils. Cadmium as a contaminant of phosphate fertilisers can build up in arable and pasture soils overtime with regular use. Cadmium accumulates in animal offal (liver and kidneys) after consumption of feed and soil in contaminated areas). To avoid high cadmium levels entering the New Zealand food supply, offal from animals older than 30 months cannot be sold. In 2019 MPI refreshed its strategy to ensure that cadmium in rural production poses minimal risks to health, trade, land use flexibility and the environment over the next 100 years.

Where available for the other contaminants, the evidence indicates the levels of contamination in the New Zealand feed environment are low by world standards.

This report provides a useful resource to aid recognition of and provide information to support management of future incidents of feed contamination in New Zealand.

Science for Communities

CONTAMINANTS IN ANIMAL FEED

June 2019

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PREPARED FOR: Ministry for Primary Industries, project code CFS/18/01, Scoping document for risk of contaminants in animal feeds, as part of the overall contract for scientific services

CLIENT REPORT No: FW19009

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CONTENTS

LIST OF TABLES

EXECUTIVE SUMMARY

The presence of contaminants (chemical, microbiological, radiological, and physical) in animal feed can constitute a risk to the animals and to humans consuming food products from the animals. In recent years, there have been several outbreaks of livestock toxicity resulting from natural contaminants (phytotoxins and mycotoxins) in feed crops. Incidents have also occurred in which contamination of animal feed has resulted in contamination of the human food chain. The current report was commissioned to provide a resource to aid recognition of and provide information to support management of incidents of feed contamination in New Zealand.

Two primary issues were addressed in relation to chemical contaminants of animal forage in New Zealand:

- The potential for hazards to elicit adverse health outcomes in food-producing animals; and
- The potential for hazards to be transferred to the human food chain and contribute markedly to human exposure.

With respect to the first of these issues, adverse health effects in animals in New Zealand have predominantly been caused by ingestion of unintended plant material (e.g. acorns, ragwort) or intended plant material containing unexpected levels of inherent toxic constituents (e.g. brassicas). A second class of feed-associated exposures causing harm in livestock animals are fungal contaminants of feed, with toxins produced by *Claviceps purpurea* and *Pithomyces chartarum* of particular note. Occasional cases of contaminant element intoxication have been reported in New Zealand, although some of these are related to non-feed sources (e.g. cattle eating old car batteries). There is no evidence of adverse health effects in New Zealand livestock from exposure to environmental contaminants or radionuclides and contamination levels of these hazards in the feed supply appear to be low.

There is little evidence that plant toxins are transferred to foods of animal origin to any great extent. Similarly, for most mycotoxins, only a small proportion of the animal exposure dose is transferred to tissues or products used as animal foods. The exception is aflatoxins, where 2-6% of ingested aflatoxin B_1 (AFB_1) may be excreted in milk as aflatoxin M_1 (AFM_1). However, New Zealand livestock will only be exposed to AFB_1 through consumption of imported supplementary feed material.

Levels of contaminant elements in foods of animal origin will generally reflect levels in feed and pasture soil. There is potential for food of animal origin to contribute to human exposure to contaminant elements if the feed environment is contaminated. Soil concentrations of cadmium are known to be elevated, due to long-term use of phosphate fertilisers based on material from Nauru Island. This mainly impacts on the cadmium content of offal (liver and kidney) and appears to have little impact on the cadmium content of muscle meat and milk.

While lipophilic environmental contaminants can transfer into the fatty component of foods of animal origin at quite high rates, levels of contamination in the New Zealand feed environment are low by world standards, where this information is available. Similarly, levels of contamination of the New Zealand environment with radionuclides is generally considered to be low.

1. INTRODUCTION

The presence of contaminants (chemical, microbiological, radiological, physical) in animal feed can constitute a risk to the animals and to humans consuming food products from the animals. In recent years there have been several outbreaks of livestock toxicity resulting from natural contaminants (phytotoxins and mycotoxins) in feed crops. Incidents have also occurred in which contamination of animal feed has resulted in contamination of the human food chain. The current report was commissioned to provide a resource to aid recognition of and provide information to support management of incidents of feed contamination in New Zealand.

1.1 SCOPE OF THE STUDY

1.1.1 Hazards

A joint FAO/WHO expert meeting was convened in 2015, which identified the following categories of risk substances that may be associated with animal feed (FAO/WHO, 2015):

- Persistent organic pollutants (dioxins and PCBs)
- Veterinary drug residues
- Organochlorine and other pesticides
- Potentially toxic elements (arsenic, cadmium, lead, mercury, selenium, copper, nickel and chromium)
- Mycotoxins
- Plant toxins
- Other potential and emerging chemical hazards (PBDEs, PFAS)
- Biological hazards
- Physical hazards

The primary focus of the consultation was risks to human health, with risks to animal health a secondary concern.

The current study is intended to address chemical hazards in feed that are not otherwise regulated. Consequently, the current study does not consider risk substances under the categories veterinary drug residues, pesticides, biological hazards or physical hazards. While some older organochlorine pesticides, such as DDT and dieldrin, are increasingly being viewed as persistent organic pollutants, their residues are regulated in New Zealand and they were not included in the current study. The categories of persistent organic pollutants and other potential and emerging chemical hazards were considered under a single category of environmental contaminants in the current report.

1.1.2 Feed types

Three broad categories of feed were identified:

- Pasture and forage and associated products, such as hay and silage
- Supplementary feed, such as copra and palm kernel expeller
- Compound formulated feed

An alternative and simpler classification of animal feeds is in terms of fodder and forage, with fodder being any feed brought to the animal, while forage is plant material eaten by grazing stock.

Discussions with MPI indicated that compound feed is outside the scope of the current study, as compound feed is currently regulated. Therefore, the focus of this report is

restricted to forage (in the wider sense, including forage products) and minimally processed supplementary feeds, such as palm kernel expeller/extract.

1.1.3 Animal species/food types considered

The definition of the feed categories largely dictates the animal species and the food types to be considered. In New Zealand, forage is predominantly consumed by ruminant species (bovines, ovines, caprines, and cervines) and, to a lesser extent porcines. The associated food products are muscle and offal meats and milk.

1.1.4 Information collected

Given the wide-ranging nature of the current study, some boundaries on the information to be collected and presented are required. For each hazard, information was sought to provide:

- A brief summary of the hazard and how it may come to be present in animal feed.
- Evidence for toxicity to animals and/or humans, including usual signs and symptoms and mechanism of toxicity
- Information related to the hazard in animal feed in New Zealand (occurrence, concentrations), providing evidence for animal and human exposure. Any information on transfer factors was included.
- New Zealand-specific case/incident reports. In many cases, New Zealand-specific reports were not available. In these cases, reports from other countries were considered.
- Regulatory limits in animal feed and human foods of animal origin.

In the context of the current report, transfer refers to the carry-over or transfer of contaminants in feed for food-producing animals into foods for human consumption, such as milk, eggs and meat (JECFA, 2017b). The rate of transfer may be expressed as a transfer factor or transfer rate, although the factors are not necessarily calculated in the same manner. In some cases, the transfer factor is calculated as the concentration in the target tissue or product compared to the concentration in the animal feed, expressed as a percentage or proportion. In other cases, the transfer factor may be expressed as the total amount of the contaminant in the tissue or products compared to the total dose administered. Where source material was explicit about the basis for transfer factors, this has been included in the current report.

2. PLANT TOXINS

2.1 CLINICAL FORAGE-ASSOCIATED ANIMAL TOXICITY IN NEW ZEALAND

The Surveillance journal, published by the Ministry for Primary Industries, includes quarterly summaries of animal diagnostic cases, including infections and intoxications.[1] These reports were investigated for the period 2006-2018 and incidents of plant-based intoxications recorded for food-producing animal species (bovine, ovine, porcine). No porcine incidents were reported during this period. Intoxication causes of more than one incident during this period are summarised in Table 1.

Table 1. Plant-based causes of animal intoxications in New Zealand, 2006-2018

Intoxication source	Intoxication cause (where given)	Number of incidents	
		Bovine	Ovine
Acorn/oak		25	5
Brassica (kale, turnip, swede, rape)	Glucosinolate toxicity S-methyl cysteine sulphoxide anaemia Not specified	13 6 9	- 2 -
Various, including kale, plantain, rape, rye grass, turnip and pasture	Nitrate toxicity	17	5
Palm kernel expeller	Copper toxicity	10	-
Fathen (*Chemopodium album*)	Oxalate toxicity	6	2
Swamp grass (*Poa aquatic*), linseed, peach tree leaves	Cyanide toxicity	5	1
Tutu (*Coraria arborea*)	Tutin toxicity	3	3
Redroot (*Amaranthus powellii, A. retroflexus*)		3	2
Staggerweed (*Stachys arvensis*)		-	2
Yarr or spurrey (*Spergula arvensis*)		2	-
Yew (*Taxus baccata*)		2	-
Onion		2	-
Ragwort (*Senecio jacobaea*)	Pyrrolizidine alkaloid toxicity	1	1
Sorghum		-	2

Single incidents were reported for hemlock (*Conium maculatum*), sorrel (*Rumex sp.*), black nightshade (*Solanum nigrum*), *Cestrum* spp., foxglove (*Digitalis purpurea*), goat's rue (*Galega officinalis*), hairy vetch (*Vicia villosa*), Himalayan honeysuckle (*Leycesteria Formosa*), horse chestnut (*Aesculus hippocastanum*), inkweed (*Phytolacca octandra*), kowhai (*Sophora microphylla*), ngaio (*Myoporum laetum*), oleander (*Nerium oleander*), poroporo (*Solanum laciniatum*), and smooth witch grass (*Panicum dichotomiflorum*).

The identified plant materials are covered in the following sections.

2.2 ACORN/OAK TOXICITY

While toxicity to ruminants in New Zealand is usually reported as due to consumption of acorns, internationally toxicity due to consumption of oak leaves and buds has also been reported. Toxicity appears to occur when other sources of feed are restricted and where animals have access to oak trees.

[1] http://www.sciquest.org.nz/surveillance Accessed 10 September 2018

2.2.1 Animal toxicity

Clinical signs of oak poisoning occur 3-7 days after consumption of oak leaves or acorns (Blakeley, 2018). The toxic agent is believed to be a hydrolysis product(s) of hydrolysable tannins; possibly pyrogallol, gallic acid or tannic acid (Blakeley, 2018). Analytical tests for pyrogallol and gallic acid have been applied as diagnostic indicators of oak toxicosis (Tor *et al.*, 1996). The toxic agent is believed to bind and precipitate proteins, resulting in gastrointestinal and renal dysfunction (Blakeley, 2018; Cortinovis and Caloni, 2013). However, it has also been suggested that the impact of antimicrobial tannins on rumen microflora may play a role in the aetiology of the disease (Belenguer *et al.*, 2010). While the condition is more common in cattle, intoxications in sheep (Eroksuz *et al.*, 2013) and moose (Flaoyen *et al.*, 1999) have been reported.

Affected animals develop anorexia, depression, rumen stasis and constipation, followed by mucoid to haemorrhagic diarrhoea, dehydration, colic, polyuria and subcutaneous oedema of the ventral area (Cortinovis and Caloni, 2013). Renal effects are characterised by necrosis of the proximal tubules and perirenal oedema (Blakeley, 2018).

2.2.2 Transfer of toxic agents to edible tissues and products

No information was found on the transfer of the suspected toxic agents from acorns or oak leaves to foods of animal origin.

2.2.3 Human toxicity

While tannins may have anti-nutritional properties in monogastric species, due to their ability to interact with proteins (D'Mello *et al.*, 1991), they do not appear to be toxic. A toxicological study in which oak-flavoured milk was fed to rats did not detect any adverse effects after 96 days of administration (Azorin-Ortuno *et al.*, 2008). Acorn flour is used as a human food (Rybicka and Gliszczynska-Swiglo, 2017).

2.2.4 New Zealand data

Acorns and oak leaves are not an intended ruminant food source in New Zealand.

2.3 BRASSICA GLUCOSINOLATE TOXICITY

Glucosinolates are sulphur-containing glucosides occurring particularly in brassica vegetables (Heaney and Fenwick, 1995). When plant tissue is broken down, such as during animal feeding, glucosinolates are broken down by myrosinase enzymes to produce isothiocyanates, nitriles, oxazolidnethiones, hydroxynitriles or epithionitriles.

2.3.1 Animal toxicity

Isothiocyanates and oxazolidnethiones are known to compete for iodine, resulting in impairment of thyroid function (EFSA, 2008a). Clinical signs secondary to hypothyroidism following exposure to toxic concentrations of glucosinolates, include impairment of growth, reduced feed conversion and impairment of fertility and reproduction. In addition, irritation of the gastrointestinal tract followed by local necroses, hepatotoxicity and nephrotoxicity have been observed, commonly attributed to the presence of nitrile metabolites. (EFSA, 2008a).

While hepatogenous photosensitisation has been reported as a common clinical sign of brassica toxicity in cattle in Australia and New Zealand (Morton and Campbell, 1997), a mechanism for this being related to glucosinolate exposure has not been confirmed, although it has been suggested that nitriles or epithionitriles may be the causative agents, based on their ability to cause liver toxicity in rats (Collett *et al.*, 2014).

In the winter of 2014, there was a major outbreak of illness and deaths amongst dairy cattle in Southland and South Otago, associated with consumption of swedes (Dalley *et al.*, 2015). Illness was particularly associated with stock grazing on herbicide resistant (HT®) swedes; a mutagenesis-derived cultivar. Haematology of affected animals revealed elevated blood

levels of liver enzymes, indicative of liver damage. Necropsy was carried out on two affected animals, with carcasses severely jaundiced and livers enlarged. Photosensitivity and reproductive problems were also frequently reported in affected animals.

Monogastric species, such as pigs, and pre-ruminant cattle and sheep (young calves and lambs) appear to be more sensitive to glucosinolate toxicity than animals with a fully-developed rumen (EFSA, 2008a).

2.3.2 Transfer of toxic agents to edible tissues and products

Most of the studies of transfer of glucosinolates and glucosinolate metabolites into animal tissues and animal products are rather old (1970s and 1980s).

Cattle were fed rapeseed meal containing 20.5 or 36.2 mmol/kg of glucosinolate (Papas *et al.*, 1979). While these concentrations were sufficient to alter the thyroid function in exposed animals, no glucosinolates, isothiocyanates or vinyl oxazolidinethione were detectable in milk from exposed animals. Small amounts of nitrile were detectable in milk from animals receiving the high-glucosinolate feed, but not in animals receiving the low-glucosinolate feed. Inorganic thiocyanate was detected in milk (28.6 and 34.9 μmol/L, respectively).

In a German study, summarised in Mawson *et al.* (1995), cattle were fed diets containing up to 3.9% of a rapeseed extract cake, containing 6 g/kg of the glucosinolate progoitrin. At the highest inclusion level, the metabolite of progoitrin, goitrin, was detected in milk at a concentration of 707 μg/L, representing an approximate 0.1% transfer of the parent glucosinolate, on a concentration basis.

No studies were found on transfer of glucosinolates or their metabolites to edible tissues (meat or offal).

EFSA concluded that human exposure to glucosinolates due to transfer from animal feed would be negligible compared to exposure due to brassica vegetables in the human diet (EFSA, 2008a).

2.3.3 Human toxicity

No data were found on the toxicity of glucosinolates, or their breakdown products, in humans.

Neither liver nor thyroid toxicities were associated with *Brassica* or glucosinolate ingestion in two human clinical trials over a period of four weeks (Heaney and Fenwick, 1995; Shapiro *et al.*, 2006). In one study, volunteers consumed cooked Brussels sprouts with a progoitrin (2-hydroxybut-3-enyl glucosinolate) content equivalent to 40 mg/day goitrin for four weeks (Heaney and Fenwick, 1995). In the more recent study, doses were either 25 or 100 μmol of glucoraphanin (4-methylsulphinylbutyl glucosinolate) equivalent to approximately 11 or 46 mg/day for seven days (Shapiro *et al.*, 2006).

A systematic review of adverse effects associated with cruciferous vegetable intake identified immunological reactions (allergy and hypersensitivity) and altered pharmaceutical metabolism, but not effects on thyroid or liver function (Scott *et al.*, 2012).

Glucosinolate metabolites, particularly isothiocyanates have been proposed as potential anti-cancer agents. Epidemiological studies have identified negative associations between cruciferous vegetable or glucosinolate intake and risk of benign prostatic hyperplasia (Eichholzer *et al.*, 2012), prostate cancer (Steinbrecher *et al.*, 2010), breast cancer (Fowke *et al.*, 2003; Zhang *et al.*, 2018), and colorectal cancer (Seow *et al.*, 2002). A large prospective cohort study identified a weak, but significant positive association between glucosinolate intake and coronary heart disease risk (odds ratio = 1.09, 95% CI 1.01, 1.17) (Ma *et al.*, 2018).

2.3.4 Evidence of glucosinolates in the New Zealand feed supply

As part of an investigation of an outbreak of illness and deaths amongst dairy cattle in Southland and South Otago, swede plants were samples and analysed for 28 glucosinolates (Dalley *et al.*, 2015). For all swede plants analysed, the total glucosinolate content was highest in the upper stem (mean = 47 μmol/g dry weight), followed by flowers (mean = 45 μmol/g dry weight) and the upper leaves (42 μmol/g dry weight). The lowest mean concentration was in the bulb (20 μmol/g dry weight). A herbicide tolerant cultivar (HT®) was found to have higher mean total glucosinolate concentrations across all plant parts than non-HT cultivars. These differences were most pronounced in the aerial parts of the plant, with the mean concentration in the upper stem of HT plants (58 μmol/g dry weight) twice that in non-HT plants (29 μmol/g dry weight). Of the 21 glucosinolates detected in swedes, progoitrin was present at concentrations 10-50-fold higher than the next most abundant glucosinolate.

2.4 BRASSICA S-METHYL CYSTEINE SULPHOXIDE (SMCO) TOXICITY

SMCO can account for as much as 5% of the dry weight in brassica vegetables (Edmands *et al.*, 2013). While SMCO is an amino acid, it does not appear to enter the mammalian free amino acid pool and is not incorporated into any sulphur-containing macromolecules.

2.4.1 Animal toxicity

SMCO toxicity was initially associated with ruminants consuming a diet of kale (Smith, 1980). In most cases, a severe haemolytic anaemia develops within 7 to 21 days of the commencement of brassica feeding. Digestion of SMCO in the rumen results in production of large amounts of dimethyl disulphide, which appears to be the haemolytic agent (Smith, 1978). Studies in goats showed a near identical haemolytic response to SMCO or dimethyl disulphide or kale containing an equivalent amount of SMCO (Smith, 1980).

Intoxication may be apparent as a decrease in blood haemoglobin levels, haemoglobinuria, tachycardia, jaundice, loss of appetite, growth stasis, decreased milk production and a decreased conception rate may follow, as may liver and kidney damage (Edmands *et al.*, 2013). The characteristic haemoglobinuria has resulted in SMCO toxicity sometimes being known as ‘red water disease’.

2.4.2 Transfer of toxic agents to edible tissues and products

No information was found on transfer of SMCO or dimethyl disulphide into foods of animal origin**.** However, dimethyl disulphide concentrations in blood were reported to increase as the intake of SMCO from brassicas progressed (Earl and Smith, 1983). Concentrations were maximal at the haemolytic crisis, but declined sharply with the appearance of young red cells or reticulocytes, but again increased as the new cells matured. It is uncertain whether this would result in dimethyl disulphide being present in meat from affected animals.

2.4.3 Human toxicity

There is no evidence of human (or other monogastric species) toxicity associated with SMCO. It has been noted that cooking of cruciferous vegetables may result in substantial removal of SMCO, particularly into cooking water when vegetables are boiled.

2.4.4 Evidence of SMCO in the New Zealand feed supply

The SMCO content of brassica forage (kale, swede, rape, turnip, radish, and mustard) grown in Canterbury during the years 2001-2003 was determined (Stewart and Judson, 2004). Mean SMCO concentrations were in the range 0.6-7.4 g/kg dry weight (0.06-0.7% w/w). The highest concentration was determined in a samples of kale leaf fodder (20.2 g/kg dry weight; 2.02%).

As part of an investigation of an outbreak of illness and deaths amongst dairy cattle in Southland and South Otago, swede plants were samples and analysed for SMCO (Dalley *et al.*, 2015). Concentrations were highest in the aerial parts of the plants, with the upper stems containing a mean SMCO concentration of 6.2 μmol/g dry weight (0.9 g/kg dry weight). The bulbs contained a mean SMCO concentration of 2.7 μmol/g dry weight (0.4 g/kg dry weight).

2.5 NITRATE POISONING

A wide range of feed crops can accumulate high (>1% dry weight) concentrations of nitrate (NO_3^-), particularly during periods of rapid crop growth following fertilisation.

2.5.1 Animal toxicity

While nitrate can be a local irritant, nitrate poisoning results from the intestinal reduction of nitrate to nitrite (NO_2^-) (Christ *et al.*, 2018). Nitrite undergoes a redox reaction, oxidising the ferrous ion (Fe^{2+}) in haemoglobin to the ferric ion (Fe^{3+}), which in turn causes reduction of haemoglobin to methaemoglobin. Methaemoglobin is unable to transport oxygen to the tissues, resulting in tissue hypoxia.

Nitrate poisoning has been reported to be common in grazing ruminants in New Zealand (Parton and Bruere, 2002). Cattle appear to be more susceptible than sheep. Pigs appear to be the most susceptible domestic animals.

Clinical signs include scour, weakness, muscle tremors, excessive salivation, cyanosis, mouth breathing and may progress to collapse, coma and death (NADIS, 2007). In post-mortem cases a diagnosis of nitrate poisoning is supported by high nitrate concentrations in the aqueous humour (eye fluid) and brown coloured blood.

2.5.2 Transfer of toxic agents to edible tissues and products

Very little information is available on transfer of nitrate or nitrite to foods of animal origin (EFSA, 2009d).

Dosing of cattle with a single dose of 150 g KNO_3 result in an increase in milk nitrate two hours after dosing, with a concentration of 34.6 mg/L (Baranova *et al.*, 1993). Nitrate was still elevated in milk taken 38 hours after dosing, but not in milk taken at 50 hours after dosing. Nitrite was not detected in any milk samples analysed.

Nitrate and nitrite were analysed for in pig meat samples (n = 120), as well as associated feed and water samples (Eleftheriadou *et al.*, 2002). Nitrite was not detected in any samples. Nitrate in meat was in the range 7.5-15.8 mg/kg; concentrations described as very low. Nitrate in meat was not correlated with nitrate in feed.

2.5.3 Human toxicity

In humans, the toxic effects of nitrate are due to its endogenous conversion to nitrite. Two adverse effects have been associated with nitrate exposure; methaemoglobinaemia and cancer (various). For methaemoglobinaemia, toxicity is due to the redox reaction between nitrite and haemoglobin. Nitrite may also combine with secondary or tertiary amines to form N-nitroso derivatives. Certain N-nitroso compounds have been shown to produce cancers in a wide range of laboratory animals.

EFSA reviewed studies examining associations between nitrate exposure and these two endpoints (EFSA, 2008c). Evidence for an association between dietary nitrate exposure and methaemoglobinaemia was described as equivocal. EFSA also concluded that “the evidence does not suggest that nitrate intake from diet or drinking water is associated with increased cancer risk”. However, two recent case-control have shown small, but statistically significant, increases in colorectal cancer risk associated with higher levels of water and dietary nitrate (Espejo-Herrera *et al.*, 2016; Schullehner *et al.*, 2018).

2.5.4 Evidence of nitrate in the New Zealand feed supply

A survey of pastures in the lower North Island reported that >90% contained nitrate at >1% dry weight (Hill, 1998). Concentrations >1% are generally considered sufficient to cause livestock poisoning.

The European Union specifies a maximum content of **nitrite** in feed materials of 15 mg/kg (12% moisture basis) (EC, 2002).

2.6 OXALATE POISONING

A number of plant species contain soluble oxalate, which can bind serum calcium, resulting in systemic hypocalcaemia (Cortinovis and Caloni, 2013). Plant species associated with oxalate poisoning in New Zealand include fat hen (*Chenopodium album*) and sorrel (*Rumex* spp.). Plant species may also contain insoluble oxalate, present as crystals of calcium oxalate.

2.6.1 Animals toxicity

Animal toxicity is usually associated with plants containing soluble oxalate (oxalic acid). Oxalate binds calcium, resulting in hypocalcaemia. Hypocalcaemia may also occur post-partum, due to reduced blood calcium levels at the onset of lactation. Post-partum hypocalcaemia is known as milk fever.

Early stages of hypocalcaemia are characterised by hypersensitivity and excitability, including restlessness, tremors, ear twitching and head bobbing. The condition then proceeds to recumbency, tachycardia, weakened heart contractions and peripheral pulses, dry muzzle, cold extremities and lowered body temperature.

Calcium oxalate can also crystallise in the renal tubules, causing necrosis, tubular obstruction and renal failure (Cortinovis and Caloni, 2013).

2.6.2 Transfer of toxic agents to edible tissues and products

No information was found on transfer of oxalate into foods of animal origin.

2.6.3 Human toxicity

Adverse reactions in humans following consumption of oxalate-containing plants depend on whether the oxalate is present in a soluble or insoluble form (Slaughter *et al.*, 2012). With plants that mainly contain insoluble calcium oxalate, the crystals may cause local irritation of the oral mucosa and occasionally vomiting. In some instances, intense burning pain and oedema of the mouth, tongue and throat may occur and may result in upper airway compromise and respiratory distress, due to oedema of the oropharynx (Slaughter *et al.*, 2012).

Exposure to soluble oxalate, usually due to consumption of rhubarb (*Rheum rhabarbarum*) leaves may result in systemic effects similar to those noted for animals; hypocalcaemia and renal dysfunction, due to crystallisation of calcium oxalate in the renal tubules (Slaughter *et al.*, 2012).

A summary of plant-associated enquiries to the New Zealand National Poisons Centre during the period 2003-2010 included four oxalate-containing plant species in the ten most enquired about species (Slaughter *et al.*, 2012). Three of these (arum lily, peace lily and taro) contain insoluble oxalate. However, there were 121 enquiries related to rhubarb, with three-quarters of enquiries related to children and all but one enquiry related to exposure through ingestion.

2.6.4 Evidence of oxalate in the New Zealand feed supply

While a number of papers have been published on the oxalate content of foods in New Zealand, no studies have specifically examined the oxalate content of animal feed.

A New Zealand review of the oxalate content of food, also included information on the oxalate content of some plants that may occasionally be consumed by livestock, including common sorrel (*Rumex acetosa*; mean 5000 mg/kg), *Chenopodium* spp. (11,000 mg/kg), purslane (*Portulaca olearacea*; 12,940 mg/kg), garden orach (*Atriplex hortensis*; 9000 mg/kg) and beet leaves (*Beta vulgaris*; 6100 mg/kg) (Noonan and Savage, 1999).

2.7 CYANIDE POISONING

More than 2000 plant species are believed to contain cyanogens (compounds with the potential to form hydrogen cyanide) (Davis, 1991). Cyanogenic glycosides account for at least 90% of the total cyanide-producing potential in most plant species. In New Zealand livestock, cyanide poisoning appears to be most commonly associated with swamp grass (*Poa aquatica*). Cyanogenic glycosides are also found in the leaves and seeds of plant species of the *Prunus* genus.

Enzymes capable of releasing cyanide from the glycoside (β-glucosidase) are present in plant material, physically isolated from the glycosides. During tissue disruption, such as during animal feeding, the glycosides and the enzyme are able to react. Additionally, some gut microflora contain β-glucosidase enzymes and are able to hydrolyse cyanogenic glycosides during their passage through the gut (EFSA, 2007).

All animal species are susceptible to cyanide poisoning (EFSA, 2007). Cyanide poisoning primarily occurs through inhibition of the mitochondrial enzyme cytochrome c oxidase. This results in disruption of the cellular energy production processes, as the cells of an organism are unable to create adenosine triphosphate (ATP), resulting in histotoxic hypoxia.

2.7.1 Animal toxicity

Ruminant animals have been reported to be more susceptible to cyanide poisoning due to exposure to cyanogenic glycosides than monogastric species (EFSA, 2007). Two reasons for this susceptibility have been suggested. The greater period of feed chewing in ruminants gives a greater opportunity for cyanide release through the action of plant β-glucosidase enzymes, and the microbial environment of the rumen provides additional opportunities for microbial hydrolysis of cyanogenic glycosides.

Acute intoxication may be characterised by salivation, staggering and somnolence and in more serious cases, trembling, gasping, prostration, convulsions and death (EFSA, 2007). The pupils may also be dilated and the pulse rapid. Necropsies have reported haemorrhage or congestion in the lungs, kidneys and heart.

Acute oral lethal doses in cattle and sheep have been reported to be about 2.0 mg/kg bw (EFSA, 2007).

Chronic intoxication results in decreased body weight, decreased T_3 concentrations and effects on the central nervous system, including effects on the brain and spinal column.

Adverse effects seen in animals are consistent with the known mode of action of cyanide. Hydrogen cyanide is a systemic toxin, interrupting cellular respiration by inhibiting the cytochrome oxidase enzyme and blocking electron transfer to oxygen, preventing the utilisation of oxygen to produce cellular energy. This results in accumulation of oxygen in tissues, while the impairment of oxygen metabolism means that metabolic processes cannot be satisfied. Tissues with high metabolic activity include those in the cardiovascular, respiratory and CNS systems (NZEPA, 2018).

The main detoxification product of cyanide, thiocyanate, can also interfere with iodine uptake by the thyroid gland, resulting in thyroid dysfunction (NZEPA, 2018).

In New Zealand, cases of ruminant cyanide poisoning have usually been confirmed by the presence of cyanide in the rumen.

2.7.2 Transfer of toxic agents to edible tissues and products

There is no evidence of accumulation of cyanogenic glycosides or cyanide in animal tissues (EFSA, 2007). Cyanogenic glycosides may be absorbed intact, followed by rapid urinary excretion, or hydrolysed to cyanide, which is metabolised rapidly and quantitatively to thiocyanate.

It is uncertain whether cyanide or cyanogenic glycosides are transferred to ruminant milk. Analysis of 50 commercial pasteurised milks, three UHT milks and several raw milk samples did not detect cyanide in freshly drawn or continuously refrigerated milk samples (Chikamoto *et al.*, 1983). However, in samples held at room temperature, cyanide concentrations reached 52 μg/L. It is uncertain whether this was due to hydrolysis of transferred cyanogenic glycosides or *de novo* formation of cyanide by bacteria present in the milk.

Petit (2010) reported that milk of cows fed 20% flaxseed hulls, containing the cyanogenic glycosides linustatin and neolinustatin, contained <0.03 mg/L of cyanide, as hydrocyanic acid.

In goats dosed with KCN (0, 1, 2 or 3 mg/kg bw/day) increased blood cyanide and thiocyanate concentrations were found in both dams and kids (Soto-Blanco and Gorniak, 2003). However, while these cyanide indicators remained fairly constant in dams over 90 days of lactation, the indicators were no longer apparent in kids after 90 days of lactation. These findings suggest that cyanide may be transferred to ruminant milk, although the degree of transfer was considered to be low.

The European Union specifies a maximum content of hydrocyanic acid in feed materials of 50 mg/kg (12% moisture basis) (EC, 2002). Higher limits are specified for linseed (250 mg/kg) and linseed cakes (350 mg/kg).

2.7.3 Human toxicity

Potential toxicity of cyanogenic glycosides arises from enzymatic degradation to produce hydrogen cyanide, resulting in acute cyanide poisoning. Clinical symptoms of acute cyanide poisoning include rapid respiration, drop in blood pressure, rapid pulse, headache, dizziness, vomiting, diarrhoea, mental confusion, stupor, blue discolouration of the skin due to lack of oxygen, twitching and convulsions (FSANZ, 2004; Speijers, 1993).

Several diseases are associated with chronic dietary intake of cyanogenic glycosides, although there is some debate over the causal relationships due to confounding nutritional factors (Davis, 1991; FSANZ, 2004; Speijers, 1993). For example, malnourished individuals appear to be more susceptible to the effects of cyanogenic glycosides. Populations with a reliance on cyanogenic foods, such as in African regions where cassava is a staple, have developed food preparation procedures that largely detoxify the food. However, the cyanogenic glycoside content of available food and adherence to detoxifying procedures are reported to be variable. Chronic diseases associated with dietary intake of cyanogenic glycosides include:

- Konzo is a motor neuron disease characterised by irreversible weakness in the legs. In severe cases, patients are not able to walk, and speech and arms may be affected. Konzo particularly affects children and women of childbearing age in East Africa in times of food shortage and is associated with a high and sustained intake of

cassava (*Manihot esculenta* Crantz) in combination with a low intake of protein (Davis, 1991; FSANZ, 2004).

- Tropical ataxic neuropathy (TAN) describes several neurological symptoms affecting the mouth, eyesight, hearing or gait of mostly older males and females. TAN is attributed to cyanide exposure from the chronic consumption of foods derived from cassava (FSANZ, 2004).
- Goitre and cretinism due to iodine deficiency can be exacerbated by chronic consumption of insufficiently processed cassava. Cyanogenic glycosides from cassava are detoxified to thiocyanate that competes with iodine in the thyroid, effectively increasing the dietary requirement for iodine (FSANZ, 2004).

2.8 TUTIN TOXICITY

Tutin is a neurotoxin produced by a New Zealand native plant, tutu (*Coriaria arborea*). The toxin occurs in the sap of the plant, but can become externalised as honeydew by feeding by passionvine hoppers (*Scolypopa australis*). Human intoxications have occurred through consumption of honey including collections of this honeydew. Animal intoxication occurs through consumption of the tutu plant (Parton and Bruere, 2002). All plant parts contain the toxin.

2.8.1 Animal toxicity

Little information is available on the animal toxicity of tutin, although it has been reported that during the pioneering period of New Zealand's history stock losses due to tutin poisoning could be as high as 75% (Hansford, 2014).

While tutin poisoning in livestock has been described as causing excitement, epileptiform convulsions, exhaustion and death, an outbreak of poisoning in sheep was characterised by a reluctance to move, apparent blindness and rapid respiration, followed by death (Ruakura Animal Health Laboratory, 1977). At necropsy, animals exhibited purple-coloured and consolidated lungs and red spots on the myocardium and peritoneal surfaces.

Diagnostic reports in the *Surveillance* publication have described blindness, circling, aggression, ataxia, foaming at the mouth, salivation, regurgitation.

2.8.2 Transfer of toxic agents to edible tissues and products

No information was found on the transfer of tutin to edible tissues of animal products, other than honey.

2.8.3 Human toxicity

Human toxicity from consumption of honey may potentially differ from animal toxicity, as the process of honeydew production converts some of the tutin to a hydroxylated metabolite, hyenanchin (FSANZ, 2014). Hyenanchin is present at concentrations approximately six-fold higher than those of tutin, but its toxicity appears to be appreciably lower. In addition, glycosides of tutin are also present, which appear to be hydrolysed *in vivo* to tutin, resulted in a delayed neurotoxicity (Fields *et al.*, 2014).

While most human cases of tutin intoxication result from consumption of contaminated honey, three cases were reported following consumption of the tutin berries (Belcher and Morton, 2013), while an earlier case resulted from drinking an infusion of tutu leaves (Chilvers, 1972).

Symptoms in humans have been reported to include gastrointestinal (diarrhoea and vomiting), neurological (dizziness, tremor, anxiety, excitement, confusion, amnesia, ataxia, tonic-clonic seizure), cardiovascular (tachycardia) and respiratory manifestations (Belcher and Morton, 2013; FSANZ, 2014). Fatalities appear to be due to respiratory complications.

2.8.4 Evidence of tutin in the New Zealand feed supply

Most attention has focused on determining the tutin content of contaminated honey. Lowe and White (1972) used a gas-liquid chromatography method to determine tutin in the tissues on seven *Coriaria* species. Concentrations were mostly higher in leaves than stems, with concentrations up to 0.23% on a dry weight basis detected.

2.9 PYRROLIZIDINE ALKALOID POISONING

Pyrrolizidine alkaloids (PAs) are toxins produced by an estimated 6000 plant species. More than 600 different PAs, mainly 1,2-unsaturated PAs and their associated nitrogen oxides (*N*-oxides) are known, and new PAs continue to be identified on a regular basis in both new and previously studied plant species. The main plant sources are the families Boraginaceae (all genera), Asteraceae (tribes Senecioneae and Eupatorieae) and Fabaceae (genus *Crotalaria*). Different plant species in these families produce characteristic mixtures of 1,2-unsaturated PAs and their saturated analogues and varying amounts of their corresponding *N*-oxides. PA-containing plants involved in livestock poisonings in New Zealand include ragwort (*Senecio jacobaea*) and viper's bugloss (*Echium vulgares*) (Parton and Bruere, 2002).

Laboratory studies have identified the liver as the most sensitive organ, with a number of 1,2-unsaturated PAs shown to be carcinogenic in rodents, primarily causing haemangiosarcomas in the liver. Carcinogenicity has not been investigated in case studies of animal or human poisoning with PAs.

2.9.1 Animal toxicity

Numerous cases of PA poisoning in animal species, including cattle, sheep, horses, and pigs, have been reported (EFSA, 2011c). All livestock species are susceptible to PA poisoning, with sheep, goats and rabbits among the more resistant species, whereas horses, pigs and poultry are more sensitive. The intoxication can be acute or chronic, depending on the individual alkaloids present, the total amount of ingested PAs and the time span over which the ingestion had taken place. The onset of disease can be within 24-48 hours or after several days or months, and is characterised by lesions in the liver in all species.

A wide range of clinical signs have been reported in animal poisoning, ranging from depression and lethargy in pigs (Ubiali *et al.*, 2011) to incoordination and aggression in cattle (Queiroz *et al.*, 2013). Post-mortem analysis of livers shows characteristic megalocytosis, fibrosis and biliary duct proliferation.

2.9.2 Transfer of toxic agents to edible tissues and products

Milk

Several studies examined the transfer to milk of PAs in cattle and other animals.

Three dairy cows (4-5 years old; 600-700 kg) with fistulated rumens were administered ragwort through the fistula at daily doses of 0 g for week 1, 50 g in week 2, 100 g in week 3, 200 g in week 4, and 0 g in week 5 (Hoogenboom *et al.*, 2011). The PAs in the ragwort consisted mostly of jacobine, jaconine, erucifoline, senecionine and seneciphylline and the corresponding N-oxides. Milk was collected twice daily. Milk samples contained measurable levels of the following PAs: jacoline, jacobine, jaconine, and senkirkine. No N-oxides were identified in the milk samples. Based on milk production and the total PA concentration, the transfer of the daily doses to milk was 0.1% of the overall daily dose of PAs. Though jacoline made up only 1% of the administered PAs, 4% of this PA and its N-oxide present in the plant material was transferred into the milk as a free base.

Dairy cows (n = 4) received dried tansy ragwort (*Senecio jacobaea L.*; 10 g/kg bw per day) for two weeks (Dickinson *et al.*, 1976). The PA content of the dried plant material was

estimated to be 0.16% by weight. This equates to a PA exposure dose of 16 mg/kg bw per day. PAs were detected in milk at concentrations in the range 470-835 µg/L, after correction for recovery. Jacoline was the only 1,2-unsaturated PAs detected in milk.

Candrian *et al*. (1991) identified 0.16% of the total dose of radiolabelled PA in the milk of a cow given a single oral dose of 1 mg/kg of ^{3}H-seneciphylline.

Three Merino sheep were treated with five capsules daily containing 6.5 mg (total 32.5 mg) of ^{14}C labelled-PAs (seneciphylline 91%, senecionine 6%, rest unidentified) for 5 days (Panariti *et al.*, 1997). The total dose was approximately 162 mg seneciphylline. The maximum PA concentration in milk was found at the end of the five dosing days, with milk found to contain 987 µg/L seneciphylline.

Goats (Nubian, *n* = 3) received approximately 1% (500 g) of their body weight in tops of tansy ragwort per day, via cannula (Deinzer *et al.*, 1982). 1,2-Unsaturated PAs and their *N*-oxides were determined in milk as retronecine equivalents. The authors estimated that approximately 0.1% of the ingested PAs were transferred to milk.

Meat

In a radiotracer study, a dairy cow received a single oral dose of 1 mg/kg bw of ^{3}H-seneciphylline (Candrian *et al.*, 1991). At slaughter, 0.06% of the dose was found in the liver.

Crotalaria novae-hollandiae subsp. *novae-hollandiae*, *Heliotropium amplexicaule* and *Senecio brigalowensis* were fed at approximately 15% of the diet to weaned calves for 6 weeks to achieve a dose of PAs of 5.5, 15 and 2.5 mg/kg bw per day, respectively (Fletcher *et al.*, 2011). Alkaloids present in *C. novae-hollandiae* subsp. *novae-hollandiae* were identified as monocrotaline, pumiline A, trichodesmine and crosemperine; in *H. amplexicaule* as mainly indicine and as a minor component heliospathine (both mainly in N-oxide form); and in *S. brigalowensis* as sceleratine (mainly as N-oxide), senkirkine, otosenine, desacetyldorininine, florosenine and dorinine. After exposure to *C. novae-hollandiae* subsp. *novae-hollandiae*, PAs were detected in muscle and liver tissue, reaching a plateau at maximum levels of 250 µg/kg and 2500 µg/kg, respectively. In tissues, the following order was found for PA-adduct levels: liver > kidney ≈ heart > muscle. After exposure to *H. amplexicaule*, PA concentrations in tissues were below or at the limit of quantification of 1 µg/kg. PA adducts were detected in muscle, liver, kidney and heart samples, and tended to increase during the trial. In the tissues, PA-adduct levels occurred in the order liver > kidney ≈ heart ≈ muscle. After exposure to *S. brigalowensis*, free PAs, all of the otonecine type, were detected in liver, reaching a plateau after two to three weeks at levels up to 400 µg/kg, and decreasing to 40 µg/kg, at the end of the trial. PA adducts were detected in tissue samples in increasing amounts up to 35 days, where after the levels declined. The PA adducts were detected in the order liver > kidney > heart ≈ muscle.

2.9.3 Human toxicity

Information on effects on humans has been derived from large outbreaks of human poisonings including deaths associated with grain crops contaminated with PA-containing weeds, as well as case reports of poisonings due to PA-containing herbal medicines and teas (EFSA, 2011c). Poisoning usually manifests as acute hepatic veno-occlusive disease. The acute disease is associated with high mortality, while sub-chronic or chronic exposure may result in liver cirrhosis. Children are particularly vulnerable.

2.9.4 Evidence of pyrrolizidine alkaloids in the New Zealand feed supply

No information was found on the PA content of animal forage or feed in New Zealand.

A study in the Czech Republic detected PAs in 83% of hay samples, 55% of silage samples and 50% of alfalfa (lucerne) samples (Bolechová *et al.*, 2015). Mean total PA concentrations,

in positive samples only, were 82, 26 and 8 μg/kg, respectively. A much lower prevalence of PAs was found in forage samples in the Netherlands, with 3% of hay, 5% of silage, 17% of grass and 74% of alfalfa samples testing positive for PAs (Mulder *et al.*, 2009). Amongst the PA-positive samples, the mean total PA concentrations were 550, 19, 81 and 610 μg/kg, respectively, in the four forage types. A German study detected PAs in 18% of grass silage samples, with a mean of 4.8 μg/kg dry weight (Gottschalk *et al.*, 2015).

2.10 OTHER

A number of other plants have been implicated in animal and/or human poisonings. However, for most of these the available information is fragmentary, particularly with respect to the causative toxic agents and the transfer of toxic agents into foods of animal origin. Brief notes are included below for plant materials implicated in livestock poisonings in New Zealand.

Unless otherwise stated, no information was found on transfer of toxicity to edible tissues or animal products and no cases of human poisoning were identified.

2.10.1 Black nightshade (*Solanum nigrum*) and Poroporo (*S. aviculare, S. laciniatum*)

While both of these plants have been implicated in animal and human poisonings, very little information is available. The toxicity in humans has been ascribed to solanine and related glycoalkaloids (Slaughter *et al.*, 2012). These glycoalkaloids are better known for their role in potato toxicity.

Potato glycoalkaloid poisoning has been documented for approximately 2000 human cases, including 30 deaths, with case reports from 1865 to as recently as 1983 (Kuiper-Goodman and Nawrot, 1993; Morris and Lee, 1984). Outbreaks of potato glycoalkaloid poisoning have been reported from Germany, Scotland, England and Canada. It has been suggested that many cases of glycoalkaloid poisoning may go undiagnosed due to the similarity of symptoms to bacterial food poisoning (Smith *et al.*, 1996). Symptoms typically include gastrointestinal (vomiting, diarrhoea and severe abdominal pain) and neurological (drowsiness, apathy, confusion, weakness and vision disturbance) aspects and, in severe cases, may progress to unconsciousness and death (Kuiper-Goodman and Nawrot, 1993).

The potato glycoalkaloids (α-solanine and α-chaconine) have been reported to have two distinct toxic mechanisms, consistent with the symptoms observed in glycoalkaloid poisoning (Morris and Lee, 1984). These are: a membrane disrupting activity, similar that to that of saponins, that causes observed gastrointestinal symptoms due to disruption of gastrointestinal tract membranes, and a cholinesterase inhibiting mechanism, causing the observed neurological symptoms due to build-up of the neurotransmitter, acetylcholine (Morris and Lee, 1984).

2.10.2 *Cestrum* spp.

Cestrum spp., particularly *Cestrum parqui* and *Cestrum laevigatum* have been associated with livestock poisonings in Brazil (Barbosa *et al.*, 2010; Neto *et al.*, 2017; Wouters *et al.*, 2013) and Australia (McLennan and Kelly, 1984).

Signs of poisoning have included apathy, anorexia, absence of rumen movements, constipation, muscle tremors, staggering gait, excitement and aggression (Barbosa *et al.*, 2010; Marinho *et al.*, 2018; Neto *et al.*, 2017). The main pathological finding is usually hepatic necrosis, with the neurological signs ascribed to interference in the urea cycle due to hepatic insufficiency resulting in hyperammonaemia (Marinho *et al.*, 2018; Wouters *et al.*, 2013).

It has been suggested that the toxic effects seen in livestock may be due the saponins, gitogenin and digitogenin (Marinho *et al.*, 2018). However, when goats were fed a saponin extract of the leaves of *Cestrum laevigatum* (equivalent to 20 g/kg of dried leaves) or dried leaves (5 or 10 g/kg) only the dried leaves produced the expected toxic effects (Marinho *et al.*, 2018). The kaurene glycoside, parquin, has also been suggested as the toxic agent in *Cestrum* spp. (Pearce *et al.*, 1992), but no evidence was found to support this suggestion.

No reports of human intoxication were found.

2.10.3 Foxglove (*Digitalis purpurea*)

Foxglove is well known for containing cardiotoxic glycosides (cardenolides), including digitoxin and digoxin (Slaughter *et al.*, 2012). Cardenolides inhibit normal function in the myocardium and cardiac conducting tissue, through inhibition of membrane-bound sodium-potassium-ATPase. This results in elevated cytosolic calcium and increased cardiac contractility. Digoxin is used in human medicine to treat various heart conditions.

Little information is available on livestock poisonings. Several cases of calf poisonings have been reported in the *Surveillance* publication. Hutton (1996) noted that, although the plant is unpalatable, calves “seem to like to try everything”. In two cases of non-fatal foxglove poisoning digoxin was measurable in the blood of the calves. Signs of toxicity included sporadic ataxia, panting respiration, tachycardia and cardiac arrhythmia.

2.10.4 Goat’s rue (*Galega officinalis*)

Goat’s rue has been investigated as a forage crop to increase milk production (Gonzalez-Andres *et al.*, 2004). This study report noted that the toxic effect of this crop is due to guanidine-derived alkaloids, galegine and hydroxyl-galegine, and quinazoline alkaloids, vasicine and vasicinone. Toxicological studies in rats suggest the liver and lungs may be considered as target organs for goat’s rue toxicity (Rasekh *et al.*, 2008).

In livestock, clinical signs are apparent 18-24 hours after ingestion, including dyspnoea, associated with severe pulmonary congestion, oedema and hydrothorax (Parton and Bruere, 2002). Similar signs were reported in a French outbreak, with 20 of 32 cattle dying within 1-2 days (Roch *et al.*, 2007) and in a case of poisoning of three sheep (Puyt *et al.*, 1981).

2.10.5 Hairy vetch (*Vicia villosa*)

Hairy vetch poisoning is a systemic granulomatous disease, characterised by dermatitis and associated alopecia, diarrhoea, decreased milk production and weight loss (Iizuka *et al.*, 2005; Panciera *et al.*, 1992; Silveira *et al.*, 2017). The inflammatory lesions that characterise the disease are multifocal or confluent monocytic, lymphocytic, plasmacytic, eosinophilic, multinucleated giant cell infiltrates (Harper *et al.*, 1993; Panciera *et al.*, 1992; Silveira *et al.*, 2017). Attempts to experimentally induce the disease have had mixed results, suggested considerable variability in tolerance within animal populations (Panciera *et al.*, 1992).

2.10.6 Hemlock (*Conium maculatum*)

Hemlock produces an array of piperidine alkaloids with coniine and γ-coniceine being the most abundant and accounting for most of the plant’s toxicity (López *et al.*, 1999). While alkaloids are present in all plant parts, concentrations are highest in the leaves. Lethal doses of fresh plant material have been reported as; cattle - 5.3 g/kg bw, sheep – 10 g/kg bw and pigs – 8 g/kg bw (López *et al.*, 1999).

It has been proposed that hemlock alkaloids exert toxicity through action on nicotinic acetylcholinergic receptors (nAChRs) (Green *et al.*, 2012; López *et al.*, 1999).

Signs of acute hemlock poisoning are similar in the various animal species (López *et al.*, 1999). Cattle, sheep and pigs exhibit muscular weakness, incoordination, trembling, pupil

dilation, salivation, cyanotic membranes and cold limbs. These signs are followed by initial stimulus of the central nervous system, then by depression, fast and shallow respiration, turning to slow and laborious, frequent urination and defecation, coma and death caused by respiratory paralysis. Necropsy findings are consistent with respiratory failure; congestion of the liver and lungs and dark, dense blood.

Chronic toxicosis in breeding animals can result in malformed offspring. It has been suggested that this may be due to an anaesthetic effect, through interaction with the foetal muscle nAChRs, of the alkaloids on the foetus; suppressing movements that are essential for proper skeletal and joint development (Green *et al.*, 2012; López *et al.*, 1999).

In an outbreak of poisoning in dairy cattle consuming freshly-cut lucerne containing up to 60% hemlock, 26 of 226 animals died and 26 had to be slaughtered (Panter and Keeler, 1990). Hemlock piperidine alkaloids were detected in milk by thin-layer chromatography and milk was discarded for several days following the toxicoses. The concentrations of alkaloids in the milk were not reported.

Human poisonings are usually accidental, from mistaking the root of hemlock for parsnip or the leaves for parsley (López *et al.*, 1999). The progression of hemlock poisoning in humans is similar that in animals, with early gastrointestinal and neurological signs followed by marked neurological and cardiovascular dysfunction (Slaughter *et al.*, 2012).

2.10.7 Himalayan honeysuckle (*Leycesteria formosa*)

Presumed Himalayan honeysuckle poisoning was reported in a mob of 60 Highland cattle (Hill and Scotland, 2010). Two cattle were found dead, with post-mortem revealing renal infarcts. A third animal appeared to recover, but then developed neurological signs, including ataxia, circling and blindness. Following subsequent humane killing of this animal, necropsy revealed chronic thrombosis and recanalisation of the carotid artery, consistent with cerebral infarct. The temporal and occipital lobes of the right cerebral hemisphere were absent.

2.10.8 Horse chestnut (*Aesculus hippocastanum*)

Horse chestnut poisoning of sheep has been reported to induce excessive salivation, abdominal pain and diarrhoea. At high exposure doses trembling, staggering and dyspnoea may develop, leading to collapse, paralysis, coma and death. The primary toxic agent is reported to be the saponic glycoside, aesculin.[2]

2.10.9 Inkweed (*Phytolacca octandra*)

A single outbreak report was found for inkweed poisoning of cattle (Collett *et al.*, 2011). Affected animals exhibited acute irritation, agitation, reluctance to walk, recumbency, hyperaemia of unpigmented skin and jaundice. As the outbreak progressed, exudative dermatitis with formation of crust occurred on unpigmented skin. Dehydration, loss of appetite and diarrhoea were also notable. Necropsy revealed discolouration and enlargement of the liver and kidneys. Crystals were noted in the bile duct. While hepatic lesions were generally considered mild, effects on the kidneys were moderate to severe. Signs associated with the skin were diagnosed as hepatogenous photosensitivity. It was noted that the water source for the cattle was also contaminated with cyanobacteria.

2.10.10 Kowhai (*Sophora microphylla*)

With respect to human toxicity, it has been reported that the toxicity of kowhai is closely related to that of hemlock, with both plant producing alkaloids with structural similarities to nicotine, that exert toxicity through action on nicotinic acetylcholinergic receptors (nAChRs)

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2 http://www.sciquest.org.nz/elibrary/download/123577/Quarterly_review_of_diagnostic_cases%3A_April-June_2.pdf?#search="chestnut"" Accessed 27 September 2018

(Slaughter *et al.*, 2012). As with hemlock, poisoning is characterised by gastrointestinal and neurological effects.

Occasional cases of cattle poisoning have been reported in the *Surveillance* publication. These are characterised by neurological symptoms, with necropsy usually revealing no particular abnormalities.

A single New Zealand outbreak report was found (Page, 2002). Affected animals exhibited varying degrees of recumbency and ataxia. In the most severe case, the animal's mucous membranes were grey and pale, the animal was tachycardic and tachypnoeic. Extremely hard dry faeces were discovered, indicating poor gastrointestinal motility. Several animals died or were euthanased. No abnormal pathology or histopathology was noted following post-mortem examination.

2.10.11 Ngaio (*Myoporum laetum*)

Ngaio has been reported to induce hepatogenous photosensitisation and severe liver damage in all livestock species (Parton and Bruere, 2002). One of the toxic agents is reported to be ngaione, a natural derivative of furan (Birch *et al.*, 1953), which is concentrated in the leaves of the ngaio (Parton and Bruere, 2002).

Experimental *Myoporum laetum* poisoning of sheep was also reported in Brazil (Raposo *et al.*, 1998). Intake of 40 g/kg bw resulted in death in five of nine sheep. Surviving sheep developed photodermatitis. Liver necrosis was noted in necropsied animals.

2.10.12 Oleander (*Nerium oleander*)

Oleander is highly toxic to animals and humans, with the toxic agents being a cardiotoxic glycoside, similar to those in foxglove (Hutton, 1996). Poisonings, including fatalities, have been reported in humans (Bandara *et al.*, 2010; Gopalakrishnan *et al.*, 2017) and livestock (Falciola *et al.*, 2015; Soto-Blanco *et al.*, 2006).

2.10.13 Onion (*Allium* spp.)

Onion toxicity in livestock appears to be haemolytic, presenting with clinical findings such as pale mucous membranes, haemoglobinuria, anaemia and tachycardia (Hutton, 1996; Parton and Bruere, 2002).

Onion poisoning has been reported in livestock (Borelli *et al.*, 2009; Pourjafar *et al.*, 2011; Rodilla *et al.*, 2004) and companion animals (Fighera *et al.*, 2002; Zhao *et al.*, 2017). Toxicity is mediated through the sulphur-containing compounds n-propyl disulphide and sodium n-propyl thiosulphate (Zhao *et al.*, 2017). These compounds convert haemoglobin to methaemoglobin, leading to haemolytic anaemia with formation of Heinz bodies (Borelli *et al.*, 2009).

There is no evidence of similar toxicity in humans. However, this may be due to the fact that humans are unlikely to consume sufficient onions to result in significant production of methaemoglobin.

2.10.14 Redroot (*Amaranthus powellii* or *A. retroflexus*)

Redroot is reported to exert its toxicity through three modes of action; the plant is a nitrate accumulator, contains soluble oxalates and contains an unknown nephrotoxic agent (Kerr and Kelch, 1998; Parton and Bruere, 2002; Spearman and Johnson, 1989). Clinical signs may include depression, muscle tremors, increased heart and respiration rates, hypocalcaemia, hypomagnesaemia, hyperkalaemia, azotaemia and elevated blood creatinine phosphokinase (Kerr and Kelch, 1998) and tubular degeneration, fibrosis and necrosis of the kidneys (Torres *et al.*, 1997).

2.10.15 Smooth witch grass (*Panicum dichotomiflorum*)

Smooth witch grass poisoning is associated with secondary (hepatogenous) photosensitisation (Johnson *et al.*, 2006; Knupp *et al.*, 2016; Riet-Correa *et al.*, 2009). The causative agents are reported to be steroidal saponins. Clinical signs include oedema of the head, followed by dermatitis, ocular discharge and corneal opacity leading to blindness, and redness of the coronary band and hoof (Riet-Correa *et al.*, 2009). Various observations have been made at necropsy, including liver discolouration and necrosis, appearance of crystals within hepatic bile ducts, gall bladder inflammation, necrosis of myocytes and vascular necrosis (Johnson *et al.*, 2006; Riet-Correa *et al.*, 2009). The crystals formed are insoluble calcium salts of the saponin metabolites (Knupp *et al.*, 2016).

Sheep appear to be more sensitive to the toxic effects of smooth witch grass than other ruminants (Riet-Correa *et al.*, 2009).

2.10.16 Staggerweed (*Stachys arvensis*)

Naturally occurring and experimentally induced staggerweed toxicity was observed in New Zealand lambs (Vaatstra *et al.*, 2011). Lambs developed hind limb paresis, muscular tremors and a hunched posture. Histopathology revealed multifocal degeneration of the central nervous system and skeletal muscles. However, the toxic agent was not identified.

Similar neurological symptoms have been reported in sheep intoxicated by staggerweed in Australia (Philbey *et al.*, 2001).

2.10.17 Yarr/spurrey (*Spergula arvensis*)

Yarr consumption was associated with clinical hypocalcaemia in New Zealand dairy cows (Hicks and Taylor, 2000). It was assumed that Yarr may contain oxalates and the cows were dosed with calcium chloride. No further cases occurred.

2.10.18 Yew (*Taxus baccata*)

All parts of the yew, except the arils (the red flesh around the seed) contain cardiotoxic alkaloids, with taxine B having the greatest activity (Wilson *et al.*, 2001). Fatalities have been reported in animals and humans (Grobosch *et al.*, 2013; Panter *et al.*, 1993; Piskač *et al.*, 2015; Wilson *et al.*, 2001).

Taxines appear to exert their cardiotoxicity by altering calcium and sodium channel conductance, resulting in an increase in cytoplasmic calcium (Wilson *et al.*, 2001).

In livestock, yew poisoning general results from the accidental feeding of yew leaf cuttings or from the animals having access to yew trees (Panter *et al.*, 1993; Wilson *et al.*, 2001). The minimum lethal doses, in terms of yew leaves, have been estimated as; cattle – 10 mg/kg bw, goats – 60 mg/kg bw, pigs – 3.5 mg/kg bw, sheep – 12.5 mg/kg bw, and humans – 3-6.5 mg/kg bw (Wilson *et al.*, 2001). A cattle poisoning incident in the United States reported 35 animals dying within four hours of consuming 360-700 mg/kg bw of yew material (Panter *et al.*, 1993).

In most cases of livestock poisoning, the animals are found dead and no signs are observed. However, in rare subacute poisonings clinical signs include ataxia, bradycardia, dyspnoea, muscle tremors, recumbancy and convulsions (Wilson *et al.*, 2001). Similar clinical signs are seen in human poisoning cases, although cases may initially be tachycardic and experience gastrointestinal symptoms (nausea, vomiting and diffuse abdominal pain) (Wilson *et al.*, 2001).

3. MYCOTOXINS

Mycotoxins are toxic secondary metabolites of fungi, mainly of the genera *Aspergillus, Fusarium* and *Penicillium* (Council for Agriculture and Technology, 2003). Fungi of the genera *Alternaria* and *Claviceps* also produce mycotoxins of concern with respect to human and animal health.

The following sections present information on food-related mycotoxins previously addressed in a risk profile of mycotoxins in the New Zealand food supply (Cressey, 2014). Two additional groups of pasture-related mycotoxins are discussed:

- Toxins produced by *Pithomyces chartarum*, particularly sporidesmin A, which is associated with facial eczema in New Zealand livestock.
- Toxins produced by the endophytic fungi *Neotyphodium lolii* and *N. uncinatum,* associated with ryegrass in New Zealand. The mycotoxins lolitrem B and ergovaline are of particular concern.

3.1 AFLATOXINS

Aflatoxins are secondary metabolites predominantly produced by three 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). While the aflatoxins comprise a group of about 20 related compounds, the four 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. 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.

3.1.1 Animal toxicity

Aflatoxins are potent liver toxins in all animal species tested and may be lethal when consumed in large doses (Council for Agriculture and Technology, 2003). Chronic sub-lethal exposure can result in liver cancer.

Clinical signs in livestock include weight loss, anorexia, jaundice and depression (Miller and Wilson, 1994). Decreased milk production and photosensitisation have also been reported in cattle. Pathology typically presents as haemorrhage, hepatic necrosis and bile ductile proliferation.

Aflatoxins have also been reported to be immunotoxic; impairing the cellular and humoral immune systems, and rendering animals more susceptible to microbial, fungal and parasitic diseases (Miller and Wilson, 1994).

3.1.2 Transfer of toxic agents to edible tissues and products

Milk

The transfer of the metabolite aflatoxin M_1 (AFM_1) into ruminant milk is probably the most studied example of the transfer of a feed contaminant into the human food supply (Fink-Gremmels, 2008; Flores-Flores *et al.*, 2015). Feeding trials have been used to estimate that approximately 2% of ingested AFB_1 is excreted into milk, in the form of AFM_1 (Fink-

Gremmels, 2008). Transfer rates as high as 6.2% have been reported for high-producing dairy cows (Veldman *et al.*, 1992).

Meat

Much less information is available on the transfer of aflatoxins to ruminant or porcine 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 aflatoxin levels in offal 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.

3.1.3 Human toxicity

Acute toxicity in humans has occasionally been reported in Africa and Asia following consumption of contaminated rice, maize or peanuts (Azziz-Baumgartner *et al.*, 2005; Council for Agriculture and Technology, 2003; Lewis *et al.*, 2005). Symptoms include vomiting, diarrhoea, abdominal pain and fever, and may progress to acute hepatic failure and death. Acutely toxic and potentially lethal doses of AFB_1 in humans have been estimated to be of the order of 20-120 μg/kg bw/day when consumed over a period of 1-3 weeks (Wild and Gong, 2010).

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). Associations between PLC and aflatoxin exposure are much stronger in populations with a high prevalence of hepatitis, particularly hepatitis B, and some studies have suggested that aflatoxin exposure only poses a significant risk in the presence of infection by hepatitis B virus (JECFA, 2017a).

Growth suppression (stunting) is an important result of aflatoxin exposure in animals and there is some evidence that a similar phenomenon may occur in human children (Gong *et al.*, 2004; Gong *et al.*, 2002). However, stunting has not been observed in all relevant studies and the populations studied are generally exposed to a number of other aetiological factors, such as low socioeconomic status, chronic diarrhoea, infectious disease and malnutrition (JECFA, 2017a).

As with animals, there is some evidence that aflatoxins are immunotoxic in humans (JECFA, 2017a).

3.1.4 Evidence of aflatoxins in the New Zealand feed supply

There is no evidence that the fungal species that produce aflatoxins are present in New Zealand and aflatoxin contamination of food and feed in New Zealand is considered to be an issue solely of imported material (Cressey, 2014). In the context of the current study, this suggests that aflatoxin contamination is only likely to be an issue in supplementary feed, but not in forage.

AFM_1 contamination in New Zealand milk has occasionally been detected in New Zealand milk and has been traced back to feeding of a coconut husk derivative; copra.[3] However, the aflatoxin concentrations in the copra were not published.

A review of animal feed in New Zealand reported that 90% of imported copra, tapioca, palm kernel and brewers grain were being fed directly to dairy cattle (Davidson and Pearson, 2009).

Several studies within the Asia-Pacific region have examined some of these materials for aflatoxin contamination. A survey of palm kernel cake and copra in Indonesia detected AFB_1 in all samples, with mean concentrations of 49 μg/kg (range 6-93 μg/kg) and 38 μg/kg (range 1-147 μg/kg), respectively (Pranowo *et al.*, 2013).

A Malaysian study detected aflatoxins in eight of 42 (19%) feed samples (Khayoon *et al.*, 2010). Aflatoxins were detected in one sample of copra (24 μg/kg) and one sample of palm kernel expeller (10 μg/kg). Other positive samples were maize, sunflower meal, wheat bran, corn, corn germ meal and a poultry feed. A further Malaysian study detected aflatoxins in 23 of 25 palm kernel cake samples (Yibadatihan *et al.*, 2014). Fourteen samples contained total aflatoxin concentrations of greater than 100 μg/kg, with a highest concentration of 225 μg/kg.

The European Union specifies a maximum content of AFB_1 in feed materials of 0.02 mg/kg (20 μg/kg,12% moisture basis) (EC, 2002).

3.1.5 Evidence of aflatoxins in New Zealand foods of animal origin

The National Chemical Contaminants Programme (NCCP) is an annual survey of New Zealand produced raw milk and processed dairy products for a range of chemical contaminants.[4] Analyses for aflatoxins (AFM_1) are included in the NCCP.

In the period July 2011 to June 2017, 1848 samples of raw milk were analysed for AFM_1 by enzyme-linked immunosorbent assay (ELISA) (MPI, 2013; 2014a; 2015; 2016b; 2017a; c). AFM_1 was detected in four samples (0.2%) at concentration between the limit of reporting (LOR) of 0.01 μg/kg and the action limit (AL) of 0.05 μg/kg. During the period July 2013 to June 2017 a further 206 samples were analysed for six aflatoxins (AFB_1, AFB_2, AFG_1, AFG_2, AFM_1 and AFM_2). None of the aflatoxins were detected. The LORs were in the range 0.009 to 0.33 μg/kg. Since 2011, AFM_1 was detected in two of 134 samples (1.4%) of colostrum at a concentration between the LOR and the AL. AFM_1 has not been detected in any colostrum samples since 2012-2013.

While a parallel programme, the National Chemical Residues Programme (NCRP), carries out analyses on animal tissues, mycotoxins are not included in this programme.

3.2 OCHRATOXIN A

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, 2001c). These organisms differ in their geographical distribution and ecological niche, in the commodities affected, and at the point at which they

[3] http://www.stuff.co.nz/business/farming/4259464/Aflatoxins-traced-back-to-feed-Fonterra Accessed 4 October 2018

[4] https://www.mpi.govt.nz/processing/dairy-products/monitoring-and-testing-dairy-products/national-chemical-contaminants-programme-nccp/ Accessed 5 October 2018

are likely to infect commodities. 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). OTA has been detected in imported and domestically produced foods in New Zealand (Cressey and Jones, 2011).

3.2.1 Animal toxicity

In ruminants, OTA is largely degraded by ruminal microflora into the less toxic ochratoxin α (Gallo *et al.*, 2015). While one study reported reduced feed intake in sheep fed a diet containing 14 mg/kg OTA, there is little evidence that OTA is toxic to ruminants.

Pigs are sensitive to OTA, resulted in a well-documented porcine nephropathy (Duarte *et al.*, 2011; Krogh *et al.*, 1973). This disease is characterised by impairment of proximal renal function, glucosuria, proteinuria, decreased renal clearance, decreased ability to concentrate urine, and growth depression. The renal changes include proximal tubular degeneration and interstitial fibrosis in the renal cortex.

3.2.2 Transfer of toxic agents to edible tissues and products

Milk

Due to ruminal metabolism of OTA it is generally considered that only negligible concentrations of OTA may occur in milk (Fink-Gremmels, 2008).

While OTA has occasionally been reported in cows' milk (Skaug, 1999), a study in Spain with extremely low limits of detection (LOD = 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 (limit of quantification (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 contamination of milk concluded that OTA concentrations would rarely exceed 0.1 μg/kg (Flores-Flores *et al.*, 2015).

Meat

In line with the known species pattern of toxicity, OTA has most often been reported as a contaminant of pigmeat.

OTA was analysed in 70 pooled slaughter pig liver samples and 25 pig muscle samples (Hort *et al.*, 2018). OTA was detected in 47 (67%; 0.1-3.7 μg/kg) and 4 (16%; 0.1-1.2 μg/kg) of liver and muscle samples, respectively.

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).

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 boar, 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.

3.2.3 Human toxicity

OTA is principally nephrotoxic. 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).

3.2.4 Evidence of ochratoxin A in the New Zealand feed supply

No information was found on OTA in forage or supplementary feed in New Zealand. However, OTA has been detected in foods produced from New Zealand-grown cereals and it is highly likely that OTA contamination will occur in New Zealand forage (Cressey and Jones, 2011).

The potential for forage contamination was demonstrated in a Polish study, with a highest concentration of OTA of 1.6 μg/kg in 'autumn saved herbage' (presumably silage or bailage) (Golinski *et al.*, 2006). However, a Dutch study did not detect OTA (LOQ = 8 μg/kg) in any of 140 maize silage, 120 grass silage and 30 wheat silage samples (Driehuis *et al.*, 2008). However, the LOQ in this study may have been too high to detect the levels of OTA likely to be present. Given the ability of ruminants to substantially metabolise OTA, such concentrations are unlikely to be a concern for animal or human health.

3.2.5 Evidence of ochratoxin A in New Zealand foods of animal origin

While surveys of OTA in consumer foods in New Zealand have been conducted (Cressey and Jones, 2009; 2011), these surveys did not include any foods of animal origin.

The French total diet study detected OTA in 'delicatessen meats', but this food accounted for <5% of dietary OTA exposure (Sirot *et al.*, 2013).

Studies outlined in section 3.2.2 suggest that OTA concentrations in foods of animal origin are usually low; in the low μg/kg range.

3.3 TRICHOTHECENES

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. Trichothecenes are mainly contaminants of cereals.

3.3.1 Animal toxicity

General signs of trichothecene toxicity in animals include weight loss, decreased feed conversion, feed refusal, vomiting, bloody diarrhoea, severe dermatitis, haemorrhage, abortion, and death (Council for Agriculture and Technology, 2003).

DON is considered to pose the greatest risk to animal health, with pigs being the most susceptible species (Council for Agriculture and Technology, 2003). Reduced feed intake and lower weight gains are the main effects seen in pigs, with complete feed refusal seen with feed containing 12 mg/kg of DON and vomiting occurring at 20 mg/kg. This 'self-regulation' of DON by pigs probably protects against more severe toxic consequences.

Tissue lesions may occasionally, but not always, be detected; mainly affecting the gastrointestinal tract and lymphoid tissues (Pestka, 2007).

Ruminants appear to be largely resistant to DON toxicity due to ruminal detoxification and dairy cattle fed a diet containing 66 mg/kg DON for five days exhibited no alteration in feed intake or milk production (Côté *et al.*, 1986).

3.3.2 Transfer of toxic agents to edible tissues and products

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 transfer of DON and de-epoxy-DON from feed into milk have been reported to be low, with percentage transfer of 0.0001-0.0002% and 0.0004-0.0024% respectively (Fink-Gremmels, 2008).

In cows 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 complete 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; corresponding to milk concentrations in the range 0.11-0.26 μg/kg and 1.5-3.1 μg/kg for DON and de-epoxy-DON, respectively.

Groups of 10 cattle received diets containing 0.07 (control), 2.62 or 5.24 mg/kg dry weight of DON (Winkler *et al.*, 2015). No DON or de-epoxy-DON were detected in milk from the control group. DON was detected at mean concentrations of 0.78 μg/L (range 0.0-2.0 μg/L) and 0.83 μg/L (range 0.3-2.5 μg/kg) in the medium and high DON feed groups, respectively. De-epoxy-DON was detected at mean concentrations of 0.17 μg/L (range 0.0-2.1 μg/L) and 2.26 μg/L (range 0.1-5.0 μg/L) in the medium and high DON feed groups, respectively. Mean estimates of transfer from feed to milk were <0.01% for both compounds.

DON was detected in the milk of sheep consuming feed containing 1.6 mg/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.

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 were detected.

A multi-trichothecene method, specifically developed for analysis of milk samples, was used to analyse 13 UHT milk samples from Spain (Flores-Flores and González-Peñas, 2015). No trichothecenes were detected. Except for nivalenol, LODs were less than or equal to 2.5 μg/L.

A Croatian study detected DON in 15 of 105 (14.3%) cows' milk samples, with concentrations in the range 5.4-67.3 μg/L (Pleadin *et al.*, 2017). These concentrations were higher than any of the other studies summarised above. Two points are worth noting; mycotoxin analyses were carried out by ELISA and feed material contained high concentrations of DON, up to 13 mg/kg in some samples. ELISA methods are usually considered to be less reliable than HPLC or LC-MS methods.

Meat

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. The pattern of DON and metabolite seen in muscle was the reverse of that seen in milk, with DON dominating in muscle, while de-epoxy-DON dominated in milk (Seeling *et al.*, 2006).

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.

In a further Chinese study, T2, but not DON, was detected in pig dorsal muscle (6 of 20 samples), obtained from local markets (Zou *et al.*, 2012). The mean concentration was 0.1 μg/kg (range 0.02-0.45 μg/kg). Both DON and T2 were detected in pig back fat samples; DON in 2 or 10 samples (mean 0.1 μg/kg, range 0.12-0.43 μg/kg), and T2 in 5 of 10 samples (mean 0.02 μg/kg, range 0.02-0.09 μg/kg).

3.3.3 Human toxicity

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, 2001a).

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, 2001a). 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, 2011c).

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, 2001d). Moulds were reported to be *F. poae* and *F. sporotrichioides*. The symptoms included necrotic lesions of the oral cavity, oesophagus and stomach and pronounced leukopenia (low white blood cell count) and resulted in high mortality rates.

3.3.4 Evidence of trichothecenes in the New Zealand feed supply

Substantial information has been published on DON and nivalenol contamination of pasture and cereals in New Zealand.

Fusarium species were isolated from a predominantly ryegrass-white clover pasture near Pukekohe (Lauren *et al.*, 1988). While isolates were reported to produce trichothecene mycotoxins in culture, the toxins were not those that have been assessed in relation to human health.

In a more recent study, 200 *Fusarium* isolates; 70 from pasture and 130 from grain, were tested for their trichothecene producing potential (Lauren *et al.*, 1992). Nivalenol derivatives were produced by 91 isolates, while 11 *Fusarium graminearum* isolates additionally produced DON derivatives.

Maize samples were taken from various points in a New Zealand feed mill and analysed for DON and NIV (Lauren *et al.*, 2006). Mycotoxin concentrations in accepted maize (post-screening) were in the range 210-710 μg/kg (NIV) and 250-1500 μg/kg (DON). While not stated, it is probable that this maize was destined for incorporation into compound feed, rather than for use as supplementary feed.

The remainder of the publications on trichothecenes in crops in New Zealand relate to field maize and wheat and it is uncertain whether these studies are relevant to animal forage.

3.3.5 Evidence of trichothecenes in New Zealand foods of animal origin

Studies on the trichothecene content of New Zealand foods have focused primarily on grain-based foods (Cressey *et al.*, 2014; Lauren and Veitch, 1996). No analyses for trichothecenes have been carried out on foods of animal origin in New Zealand.

3.4 FUMONISINS

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). While at least six fumonisins are known, fumonisin B_1 and B_2 (FB_1, FB_2) are considered to be the most important. It has recently been discovered that *Aspergillus niger* strains are also capable of producing fumonisin mycotoxins (Frisvad *et al.*, 2007; Scott, 2012). 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.

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.*, 2002; Sayer, 1991; Sayer and Lauren, 1991). *F. proliferatum* has not been reported in New Zealand maize.

3.4.1 Animal toxicity

Fumonisin B_1 is the aetiologic agent of two well-characterised animal diseases (Council for Agriculture and Technology, 2003):

- Equine leukoencephalomalacia (ELEM) affects horses, ponies, donkeys and mules, causing liquefaction of the brain. Fumonisin-contaminated feed has been implicated in the disease and the symptoms were reproduced by intravenous administration of FB_1 to horses (JECFA, 2001b).
- Porcine pulmonary oedema (PPO) is believed to be induced by cardiovascular dysfunction, followed by acute left-side heart failure. Hepatotoxicity occurs concurrently with PPO. PPO has been reproduced by intravenous administration of purified FB_1, but not by oral administration (JECFA, 2001b).

Cattle appear to be relatively resistant to fumonisin toxicity. Experimental hepatic toxicity was induced in calves by feeding corn containing 328 mg/kg of FB_1 (Baker and Rottinghaus, 1999) and hepatic and renal toxicity was found in calves receiving FB_1 at 1 mg/kg bw (Mathur *et al.*, 2001). Tubular necrosis and mild hepatotoxicity were also seen in lambs administered up to 45.5 mg/kg bw of total fumonisins for four days (Edrington *et al.*, 1995).

A herd of cattle grazed on standing corn experienced cases of blindness and ataxia (Sandmeyer *et al.*, 2015). The blindness was found to be due to degeneration of the optic nerve. Fumonisin-producing *Fusarium* species were isolated from the corn. The authors of the study ascribed the blindness to fumonisin toxicosis, although they admitted that this diagnosis was largely circumstantial.

Fumonisin contamination of pasture was implicated as the cause of an idiopathic syndrome in New Zealand wapiti and wapiti-red deer hybrid, characterised by scouring and liver dysfunction (Mirocha *et al.*, 1992).

3.4.2 Transfer of toxic agents to edible tissues and products

Milk

Scott *et al.* (1994) studied transmission of FB_1 in four cows dosed either orally (1.0 and 5.0 mg FB_1/kg body weight) or intravenously (0.05 and 0.20 mg FB_1/kg body weight) with pure

FB_1. No residues of FB_1 or its metabolite AP_1 were detected in milk. Richard *et al*. (1996) fed two Jersey cows a diet containing approximately 75 mg/kg of fumonisins for 14 days. The cows consumed an average of 3 mg FB_1/kg body weight/day. No FB_1 residues were detected in milk. Holstein-Friesian cows (*n* = 3) received intravenous doses of 30 mg FB_1, with traces (<1 μg/kg) of the toxin detected in milk up to 8 hours after dosing (Hammer *et al.*, 1996). On average, the transfer rate was estimated to be 0.05%.

FB_1 was detected in one of 165 milk samples, using a LC-MS method (Maragos and Richard, 1994). However, the LOD (5 μg/L) may have been insufficiently sensitive for this investigation.

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).

A Croatian study detected fumonisins in dairy cattle feed at concentrations up to 6.3 mg/kg, but not in any of 105 associated milk samples (Pleadin *et al.*, 2017). However, the LOQ of the ELISA method used in this study (25.3 μg/L) was probably too high to allow detection of fumonisin residues.

Meat

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.

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).

3.4.3 Human toxicity

Incidents of human toxicosis have been associated with fumonisin-contaminated foods. However, it should be noted that in most cases the implicated foods may contain more than one known mycotoxin and may potentially contain other, as yet uncharacterised, toxins. An outbreak of acute mycotoxicosis occurred in southern India in 1995 due to consumption of rain-damaged, mouldy sorghum and maize. FB_1 was the most common mycotoxin in both crops, with concentration up to 8 mg/kg in sorghum and 65 mg/kg in maize. However, a relatively high concentration of aflatoxin B_1 was also detected in the maize (Shetty and Bhat, 1997). Cases exhibited gastrointestinal symptoms, including abdominal pain, borborygmi (rumbling stomach) and diarrhoea.

High concentrations of FB_1 in the diet have been correlated with oesophageal cancer (Shephard *et al.*, 2002; Shephard *et al.*, 2007; Sun *et al.*, 2007; Sun *et al.*, 2011), neural tube defects (Missmer *et al.*, 2006), increased mortality rates in HIV cases (Williams *et al.*, 2010), and impaired child growth (stunting) (Kimanya *et al.*, 2010; Shirima *et al.*, 2015). However, these associations are largely based on concurrent differences in fumonisin dietary exposure between regions with differing disease incidence and populations in high

incidence regions were often also exposed to higher levels of other mycotoxins, as well as suffering a range of micronutrient deficiencies (JECFA, 2012).

3.4.4 Evidence of fumonisins in the New Zealand feed supply

As part of an investigation of idiopathic disease in New Zealand wapiti and wapiti-red deer hybrids, 40 pasture samples were analysed for the presence of FB_1 (Mirocha *et al.*, 1992). FB_1 was detected in four of 40 samples, with concentrations in the range 1.0-9.0 mg/kg.

A Mexican study also reported detection of fumonisins in forage grass, although at much lower concentrations (mean 0.29 mg/kg) (Huerta-Trevino *et al.*, 2016).

Alonso *et al*. (2013) reviewed the literature on mycotoxin contamination of silage. While fumonisins have been reported in corn (maize) silage, no information was reported on fumonisins in other silage types. A Dutch study detected fumonisins in maize silage, but not in grass or wheat silage (Driehuis *et al.*, 2008). A Croatian study detected fumonisins in 88% of maize silage samples, at a mean concentration of 0.85 mg/kg and in 71% of 'concentrated dairy cattle feed', at a mean concentration of 0.86 mg/kg (Pleadin *et al.*, 2017). FB_1 was detected in 52% of 25 hay samples, with a mean concentration of 0.12 mg/kg (120 μg/kg) (Yu *et al.*, 1999). In a study carried out in the Czech Republic, the influence of grass species, season and ensiling were examined for their impact on the mycotoxin content of forage (Skladanka *et al.*, 2013). Fumonisins were not detected in any fresh cut grass samples, but were detected in silage prepared from *Festulolium braunii* (a hybrid of ryegrass and fescue) at a concentration of 6.1 μg/kg.

A European survey detected fumonisins in feeding maize, maize silage, soy meal, sugar beet pulp, and maize and wheat based dried distillers' grains with solubles (DDGS), but not hay, feeding wheat, feeding barley, feeding oats, extracted oil seeds, clover, grass and alfalfa silages, malt sprouts, or brewers' grains (Zachariasova *et al.*, 2014).

No information was found from New Zealand or overseas on the fumonisin content of supplementary feed materials, such as copra and palm kernel expeller.

3.4.5 Evidence of fumonisins in New Zealand foods of animal origin

The single study on the fumonisin content of New Zealand foods focused primarily on grain-based foods (Cressey *et al.*, 2017). No analyses for fumonisins have been carried out on foods of animal origin in New Zealand.

3.5 ZEARALENONE

Zearalenone (ZEN), (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 oestrogenic 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, 2011d). In plants and animals, ZEN 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). 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.

3.5.1 Animal toxicity

While ZEN is generally of low toxicity, its structural similarity to the female sex hormone, 17β-oestradiol, may result in induction of hyperoestrogenism in animals, particularly pigs. Effects have been reported at exposure levels as low as 1.5-3.0 mg/kg of diet (D'Mello *et al.*, 1999). Effects observed in female pigs include vulvovaginitis, disruption of the oestrus cycle, reduced embryonic survival and reduced foetal weight. In male pigs, ZEN exposure decreases serum testosterone, testes weight and spermatogenesis.

In ruminants, infertility or reduced fertility, reduced milk production and hyperoestrogenism have been reported following ZEN exposure (D'Mello *et al.*, 1999). However, a number of studies in which cattle received ZEN doses <1 mg/kg of diet resulted in no overt signs of hyperoestrogenism or reproductive disorders (Knutsen *et al.*, 2017). While cattle appear less susceptible to the effects of ZEN than pigs, quite low ZEN exposure (<1 mg/kg in feed) has been shown to cause changes in ovarian follicle populations, even though fertility was not impacted (Fushimi *et al.*, 2015).

Studies on the impact of ZEN exposure on sheep, carried out in New Zealand, demonstrated disturbance of the oestrus cycle, reduced ovulation rate and reduced fertilisation of ova, contributing to lowered lamb production (Smith and Morris, 2006). Effects become apparent at exposures >1 mg/day.

3.5.2 Transfer of toxic agents to edible tissues and products

Milk

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

A predictive model was used to estimate the ZEN concentration of bovine milk given the level of contamination in feed products (Signorini *et al.*, 2012). The model estimated a mean ZEN 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 ZEN to more (α-ZOL) or less (β-ZOL) estrogenic forms and used the transfer rate from the study summarised in the previous paragraph.

In contrast the studies summarised above, a Chinese study detected β-ZOL, but not α-ZOL in two of five milk samples, with concentrations of 0.69 and 1.25 μg/kg (Chen *et al.*, 2013).

Meucci *et al.* (2011) analysed 185 samples of milk-based infant formula for ZEN and its metabolites. ZEN was detected in 17 samples (9.2%), with a mean concentration of 0.03 μg/L. The metabolites, α-ZOL and β-ZOL were detected in 49 (26.4%) and 53 (28.6%) samples, respectively. ZEN was predominantly present in the form of β-ZOL (mean concentration 6.6 μg/L) with lower concentrations of α-ZOL present (mean concentration 0.27 μg/L).

A Croatian study detected ZEN in 99 of 105 milk samples, with a mean concentration of 5.5 μg/L (range 0.3-89 μg/L) (Pleadin *et al.*, 2017).

Groups of 10 cattle received diets containing 0.02 (control), 0.33 or 0.66 mg/kg dry weight of ZEN (Winkler *et al.*, 2015). No α-ZOL or β-ZOL was detected in milk from the control group; ZEN was detected with concentrations in the range 0.02-0.10 μg/L. ZEN was detected at mean concentrations of 0.14 μg/L (range 0.0-0.26 μg/L) and 0.13 μg/L (range 0.04-0.29 μg/L) in the medium and high ZEN feed groups, respectively. While α-ZOL and β-ZOL were occasionally detected in milk from the low and high dose groups, at maximum concentration of 0.17 and 0.95 μg/L, respectively, only β-ZOL achieved a mean concentration >0.01 μg/L (0.15 μg/L in high dose group). Mean estimates of transfer from feed to milk were <0.01% for both compounds.

Meat

There appears to be little carryover of ZEN or its metabolites to edible animal tissues. ZEN and metabolites were not detected in any of 300 bovine muscle samples (Kaklamanos *et al.*, 2009). However, this study gave no information on the ZEN content of animal diets. Of 1256 'meat and meat product' samples for which data were submitted to EFSA, ZEN was not detected in any sample (EFSA, 2011d).

However, a Chinese study detected α-ZOL, but not β-ZOL, in one of 10 pig meat samples (1.1 μg/kg) and three of 10 pig liver samples (1.1-2.2 μg/kg) (Chen *et al.*, 2013).

Meat-based infant foods (*n* = 44) were analysed for ZEN and metabolites (Meucci *et al.*, 2011). With the exception of detection of α-ZAL in one sample, only α-ZOL was detected, in 12 of 44 samples (27.3%). The highest concentration was in a veal-based food (30.5 μg/kg), with a mean for the 12 detections of 3.8 μg/kg.

3.5.3 Human toxicity

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

ZEN or ZAL was suspected to be a causative agent of precocious puberty after being found in the blood of Puerto Rican girls aged between six months to eight years with early sexual development and who had been exposed to contaminated food (Saenz de Rodriguez *et al.*, 1985). Early breast development has also been reported from Hungary where ZEN was detected in the serum of 5 out of 36 affected subjects and in foods consumed by the subjects (Szuets *et al.*, 1997).

An Italian cohort study compared serum ZEN concentrations in 32 girls with central precocious puberty (CPP) with 31 healthy controls (Massart *et al.*, 2008). ZEN and α-ZOL were detected in serum of six CPP cases. ZEN-positive girls were taller and heavier than ZEN-negative girls.

A US study detected ZEN in urine of 78.5% of 163 girls aged 9 and 10-years (Bandera *et al.*, 2011). In contrast to the studies summarised above, ZEN-positive girls tended to be shorter and were less likely to have reached onset of breast development.

ZEN was found together with other *Fusarium* mycotoxins in a condition known as “scabby grain toxicosis” reported in China, but the significance of this finding is not clear (Peraica *et al.*, 1999).

3.5.4 Evidence of zearalenone in the New Zealand feed supply

ZEN was detected in 10 of 60 pasture samples, taken during January to April 1985 at sites near Pukekohe, Whanganui and Gisborne (Di Menna *et al.*, 1987). Concentrations of ZEN were in the range 0.4-4.0 mg/kg dry weight. Further surveys detected ZEN in 9% of 6000 pasture samples at concentration high enough to depress ewe fertility and in a further 35% at concentrations sufficient for flocks to be ‘at risk’ (Smith and Morris, 2006). However, the actual concentrations determined were not reported.

Fusarium crookwellense and *F. culmorum* isolates from a New Zealand pasture were shown to produce ZEN and α-ZOL in culture (Lauren *et al.*, 1988).

ZEN was detected in received maize from a New Zealand feed mill (0.24-1.14 mg/kg), in screenings (0.46-5.8 mg/kg) and in accepted maize post-screening (0.08-0.67 mg/kg) (Lauren *et al.*, 2006).

ZEN was detected in 8 of 22 Australian pasture samples, at concentrations up to 5.0 mg/kg dry weight, and in 15 of 24 silage samples, with concentrations up to 80 mg/kg dry weight (Reed and Moore, 2009). ZEN concentrations were higher in legume-dominant silages compared to grass-dominant silages.

ZEN was detected in both maize silage (69/140 samples; 49%) and grass silage (7/120 samples; 6%) collected in the Netherlands during 2002-2004 (Driehuis *et al.*, 2008). The respective mean ZEN concentrations (positive samples only) were 0.17 and 0.07 mg/kg in maize and grass silage.

Gallo *et al*. (2015) reviewed worldwide data on mycotoxins in animal feed. Across different studies, the prevalence of ZEN in maize silage was in the range 28-100%, with mean concentrations ranging from 0.07-0.43 mg/kg. In forage, hay and hay silage prevalence varied between 0 and 100%, with mean concentrations ranging from 0.02 to 0.94 mg/kg.

A Mexican study detected ZEN in 100% of alfalfa, sorghum and grass forage samples (*n* = 40 of each), with mean concentrations of 0.20, 0.17 and 0.05 mg/kg for the three forage types, respectively (Huerta-Trevino *et al.*, 2016).

A Croatian study detected ZEN in 74% of maize silage samples and 58% of concentrated cattle feed samples, with mean concentrations of 2.1 and 0.53 mg/kg, respectively (Pleadin *et al.*, 2017).

A European study detected ZEN in most animal feed types, but not in clover, grass and alfalfa silage (*n* = 12; LOD = 0.001 mg/kg dry weight) (Zachariasova *et al.*, 2014). However, concentrations of ZEN were generally not high, with the highest mean and individual ZEN concentrations were in maize-based DDGS (0.10 and 0.26 mg/kg dry weight, respectively).

3.5.5 Evidence of zearalenone in New Zealand foods of animal origin

No analyses for zearalenone have been carried out on foods of animal origin in New Zealand.

While there are no maximum permitted limits for ZEN in New Zealand foods of animal origin, limits for α-ZAL are defined for ruminant offal (0.01 mg/kg) and meat, fat, blood and urine of cattle, sheep, deer, horse and goat (0.005 mg/kg) (MPI, 2016a).

3.6 ERGOT ALKALOIDS

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). 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.

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).

3.6.1 Animal toxicity

Ergotism is a well characterised disease of ruminants and horses (Riet-Correa *et al.*, 2013). In animals, the EAs exert a vasoconstrictive effect, resulting in gangrenous ergotism; a dry gangrene of the limb extremities. Initially the animal may show a painful lameness. On closer examination, the extremities are cool to the touch and a line of demarcation may be seen between the normal and unhealthy tissue. Other initial signs are decreased feed intake, rough hair and weight loss.

Since 2005, outbreaks of ergotism have occasionally been reported in the summaries of diagnostic cases in the *Surveillance* publication. Outbreaks have usually occurred in Southland (5 of 7 outbreaks), were all associated with cattle, and resulted from consumption of ryegrass or ryegrass silage or bailage. Clinical signs reported have included lameness, swollen lower limbs, dry gangrene, necrosis of the distal limbs and pyrexia.

Limited experimental studies have been carried out on animals and usually involve feeding of whole ergot, rather than individual alkaloids (WHO, 1990). Study results reported include:

- Cattle. Feed containing more than 10 g ergot/kg (1%) commonly produced lameness in cattle, sometimes leading to gangrene. Cattle fed 1 mg ergotamine tartrate/kg body weight became ill in 1-2 days and four of six died within 10 days. Symptoms included anorexia, hyperventilation, cold extremities, salivation and tongue necrosis. Post-mortem examination found extensive intestinal inflammation (WHO, 1990).
- Sheep. Four lambs were fed 0.12 to 0.75 g ergot/kg body weight for two months. Lambs on higher doses became ill within 2-6 days, with symptoms including diarrhoea, oedema of the hind legs and tail and lameness. Post-mortem examination found inflammation and necrosis of the forestomach and intestinal mucosa (WHO, 1990).
- Swine. A diet containing 40 g ergot/kg (4%) was well tolerated. Depression of growth rate was observed with diets containing 100 g ergot/kg (10%) (WHO, 1990). Diets containing 0, 1 or 10 g ergot/kg (0.05, 0.6 or 4.66 mg total alkaloids/kg) fed *ad libitum* to 12 pigs produced no symptoms of ergot poisoning or carryover of alkaloids into meat. Reduced feed intake and reduced body weight gain were observed at the highest dose level (Mainka *et al.*, 2005).

3.6.2 Transfer of toxic agents to edible tissues and products

There have been no reports of transfer of EAs to foods of animal origin (Fink-Gremmels, 2008; Flores-Flores *et al.*, 2015).

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 transfer of EAs into tissues (liver, muscle, kidneys) was detected.

3.6.3 Human toxicity

Ergotism has been known to man for centuries and numerous epidemics of intoxication 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 alkaloids (ergotamine-like). Symptoms include oedema, 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 alkaloids 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).

Outbreaks of ergotism still occur occasionally. An outbreak of ergotism occurred in the Wollo region of Ethiopia in 1978 (Demeke *et al.*, 1979; King, 1979). Locally-grown barley became heavily contaminated with wild oats (70%). Ergometrine was detected in sclerotia from the crop. A total of 93 cases of ergotism were reported in addition to 47 deaths reported to be due to ergotism (case fatality rate = 47/140 = 34%). Examination of 44 cases revealed dry gangrene of one or more limbs (7.5%), feeble or absent peripheral pulses (36.5%), swelling of limbs (11.2%), desquamation of skin (12.8%) and loss of one or more limbs (21.5%).

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).

Several outbreaks of illness associated with consumption of ergot-contaminated bajra (pearl millet) in the state of Rajasthan have been reported since 1958, with the most recent occurring in 1975 (Krishnamachari and Bhat, 1976). In total, 78 persons from 21 villages reported symptoms of nausea, vomiting and giddiness. Symptoms developed within 1-2 hours of consuming the contaminated meal and lasted for 24-48 hours. Contamination was due to *C. fusiformis* and resulted in ergot levels in grain of 15-174 g/kg, equating to ergoline levels of 15-199 mg/kg. Although there were insufficient data to determine a no effect level, the authors concluded that an exposure of 28 µg ergoline/kg body weight would be non-toxic.

3.6.4 Evidence of ergot alkaloids in the New Zealand feed supply

The Institute of Environmental Science and Research (ESR) received samples of bailage associated with an outbreak of ergotism in Southland. The samples contained up to 26 mg/kg total alkaloids on a fresh weight basis, with ergotamine and its epimer, ergotaminine, being the major EAs present (Ellen Ashmore, ESR, personal communication).

Ergot is known to occur in Australian rye grasses and 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.

Ergotamine, an EA commonly found in ergot-affected samples, was not detected in any of 240 maize and grass silage samples in the Netherlands (Driehuis *et al.*, 2008).

A European study included analysis of four EAs (ergocornine, ergocryptine, ergocristine and ergocristinine) in a wider analysis of mycotoxins in feedstuffs (Zachariasova *et al.*, 2014). EAs were detected at low concentrations (μg/kg) in samples of feeding wheat, feeding barley, soy meal, extracted oil seeds, maize- and wheat-based DDGS and compounded pig feed.

The European Union specifies a maximum content of 'rye ergot (*Claviceps purpurea*)' in feed materials of 1000 mg/kg (12% moisture basis) (EC, 2002).

3.6.5 Evidence of ergot alkaloids in New Zealand foods of animal origin

No analyses for EAs have been carried out on foods of animal origin in New Zealand.

3.7 OTHER MYCOTOXINS

3.7.1 Patulin

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.

No reports were located of adverse health effects in livestock or 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).

While the main crop affected by patulin contamination, apples, may be incidentally consumed by food-producing animals, no information was found on the transfer of patulin into foods of animal origin.

3.7.2 Citrinin

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, 2012b). *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.* 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, 2012b).

Experimental data regarding systemic toxic effects in ruminants are not available. It is likely that CIT is highly degraded and metabolised through the microbial activity in the rumen. However, an impairment of the rumen performance due to the antibacterial effect of CIT cannot be excluded. A small number of clinical studies on pigs were reviewed by EFSA (EFSA, 2012b). The studies were small and mostly poorly reported. While some early signs of renal dysfunction were apparent in one study, EFSA concluded that no effects have been reported from pigs given 20 µg/kg bw/day.

No reports of transfer of CIT into milk or meat were found, except for a single study on chickens (Abdelhamid and Dorra, 1990).

CIT has occasionally been detected in animal feed samples. CIT was detected in 6% of 233 silage samples with a mean concentration of 9 µg/kg (Gallo *et al.*, 2015).

A Croatian study detected CIT in 5 of 90 fermented meat products, with a maximum concentration of 1.3 µg/kg (Markov *et al.*, 2013). However, it is uncertain whether the CIT present originated from transfer from animal feed or from cultures used to ferment the meat products. *Penicillium* strains capable of producing CIT were found on cheese, but no CIT was detected in the cheese (Taniwaki and Van Dender, 1992).

3.7.3 Cyclopiazonic acid

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).

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).

Isolated cases of apparent ruminant toxicity have been reported (Burdock and Flamm, 2000), presenting as sway back and tremors, progressing to convulsions and death. Experimental toxicity has been demonstrated in pigs, with clinical signs including weakness, inactivity, anorexia, rough hair and reduced body weight (Burdock and Flamm, 2000). Lesions of the gastrointestinal tract and hepatic and renal effects were sporadically observed.

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.

Lactating ewes (*n* = 3) were administered 5 mg/kg body weight of CPA for 2 days (Dorner *et al.*, 1994). CPA concentration in ewes' 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.

A survey of *A. flavus* isolates (*n* = 38) from Queensland found that 34 (89%) produced CPA in culture (Blaney *et al.*, 1989).

Studies in the USA and the Netherlands detected CPA in up to 80% of maize and hay silage samples, with mean concentrations in the range 55-390 μg/kg (Gallo *et al.*, 2015).

3.7.4 Sterigmatocystin

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, 2013). 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 biotransform 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).

STC has been reported in cereals and cereal products (including beer), nuts, green coffee beans, spices and cheese.

A case of potential STC poisoning has been reported in dairy cattle on an US farm, related to feed contaminated with several fungal strains dominated by *A. versicolor* and *A. candidus*. The concentration of STC was 7.75 mg/kg feed. The animals exhibited bloody diarrhoea, loss of milk production and death in some cases (Vesonder and Horn, 1985).

The transfer of STC from feed to milk was investigated in two cows receiving feed to give an exposure of approximately 5 to 10 mg/day of STC for two weeks (EFSA, 2013). No STC was detected in milk (LOD 1 μg/kg). Based on this LOD it was estimated that less than 0.4 % of the STC was transferred to milk. No studies examining transfer of STC into meat were found.

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 hepatocellular carcinoma (EFSA, 2013).

STC was not detected in any of 140 maize silage and 120 grass silage samples collected in the Netherlands (Driehuis *et al.*, 2008). A large European study reported occasional detection of STC in feeding wheat and maize-based DDGS, but not in any other feed type examined (Zachariasova *et al.*, 2014). Mean concentrations in these two feed types were <1 μg/kg.

In a Chinese study, STC was detected in 35% of pig feed samples (mean 2.0 μg/kg, maximum 9.1 μg/kg) and 25% of cattle feed samples (mean 1.4 μg/kg, maximum 17.2 μg/kg) (Hu *et al.*, 2016).

An Argentinian study analysed native grasses intended for cattle grazing for a range of mycotoxins (Nichea *et al.*, 2015). The study was conducted in each of two years (2011 and 2014). In 2011, STC was detected in 96 of 106 samples (91%) with a median concentration

of 4.2 μg/kg dry weight (maximum 733 μg/kg dry weight), while in 2014 STC was detected in 41 of 69 samples (59%) with a median concentration of 6.8 μg/kg dry weight (maximum 147 μg/kg dry weight).

An EFSA report summarised several older studies, most of which did not detect STC in animal feed samples (EFSA, 2013). Studies that did detect STC, detected it infrequently.

While STC has occasionally been detected in cheese (Veršilovskis *et al.*, 2009; Veršilovskis and De Saeger, 2010), it has not been reported in milk and its presence in cheese may be the result of direct environmental contamination (Flores-Flores *et al.*, 2015).

3.7.5 *Alternaria* toxins

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. *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).

While a small number of studies have considered the toxicity of individual *Alternaria* toxins in chickens, no studies are available on toxic effects in livestock animals (EFSA, 2011a).

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). Tenuazonic acid (TeA) has also been implicated in onyalai, a haemorrhagic disease occurring in southern Africa (Steyn and Rabie, 1976).

Several *Alternaria* toxins, including alternariol (AOH), alternariol methyl ether (AME), *A. alternata* f. sp. *Lycopersici* toxins (AAL toxins), AAL-TA and AAL-TB, have been detected in animal feed material, including maize and hay silage (Gallo *et al.*, 2015). The AAL toxins were detected in 15-100% of feed samples with mean concentrations in the range 50-720 μg/kg. AOH and AME were only detected in 2% of maize silage samples, with mean concentrations of 18 and 8 μg/kg, respectively.

An Argentinian study analysed native grasses intended for cattle grazing for a range of mycotoxins (Nichea *et al.*, 2015). The study was conducted in each of two years (2011 and 2014). Four *Alternaria* toxins were analysed for, with all being detected. In 2011, AOH was detected in 105 or 106 samples (99%) with a median concentration of 65.3 μg/kg dry weight (maximum 1036 μg/kg dry weight), AME was detected in 67 of 106 samples (63%, median 12.6 μg/kg, maximum 377 μg/kg), tenuazonic acid (TeA) was detected in 28 of 106 samples (26%, median 31.4 μg/kg, maximum 222 μg/kg) and tentoxin (TEN) was detected in 90 of 106 samples (85%, median 1.6 μg/kg, maximum 324 μg/kg). In the 2014 year, the prevalences of TeA and AME were higher (39% and 97%, respectively), while prevalences of AOH and TEN were lower (88% and 30%, respectively). Median and maximum concentrations were lower than for 2011 for all toxins.

A large survey of European feedstuffs included analysis for altenuene (ATE), AOH, AME and TEN (Zachariasova *et al.*, 2014). AOH and AME were the most frequently detected *Alternaria* toxins, being detected in hay, feeding wheat, feeding maize, feeding oats, soya meal, extracted oil seeds, maize silage, clover, grass and alfalfa silage (AOH only), and maize and wheat-based DDGS. Mean concentrations were mostly <20 μg/kg, except for AOH in hay (89 μg/kg) and feeding oats (295 μg/kg), AME in hay (92 μg/kg) and feeding oats (223 μg/kg), ATE in hay (53 μg/kg) and TEN in soya meal (37 μg/kg).

No information was found on the presence of *Alternaria* toxins in milk or meat. *Alternaria alternata* has been isolated from milk powder, suggesting that any results on the *Alternaria* toxin content of milk may need to be interpreted with caution, as the toxins may be present due to the presence of the organism in milk, rather than transmission from feed (Ismail and Saad, 1997).

3.7.6 Penicillic acid

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).

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.

A review of mycotoxin contamination of forage and feed did not include any reports of PEN contamination, but noted that two studies had not detected PEN in maize silage (Gallo *et al.*, 2015). PEN was analysed for, but not detected in any of 260 samples of maize and grass silage collected in the Netherlands during 2002-2004 (Driehuis *et al.*, 2008).

A study carried out in Tamil Nadu state, India analysed 441 feed ingredients and 475 compound feed samples for the presence of various mycotoxins, including PEN (Sarathchandra and Muralimanohar, 2013). PEN was detected in 13 feed ingredient samples (2.9%). PEN was only detected in two of 18 ingredient types (maize and groundnut oil cake), with mean concentrations of 30 and 20 μg/kg, respectively. PEN was also detected in three of 475 compound feed samples (0.6%). All three samples were layer mash, with a mean concentration of 20 μg/kg.

Despite the presence of *Penicillium roqueforti* in many cheese types, PEN has not been detected (Sengun *et al.*, 2008).

3.7.7 *Pithomyces chartarum* mycotoxins

Pithomyces chartarum is a saprophytic fungus, colonising decaying vegetative matter in the bed of pasture grass (Di Menna *et al.*, 2009; Riet-Correa *et al.*, 2013; Towers, 2006). All New Zealand strains of the fungus examined produce the mycotoxin sporidesmin. Sporidesmin is a potent hepatic toxin, but can also cause adverse effects on the bladder and mammary glands.

Sporidesmin intoxication in New Zealand is often referred to as facial eczema, due to the visual signs of hepatogenous photosensitisation (Towers, 2006). The condition has been reported in cattle, sheep, deer, goats and alpaca in New Zealand. Early signs of intoxication include transient diarrhoea and loss of appetite. In lactating animals, a pronounced fall in milk production may occur, even following a single exposure (Matthews *et al.*, 2018). Clinical signs of, usually ongoing, photosensitisation appear in animals with severe liver damage and occlusion of the major bile ducts. There is also some evidence that intoxication may result in reduced fertility in sheep (Oliver and Harding, 2009).

No information was found on the transfer of sporidesmin into animal tissues or milk.

No information was found on human health effects of sporidesmin.

3.7.8 *Neotyphodium* toxins

Some *Neotyphodium* species can colonise perennial ryegrass as endophytes. The presence of these endophytes imparts beneficial pest resistance to the ryegrass, but the toxins produced may also have adverse effects on animal health.

Two distinct endophyte-related animal health issues have been identified; ryegrass staggers and fescue toxicosis (Towers, 2006). Fescue cultivars used in New Zealand are largely endophyte-free and fescue toxicosis is now rare in New Zealand.

The endophyte of ryegrass, *Neotyphodium lolii*, produces three types of mycotoxins; tremorgenic paxilline and lolitrem B, ergovaline an ergot-type alkaloid, and the herbivorous insect repellent compound peramine (Towers, 2006). Lolitrem B is the cause of ryegrass staggers, while ergovaline can cause heat stress in livestock (Fletcher *et al.*, 2017). Peramine is not associated with adverse effects in livestock. A range of commercial endophyte-containing ryegrass cultivars are now available, with differing mycotoxin profiles.

Lolitrem B is believed to primarily act at the calcium-activated potassium channel, resulting in disruption of neuromuscular junction signalling (Morris *et al.*, 2017). Clinical symptoms range from slight muscular tremors to ataxia and collapse (Prestidge, 1993). Growth rates and productivity may be affected. Horse and deer are particularly susceptible to ryegrass staggers, but cattle and sheep may also be seriously affected.

As with ergot alkaloids in general, ergovaline is vasoconstrictive (Nicol and Klotz, 2016). Constriction in the peripheral vasculature can compromise the animal's ability to dissipate heat and can contribute to increased core temperature and development of heat stress. An increased respiratory rate may also be seen as a compensatory mechanism, to increase heat dissipation. Vasoconstriction at the rumen epithelium has been suggested to affect nutrient absorption, resulting in decreased weight gains.

Ewes were fed on ryegrass hay containing 674-1006 μg/kg of ergovaline and 800-1027 μg/kg lolitrem B (Zbib *et al.*, 2015). After 28 days of exposure, ergovaline was detectable in 4 of 8 milk samples, at trace concentrations (between 0.15 and 0.7 μg/L), while loitrem B was present in 2 of 8 samples at trace concentrations (between 0.15 and 0.5 μg/L). Ergovaline was not detected in muscle samples, but was detected in liver and kidney at mean concentrations of 0.68 and 0.53 μg/kg, respectively. Lolitrem B was detected in liver, muscle and fat at mean concentrations of 0.71, 0.77 and 2.39 μg/kg, respectively.

Groups of 10 dairy cattle were fed either wild-type or commercial (AR37) endophyte-infected perennial ryegrass for 12 days (Finch *et al.*, 2013). The lolitrem B content of wild-type feed was 1.8 mg/kg. Lolitrem B was detectable in milk after one day of feeding, with a maximum concentration of 5 μg/L measured during the study period. After the cessation of ryegrass feeding, the concentration of lolitrem B in milk had decreased to near zero within eight days.

Analysis of four perennial ryegrasses, two endophyte-containing (NEA2 and AR37) and two endophyte-free, was conducted over a 3-month period (Fletcher *et al.*, 2017). NEA2 contained a classical profile of mycotoxins, including ergovaline (0.4-0.9 mg/kg), lolitrem B (0.4-1.1 mg/kg) and peramine (2.1-11.0 mg/kg), while AR37 contained epoxy-janthitrems (18.5-26.0 mg/kg). Mycotoxin concentrations were then compared to a standard endophyte-containing ryegrass. NEA2 contained similar ergovaline concentrations to the standard ryegrass 1.0-1.7 and 0.5-1.2 mg/kg, respectively), but lower concentrations of lolitrem B (0.9-1.0 and 2.8-4.1 mg/kg) and peramine (4.4-4.7 and 27-51 mg/kg). Lambs grazed on the standard endophyte-containing ryegrass had higher rates of serious ryegrass staggers than those grazed on NEA2 or AR37.

4. POTENTIALLY TOXIC ELEMENTS

The 2015 Joint FAO/WHO expert meeting on hazards associated with animal feed identified the elements arsenic, cadmium, lead, mercury, selenium, copper, nickel and chromium as of potential concern as contaminants of feed, that may be transferred to foods of animal origin (FAO/WHO, 2015).

The contaminant element status of forage can be influenced by the status of the underlying soils and by atmospheric deposition. In most cases the latter source of elemental contamination will be negligible. Forage plants can vary in their ability to translocate toxic elements from soils, both between plant species and between different cultivars of a single species (Silva *et al.*, 2016; Zhang *et al.*, 2010). In New Zealand, the study of Longhurst *et al*. (2004) divided pasture forage into grass, legumes and weeds and compared the concentrations of selected toxic elements in these three plant types to concentrations in the underlying topsoils. Relevant results from this study are included in the following sections.

It is also worth noting that stock animals may directly ingest considerable amounts of soil during grazing. It has been estimated that up to 18% of dry matter intake by cattle may be soil, while for sheep this figure may be even higher, up to 30% (Thornton and Abrahams, 1983).

4.1 ARSENIC

Arsenic is a metalloid occurring widely in the earth's crust, with an average abundance of approximately 5 mg/kg (IARC, 2012). Arsenic is the 20th most abundant element in the earth's crust and is present in more than 200 mineral species.

Arsenic can exist in four oxidation states; -3, 0, +3 and +5 (IARC, 2012). However, under normal environmental conditions the +5 oxidation state is the most stable and the majority of arsenic species in organisms and in food contain arsenic in the +5 oxidation state (EFSA, 2009a). From a biological and toxicological perspective the most important structural distinction is that arsenic may occur in both inorganic and organic forms, of which the inorganic forms are the more toxic (EFSA, 2009a; IARC, 2012; JECFA, 2011c).

4.1.1 Animal toxicity

Arsenic poisoning in livestock has previously been attributed to ingestion of arsenic from herbicides, insecticides and medicines (McClanahan *et al.*, 2000). However, such products have been largely phased out and more recent poisonings have been associated with ash from burning of copper-chromium-arsenic treated timber (Hullinger *et al.*, 1998). Arsenic poisoning of dairy cattle has occurred in New Zealand due to soil contamination from naturally-occurring arsenic pyrites (Hopkirk, 1987)

A meta-analysis was carried out of arsenic toxicosis in 156 cattle from 16 outbreaks (Bertin *et al.*, 2013). The most common clinical signs reported were sudden death (68%), diarrhoea (33%), ataxia (29%), dehydration (22%), and respiratory distress (4%). The most common clinicopathologic abnormalities included azotaemia (100%), haematuria (100%), increased liver enzyme activity (86%), and increased haematocrit (60%). Other clinical signs reported in cattle include abdominal pain, trembling, weakness and salivation (McClanahan *et al.*, 2000). Ulceration, oedema and congestion of the abomasum and necrosis of the gastrointestinal tract have also been reported (McClanahan *et al.*, 2000). The clinical course appears to be similar for small ruminants (sheep and goats) (EFSA, 2005).

Clinical signs are similar in pigs and include transient diarrhoea, tremor, ataxia, weakness and progressive blindness (EFSA, 2005). Dermatitis has also been reported.

4.1.2 Transfer of toxic agents to edible tissues and products

Literature data indicate that arsenic compounds are deposited in tissues of livestock proportionally to dietary intake and rate of absorption, although the absolute arsenic concentrations are dependent on animal species, arsenic compound and duration of exposure (EFSA, 2005).

Monagail *et al*. (2018) reviewed and summarised transfer factors for arsenic from feed to beef and milk. For beef (cattle muscle) transfer factors were in the range 0.0003 to 0.0024 (0.03 to 0.24%) and for milk were in the range 0.000044 to 0.006 (0.004 to 0.6%).

In a study summarised by EFSA (2005), cows were administered 33 mg/day of arsenate for 3 months. Exposure resulted in elevated arsenic concentrations in muscle (20 μg/kg compared in 5 μg/kg in controls) and liver (30 μg/kg compared to 12 μg/kg in controls), but no difference in arsenic concentrations in milk or kidney. Arsenite was administered to cows for 15-28 months (33 mg/day), resulting in increased arsenic concentrations in muscle (30 μg/kg compared to 5 μg/kg in controls), liver (100 μg/kg compared to 12 μg/kg in controls), kidney (160 μg/kg compared to 53 μg/kg in controls) and milk (2 μg/kg compared to <1μg/kg in controls). The control arsenic concentrations reported in this study are consistent with arsenic concentrations in milk and ruminant tissue foods in New Zealand (Pearson *et al.*, 2018).

Lactating dairy cows were administered arsinilic acid (1.6 or 3.2 mg/kg bw/day) for five days (Calvert and Smith, 1980). Arsenic concentrations in milk increased (from 80 to 210 μg/kg dried milk) during the exposure period, but only in the animals receiving the higher dose. One week after arsenic administration was stopped, milk arsenic concentrations returned to pre-experiment levels.

A study carried out in Pakistan found strong Pearson correlation coefficients (0.93-0.97) for the relationship between livestock drinking-water arsenic concentrations and concentrations of arsenic in the milk of sheep, goats, cows, buffalo and camels (Kazi *et al.*, 2016). Drinking-water arsenic concentrations in this study were high (0.23-2.0 mg/L, compared to the New Zealand maximum acceptable value for human drinking-water of 0.01 mg/L). Mean milk arsenic concentrations were in the range 13-18 μg/L, with individual concentration up to 37 μg/L.

4.1.3 Human toxicity

Inorganic arsenic (iAs) is acutely toxic with a minimum lethal dose of approximately 2 mg/kg bw (ATSDR, 2007a). However, acute arsenic poisoning is usually only associated with accidental, suicidal, homicidal, or medicinal ingestion of arsenic-containing powders or solutions. No information has been reported on human deaths following ingestion of organic arsenic species (ATSDR, 2007a; EFSA, 2009a), but LD_{50} for monomethyl arsonate (MMA), dimethylarsonite (DMA) and roxarsone[5] have been reported in the range 102 to 3184 mg As/kg bw (ATSDR, 2007a). Arsenobetaine (AB) and trimethylarsine oxide (TMAO) have been reported to be virtually non-toxic following acute administration, with LD_{50} greater than 10,000 mg/kg bw (JECFA, 2011c).

Laboratory animals appear to be substantially less susceptible to the toxic effects of iAs than humans and most information on the adverse health effects of arsenic exposure comes from human epidemiological investigations. These investigations have usually assessed arsenic exposure in terms of the concentration of arsenic in the water supply and, therefore, relate to

[5] Roxarsone is an organoarsenic compound that may be added to poultry feed as a coccidiostat. Roxarsone has been voluntarily withdrawn from use in the USA and is not registered for use in the EU or New Zealand.

iAs. Studies have focussed on five regions (south-west and north-east Taiwan, northern Chile, the Cordoba region of Argentina, Bangladesh and the West Bengal region of India) with particularly high water arsenic concentrations (IARC, 2012).

IARC concluded there was sufficient evidence of a causal relationship between ingestion of iAs and cancer of the lung, urinary bladder and skin (IARC, 2012). Skin cancer was considered to be primarily squamous cell carcinoma (non-melanoma skin cancer). Associations with kidney, liver and prostate cancer were considered to be suggestive, but evidence fell short of establishing a causative relationship.

Skin lesions, including hyperpigmentation and hyperkeratosis, are sensitive indicators of chronic iAs arsenic exposure (EFSA, 2009a). Significant associations between skin alterations and risks of skin cancer have also been identified.

Effects on foetal development (increased risk of spontaneous abortion, stillbirth, preterm birth and neonatal death, birth defects, lower birth weight, lower head or chest circumference), child health and development (neurobehavioural deficits, central nervous system disorders), neurotoxicity (peripheral neuropathy, central nervous system toxicity), cardiovascular disease, and abnormal glucose metabolism and diabetes have all been associated with water iAs levels in regions with high water arsenic (>100 μg/L). However, these associations have not been demonstrated in regions with lower water arsenic concentrations.

No human toxicity data are available for organoarsenic compounds.

4.1.4 Evidence of arsenic in the New Zealand feed supply

Soil and herbage samples were collected from 398 sites in New Zealand (Longhurst *et al.*, 2004). Herbage was dissected into grass, legume and weed. No consistent differences were seen in the ability of these three herbage types to accumulate arsenic. Median arsenic concentrations across soil and herbage types were in the range 0.07-0.24 mg/kg dry weight. The highest arsenic concentrations were seen in grass growing in peat soils and reflected the higher median arsenic content of these soils (9.5 mg/kg dry weight). Far higher soil arsenic concentrations have been reported in New Zealand, with concentrations in excess of 6000 mg/kg being reported in soils associated with an outbreak of arsenic poisoning in cattle (Hopkirk, 1987).

Analysis of soils under pasture in the southern part of New Zealand's South Island (n = 284) contained a mean arsenic concentration of 3.5 mg/kg (median 3.8 mg/kg, maximum 10.9 mg/kg) (Martin *et al.*, 2017). While the basis for expression of these results is not explicitly stated, the methodology suggests these results are on a dry weight basis.

A study in the Bay of Plenty examined the trace element profile of soils under a range of different agricultural land uses (Guinto, 2011). Mean arsenic concentration were in the range 2.6-6.8 mg/kg dry weight, with the highest mean concentration under kiwifruit orchards and the lowest under deer pasture. Only one of 47 soil samples contained arsenic at a concentration above the New Zealand environmental guideline value of 20 mg/kg.

A similar study in the Marlborough region found median arsenic concentrations in the range 3.4-5.1 mg/kg dry weight in soils under a range of agricultural use types (Gray, 2011). The maximum soil arsenic concentration determined was 7.3 mg/kg dry weight.

A European study looking at contaminant element concentrations in animal feed found a mean concentration of 0.1 mg/kg or approximately 3% of the maximum limit (ML) of 2 mg/kg (Adamse *et al.*, 2017). Two feed categories contained higher arsenic concentrations than the rest; seaweed meal and feed materials derived from seaweed (ML = 40 mg/kg, mean concentration = 24% of ML, 11% of samples exceeded the ML) and copper and iron feed additives (ML = 50 mg/kg, mean concentration = 45% of ML, 5.4% of samples exceeded the

ML). Meals made from dried grass, lucerne or clover contained arsenic at a mean concentration of 14% of the ML (4 mg/kg), with no samples exceeding the ML.

4.1.5 Evidence of arsenic in New Zealand foods of animal origin

Arsenic is present in all foods, at some level. The highest concentrations are usually found in marine foods (fish, shellfish, crustacea). In the most recent NZTDS, arsenic concentrations in foods of marine origin were in the range 0.2-4.3 mg/kg (Pearson *et al.*, 2018). Arsenic was not detected (LOD = 0.001 mg/kg) in any milk samples and at concentrations not exceeding 0.01 mg/kg in meat samples. These concentration are consistent with the controls in studies summarised in section 4.1.2 and suggest that there is no marked contribution of contaminated feed to arsenic in foods of animal origins in New Zealand.

The maximum permitted limits for arsenic, as inorganic arsenic, in animal offal and meat are 0.5 and 0.1 mg/kg, respectively (MPI, 2016a).

Arsenic is analysed in a random sample of 150-300 milk samples per annum and a smaller number of colostrum samples, as part of the National Chemical Contaminants Programme (NCCP). In the period July 2011 to June 2017, no samples were found to contain arsenic above the action level of 0.01 mg/L and only four individual samples contained detectable (>0.001 mg/L) concentrations of arsenic (MPI, 2013; 2014a; 2015; 2016b; 2017a; c).

While muscle, liver or fat samples are taken and tested for ‘heavy metals’ from a range of livestock species under the National Chemical Residues Programme (NCRP), it is unclear whether arsenic is included.

4.2 CADMIUM

Cadmium is a metal that occurs naturally at low levels in the environment (EFSA, 2009b). Anthropogenic activity can add amounts of cadmium to soil, water and air. Industrial processes, such as mining and smelting for non-ferrous metals, or electroplating, are often linked to incidents of cadmium pollution. Agricultural practices, particularly the addition of fertilisers (both natural and manufactured), may also increase the levels of cadmium in agricultural areas. Volcanic activity is also a major source of cadmium released into the environment. This is of relevance to New Zealand because of its extinct, dormant and active volcanoes and geothermal areas.

4.2.1 Animal toxicity

Although cadmium toxicity in farmed ruminants has been demonstrated experimentally, there are no published reports of naturally occurring cadmium toxicity in farmed ruminants (Lane *et al.*, 2015). Experimental studies suggest that clinical signs of toxicity are unlikely at feed concentrations less than 5 mg/kg. It is expected that acute cadmium toxicity would only occur if exposure exceeded the liver’s ability to sequester cadmium (Lane *et al.*, 2015).

Calves (Holstein and Jersey) were administered diets containing 40, 160, 640 or 2560 mg/kg of cadmium (Powell *et al.*, 1964). While few clinical symptoms were apparent at the two lower dose levels, at the two higher dose levels calves exhibited; unthrifty appearance, rough hair coat, severe body dehydration, dry and scaly skin, loss of hair, mouth lesions, shrunken and scaly scrotum, sore and enlarged joints, impaired sight, and liver and kidney damage. In the highest dose group, calves did not gain weight and all died within eight weeks. In the 640 mg/kg dose group severe growth retardation was apparent and one of four calves died within six weeks. Reduced growth rates were also seen in the lower dose groups, although the reduction was not statistically significant in the lowest dose group.

Sheep (*n* = 10) were administered 4.5 mg/kg bw of cadmium sulphate daily for eight days (Stoev *et al.*, 2003). The sheep were maintained in the same living environment as five control sheep. Clinical signs were scarce and only apparent after day four. Signs included loss of appetite, increased thirst, atony of the rumen, tachycardia and irregular breathing.

Post-mortem analysis revealed no gross pathological change to the internal organs. Histological changes were observed in a number of organs, particularly in the liver and kidneys.

Barki sheep were administered 0, 50 or 100 mg/kg of cadmium chloride for four weeks (Zaki *et al.*, 2013). Atrophy of the testes and necrosis of the liver and kidneys were observed.

Some evidence of adverse effects from non-experimental cadmium exposure were apparent in a study of reproductive effects in dairy cows. Effects were examined by comparison of 10 dairy farms in a cadmium-polluted part of the Netherlands with 40 dairy farms from a reference area (Kreis *et al.*, 1993). Significant odds ratios were calculated for a lower twinning rate, a higher rate of birth complications for both the calves and cows, and a need for more inseminations to achieve conception in the cadmium-affected area. Perinatal death, premature death, and age at or reason for death were not significantly different between the two cohorts.

4.2.2 Transfer of toxic agents to edible tissues and products

Lambs (n = 33) received a single intra-rumenal dose of ^{109}Cd (Beresford *et al.*, 1999). Animals were progressively sacrificed from 0.5 to 365 days post-administration. Radioactivity was largely excreted in the faeces. The greatest proportion of the retained radioactivity was in the liver and kidneys, with the liver the predominant reservoir during the early part of the study, but with similar proportions of total radioactivity in the liver and kidneys by the end of the study. Maximum activity concentrations in liver, kidney and muscle were reached at about 10 days. While there was a slow decline in muscle cadmium, there was little evidence of liver and kidney concentrations decreasing across the course of the study. Transfer coefficients (the ratio between the equilibrium concentration of the pollutant in a tissue and its daily intake) were derived for a 100- and a 1000-day exposure period. For liver and kidney, transfer coefficients were 0.080 and 0.078, respectively, at 100 days and 0.71 and 0.80 at 1000 days, reflecting the slow accumulation and equilibration for this contaminant. Transfer coefficients for muscle at 100 and 1000 days were estimated to be 0.00022 and 0.0012, respectively.

An Iranian study, while not directly determining cadmium transfer, analysed liver, kidney and muscle samples from 72 cows and 216 feed samples from 18 farms in the same region (Hashemi, 2018). Mean cadmium concentrations in liver, kidney, muscle meat and feed were 0.047, 0.114, 0.028 and 0.021 mg/kg wet weight, respectively.

Lactating and non-lactating sheep (n = 6 of each) each received two doses of cadmium chloride; 0.1 mg/kg by intravenous catheter and 25 mg/kg orally (Houpert *et al.*, 1997). For lactating sheep the mean percentage of orally administered cadmium excreted in milk across the entire lactation period was 0.017%.

A meta-analysis found that the concentration of cadmium in feed and the duration of exposure to the feed were significant predictors of the cadmium concentration in livers and kidneys of sheep (Prankel *et al.*, 2004). However, the study does not report a rate of transfer of cadmium into liver and kidney.

4.2.3 Human toxicity

While cadmium is not usually considered in terms of its acute toxicity, intentional ingestion of cadmium has occurred in connection with successful suicidal attempts. The cause of death is massive fluid loss, oedema and widespread organ failure (ATSDR, 2012). Doses associated with two cases were estimated to be 25 mg/kg and 1840 mg/kg. In humans, ingestion of food or beverages contaminated with high concentrations of cadmium gives rise to acute gastrointestinal symptoms, including nausea, vomiting, salivation, abdominal pain, cramps and diarrhoea (ATSDR, 2012; EFSA, 2009b). The no-observed-effect level (NOEL)

of a single oral dose has been estimated to be 3 mg/person (EFSA, 2009b), or 0.07 mg/kg bw (ATSDR, 2012).

Cadmium is primarily toxic to the kidney, especially to the proximal tubular cells, where it accumulates over time and may cause renal dysfunction (EFSA, 2009b). Cadmium can also cause bone demineralisation, either through direct bone damage or indirectly as a result of renal dysfunction. In severe cases this may result in *itai itai* disease[6], involving osteomalacia and osteoporosis (JECFA, 2011b). After prolonged and/or high exposure the tubular damage may progress to decreased glomerular filtration rate, and eventually to renal failure.

The International Agency for Research on Cancer has classified cadmium as a human carcinogen (Group 1) on the basis of occupational studies (IARC, 2012). Newer data on human exposure to cadmium in the general population have shown statistical associations with increased risk of cancers such as in the lung, endometrium, bladder, and breast.

4.2.4 Evidence of cadmium in the New Zealand feed supply

There has been interest in the cadmium content of New Zealand soils and pastures, due to the long-term use of phosphatic fertilisers from Nauru island. Phosphate rock from this source has been reported to contain 75-110 mg/kg of cadmium (Bramley, 1990).

Surface soil cadmium concentrations were compared between farms receiving high (HF; 765 kg P/ha), low (LF; 113 kg P/ha) or no (UF) phosphate fertiliser inputs over the previous 20 year period (Loganathan *et al.*, 1995). Surface soil cadmium concentrations were markedly higher in HF farm soil (mean 0.4, range 0.18-0.60 mg/kg) than LF and UF farm soils (mean 0.10, range 0.02-0.19 mg/kg). Cadmium concentrations in mixed herbage reflected soil cadmium content with herbage from HF farms having a mean cadmium content of 0.32 mg/kg dry weight, while herbage from LF farms had a mean cadmium content of 0.063 mg/kg dry weight.

A four-year study was carried out to determine cadmium cycling on a sheep farm with variable fertiliser application rates in different paddocks (Roberts and Longhurst, 2002). The mean soil cadmium content was 0.36 mg/kg (range 0.15-0.60 mg/kg), but varied with fertiliser application rate (20, 50 or 100 kg P/ha). The mean pasture cadmium concentration was 0.28 mg/kg (range 0.17-0.46 mg/kg) and was correlated with soil cadmium. Cadmium concentrations were higher in weeds than in grass or legumes.

Similar soil cadmium concentrations were found in a study that compared the cadmium content of farmed soils (n = 312; median 0.44 mg/kg) to non-farmed soils (n = 86; median 0.20 mg/kg) (Longhurst *et al.*, 2004). Cadmium concentrations were highest in yellow-brown loam soils (median 0.67 mg/kg). Cadmium content of grasses on farmed soils was significantly correlated with soil cadmium and was in the range 0.03-0.31 mg/kg. Cadmium concentrations were lower in legumes (range 0.02-0.11 mg/kg) than grasses, but higher in weeds (range 0.09-0.50 mg/kg).

A larger data set, containing 293 soil samples from minimally disturbed conditions (MDC) and 1043 soil samples from a range of agricultural land uses, was analysed in association with land use data (McDowell *et al.*, 2013). The geometric mean cadmium concentration under the MDC land was 0.093 mg/kg (range <0.001-0.61 mg/kg), while under cultivated land the geometric mean concentration was 0.23 mg/kg (range 0.001-2.7 mg/kg). Cadmium

[6] The disease was the name given to the mass cadmium poisoning of Toyama Prefecture, Japan, starting around 1912. The term "*itai-itai* disease" was coined by locals for the severe pains (Japanese: 痛い *itai*) victims felt in the spine and joints (https://en.wikipedia.org/wiki/Itai-itai_disease)

concentrations were highest under land used for dairy and horticulture and lowest under land used for forestry.

Pasture herbage and soil samples were collected from 69 sites around New Zealand (Reiser *et al.*, 2014). The mean topsoil cadmium concentration (0.89; range 0.25-1.58 mg/kg) was higher than in other New Zealand studies. The pasture herbage sample had a mean cadmium content of 0.13 mg/kg and was correlated with soil cadmium.

While lower cadmium concentrations were seen in soils in Southland, the impact of agriculture was still apparent, with the mean cadmium content of pasture soil (0.097; range 0.02-0.61 mg/kg) being markedly higher than that of undisturbed land under native bush (0.028; range 0.005-0.24 mg/kg) (Martin *et al.*, 2017). Herbage was not analysed.

Differences between soil cadmium concentrations on North and South Island farms were also found in a long-term study of two dairy farms (Stafford *et al.*, 2018). A farm in the Waikato had a mean soil cadmium concentration of 1.04 mg/kg (range 0.48-1.64 mg/kg), while a farm in Canterbury had a mean soil cadmium concentration of 0.34 mg/kg (range 0.15-0.64 mg/kg). As with other studies, soil cadmium was correlated with soil phosphorus; indicating that phosphorus fertilisation was the primary source of soil cadmium.

The European Union specifies a maximum content of cadmium in feed materials of vegetable origin of 1 mg/kg (12% moisture basis) (EC, 2002).

4.2.5 Evidence of cadmium in New Zealand foods of animal origin

Dairy products and muscle meat in New Zealand generally contain very low concentrations of cadmium (<0.005 mg/kg). However, cadmium can accumulate in livers and kidneys of livestock. The maximum permitted limits for cadmium in kidneys, liver and meat of cattle, sheep, pigs, goat and deer are 2.5, 1.25 and 0.05 mg/kg, respectively (MPI, 2016a). These limits are aligned with maximum limits specified in the Australia New Zealand Food Standards Code, Schedule 19.[7]

Table 2 summarises information on the concentration of cadmium in dairy and meat/offal products from recent NZTDSs.

Table 2. Concentration of cadmium in selected foods from NZTDSs

Food	Cadmium concentration (mg/kg) for NZTDS year, mean (range)[a]			
	2016	2009	2003/2004	1997/1998
Milk, 0.5% fat	(<0.0002)	0.0031 (<0.0002-0.024)	0.0002 (<0.0002-0.0003)	0.002 (0.001-0.002)
Milk, 3.25% fat	(<0.0002)	0.0001 (<0.0002-0.0003)	0.0002 (<0.0002-0.0003)	0.002 (0.001-0.002)
Milk, flavoured	0.003 (0.001-0.005)	0.0009 (0.0003-0.002)	0.0008 (0.0003-0.0028)	
Butter	(<0.002)	(<0.002)	(<0.002)	0.003 (<0.002-0.005)
Cheese	(<0.0019-<0.002)	(<0.002)	0.0011 (<0.002-0.002)	0.004 (0.004-0.005)
Cream		(<0.0004)	(<0.0004-<0.0005)	
Dairy dessert	0.005 (0.0004-0.0112)	0.003 (<0.0004-0.008)	0.0008 (<0.0004-0.0017)	0.002 (0.002-0.002)
Ice cream	(<0.0004)	0.0017 (<0.0004-0.0077)	0.0004 (<0.0004-0.0017)	0.001 (0.001-0.001)
Infant/follow-on formula	(<0.002)	0.0002 (<0.0002-0.0004)	0.0002 (<0.0002-0.0007)	
Yoghurt	0.0004 (<0.0004-0.001)	0.0007 (<0.0004-0.0028)	0.0003 (<0.0004-0.0007)	0.002 (<0.001-0.003)
Beef, mince	0.0003 (<0.0004-0.0007)	0.0003 (<0.0004-0.0005)	0.0004 (<0.0004-0.0012)	(<0.0012-<0.0016)

[7] https://www.legislation.gov.au/Details/F2017C00333 Accessed 22 March 2019

Food	Cadmium concentration (mg/kg) for NZTDS year, mean (range)[a]			
	2016	2009	2003/2004	1997/1998
Beef, rump	(<0.0004)	0.0005 (<0.0004-0.0009)	0.0003 (<0.0004-0.0006)	(<0.0012-<0.0016)
Ham	0.0021 (0.001-0.005)	0.003 (0.0019-0.0049)	0.0021 (0.0017-0.0025)	
Lamb/mutton	(<0.0004)	0.0007 (<0.0004-0.0014)	0.0003 (<0.0004-0.0006)	0.002 (0.001-0.003)
Lambs' liver	0.078 (0.016-0.219)	0.103 (0.033-0.239)	0.102 (0.024-0.166)	0.113 (0.038-0.244)
Pork roast/chop	0.0003 (<0.0004-0.0006)	0.0009 (<0.0004-0.0033)	(<0.0004)	0.0008 (<0.0009-0.002)

[a] References: 2016 (Pearson *et al.*, 2018), 2009 (Vannoort and Thomson, 2011), 2003/2004 (Vannoort and Thomson, 2005), 1997/1998 (Vannoort *et al.*, 2000)

Foods of terrestrial animal origin are only minor contributors to dietary cadmium exposure in New Zealand (Pearson *et al.*, 2018).

A New Zealand survey was carried out on cadmium concentrations in retail sheep kidneys (*n* = 21), beef kidneys (*n* = 19) and pig livers (*n* = 20) (Rush, 1995). Mean concentrations were 0.277 mg/kg (range 0.022-3.03 mg/kg), 0.245 mg/kg (range 0.06-0.63 mg/kg) and 0.024 mg/kg (range 0.010-0.064 mg/kg), respectively. No information was available on the age of the animals that the offal were derived from.

A survey of standard milk samples (*n* = 32) found that all samples contained cadmium concentrations below the LOD (0.001 mg/kg) (Vannoort, 2001).

A four-year New Zealand farm study demonstrated negligible change in muscle cadmium concentrations of sheep from 18 months of age to 66 months (Roberts and Longhurst, 2002). While there were some increases in liver cadmium (0.31-0.40 mg/kg at 18 months to 0.45-0.51 mg/kg at 66 months), the main increase was in the cadmium content of kidneys (0.90-0.94 mg/kg at 18 months to 2.54-2.77 mg/kg at 66 months).

4.3 LEAD

Lead is ubiquitous in the environment and varies widely in concentration (EFSA, 2010). Human exposure to lead has largely been the result of pollution, particularly from alkyl lead fuel additives and lead-based paints. The concentration of lead in foods is extremely variable. In crops, the concentrations of lead reflect the level of pollution during the growing season. The use of lead solder in the manufacture of cans has also been a significant contributor to dietary intakes of lead. This manufacturing process has been discouraged and is now discontinued in New Zealand, and similarly for imported canned foods.

4.3.1 Animal toxicity

Lead poisoning of livestock is occasionally reported in New Zealand, but most usually is related to livestock chewing on lead automotive batteries left in paddocks. Lead-based paint on farm building can also be a source of lead poisoning, particularly in young cattle, due to their curiosity and propensity to chew items. Ingestion of ash residues from burning of items such as tyres has also been reported as a cause of lead poisoning in cattle (Schlerka *et al.*, 2004). Lead poisoning has also been reported in cattle grazing on fodder beet grown on gun club land (Anonymous, 2014). Inspection of the land found a large number of lead pellets, both in the soil and embedded in fodder beet stems and leaves. Worldwide, cattle are the livestock species most commonly affected by lead toxicity (Bischoff *et al.*, 2012).

Animals are usually reported with neurological signs, including ataxia, depression, blindness and seizures (Rumbeiha *et al.*, 2001). A diagnosis of lead poisoning is usually reached through testing of blood (>0.35 mg/L) or post-mortem analysis of liver (reference value 10-20 mg/kg) or kidney (reference value ≤25 mg/kg) (Barbosa *et al.*, 2014).

While chronic exposure to lead at sub-clinical concentrations has been shown to cause increases in biomarkers, such as blood and hair lead (Polizopoulou *et al.*, 1994), chronic lead exposure in livestock is generally asymptomatic (Bischoff *et al.*, 2012).

4.3.2 Transfer of toxic agents to edible tissues and products

Plants and animals may bioconcentrate lead, but lead is not biomagnified in the aquatic or terrestrial food chains (ATSDR, 2007b). This is partly explained by the fact that in vertebrates, lead is stored mainly in bone, which reduces the risk of lead transmission to other organisms in the food chain.

Holstein cows (3 groups of 5 animals) were administered 0.9, 1.8 or 3.6 g/day of lead for 30, 30 and 25 days, respectively (Wang *et al.*, 2018). Lead was added to feed as lead acetate. Peak concentrations of lead in milk were 0.083, 0.215 and 0.232 mg/kg for the three dose levels, respectively. The dose levels were very high and probably unrealistic. It should also be noted that the lead would not be present in the same form as lead incorporated into plant material during the growing process.

An accidental cattle lead poisoning incident, caused by cattle licking burnt storage batteries, was used to examine the transfer of lead into tissues and milk (Oskarsson *et al.*, 1992). In cattle without acute signs of lead poisoning (n = 8), mean lead levels in milk two weeks after exposure were 0.08 mg/kg. In eight animals, slaughtered due to clinical acute lead poisoning, lead concentration in edible muscle, kidney and liver were in the range 0.23-0.50, 70-330 and 10-55 mg/kg, respectively. The accidental nature of the exposure meant the exposure dose and the pre-exposure lead concentrations were unknown.

Soil, grass and milk lead concentrations were measured for a situation where cows were grazed on an area contaminated with mine tailings in Romania (Smical *et al.*, 2016). Soils were quite contaminated, with a mean lead concentration of 39.6 mg/kg dry weight, compared to an alert level of 20 mg/kg. The mean lead concentration in grass was 1.22 mg/kg dry weight, with a range in milk of 0.033-0.076 mg/L. Transfer factors were calculated, with the transfer factor from grass to milk (approximately 0.22) being higher than the transfer factor from soil to grass (approximately 0.14).

A study carried out in Pakistan measured lead in soil, forage and cows' milk from 13 farms (Batool *et al.*, 2016). Soil lead concentrations were in the range 1.16-1.46 mg/kg, while forage concentrations were also in the range 1.16-1.46 mg/kg. Raw milk lead concentrations (1.3-2.7 μg/L) were not correlated with lead concentrations in forage (Pearson correlation coefficient = -0.01).

Feed, muscle, kidney and liver lead concentrations were determined for cattle from 18 Iranian farms over four years (Hashemi, 2018). The mean concentrations in all matrices were remarkable similar, with mean concentrations in feed, muscle, kidney and liver of 0.236, 0.221, 0.244 and 0.273 mg/kg wet weight. A strong seasonal effect was seen, with lead concentrations in all three tissue types substantially higher in summer than the other three seasons. The authors suggested this may be associated with the low rainfall in the summer season, but did not identify an actual mechanism for the higher tissue concentrations.

4.3.3 Human toxicity

Lead has been implicated in a wide range of adverse chronic human health effects, including effects on the nervous system, cardiovascular effects, renal effects, immune system effects, haematologic effects, reproductive and developmental effects and cancer (EFSA, 2010; JECFA, 2011a; USEPA, 2013). The acute toxicity of lead is low (JECFA, 2011a).

IARC concluded that inorganic lead compounds were probably carcinogenic to humans, while organic lead compounds were not classifiable as to their human carcinogenicity (IARC, 2006).

The most sensitive adverse health effects from lead exposures are impairment of cognitive function in children, effects on systolic blood pressure in adults and renal effects.

Lead can impair cognitive function in children and adults, but children are more vulnerable than adults (ATSDR, 2007b). The greater impact of lead on the cognitive function of children than adults is partly due to their greater absorption of lead, but also due to the particular susceptibility of the developing nervous system to lead toxicity.

Meta-analysis of seven international population-based longitudinal cohort studies demonstrated a negative relationship between child blood lead levels (PbB) and IQ score (Lanphear *et al.*, 2005). The associated dose-response relationship shows no lower threshold, that is, there is no PbB where no decrement in IQ is observed. This health endpoint is considered to be the most sensitive for children and has been used as the basis for subsequent international risk assessments for the effects of lead on children (EFSA, 2010; JECFA, 2011a).

Evidence from epidemiologic and toxicological studies has demonstrated consistent effects of lead exposure on hypertension (USEPA, 2013). Longitudinal prospective studies consistently support the association of biomarkers of lead exposure with hypertension incidence and increased blood pressure, while a meta-analysis across three prospective studies and five cross-sectional studies reached similar conclusions (Navas-Acien *et al.*, 2008).

This health endpoint is considered to be the most sensitive for adults and has been used as the basis for subsequent international risk assessments for the effects of lead on adults (EFSA, 2010; JECFA, 2011a) (Sections 3.5, 3.6).

A number of potential mechanisms have been suggested for the impact of lead exposure on hypertension, including impairment of renal function, oxidative stress, effects on the renin-angiotensin system (hormone regulation of blood pressure), suppression of nitric oxide and induction of increased levels of homocysteine (EFSA, 2010; JECFA, 2011a).

It should be noted that increases in blood pressure associated with increases in lead exposure are consistent, but relatively modest.

Exposure to lead has been associated with deficits in renal function, such as changes in proteinuria, glomerular filtration rate (GFR) and creatinine levels and clearance (EFSA, 2010). Several epidemiological studies have shown associations between PbB and chronic kidney disease, defined as a GFR below 60 mL/1.73 m^2 body surface/minute (Fadrowski *et al.*, 2010; Muntner *et al.*, 2005; Navas-Acien *et al.*, 2009).

Associations have been observed in both cross-sectional and prospective epidemiological studies.

4.3.4 Evidence of lead in the New Zealand feed supply

A study was carried out to compare the lead content of different New Zealand soil types and associated herbage from farmed soils (n = 312) and non-farmed soils (n = 86) (Longhurst *et al.*, 2004). Lead concentrations were highest in brown granular loam soils (median 16 mg/kg) and lowest in peat soils (6 mg/kg). No significant differences were found between lead in farmed and non-farmed soils. Median lead concentrations in herbage were in the range 0.10-0.35 mg/kg, with concentrations in grass higher, on average, than concentrations in legumes or weeds. The authors noted that the lead concentrations in New Zealand pastoral soils and herbage were towards the lower end of the range seen internationally.

A study carried out in Southland showed broadly similar results, with a mean soil lead concentration under pasture of 11.3 mg/kg (Martin *et al.*, 2017). It was noted that the lead content of soils was influenced by proximity to urban centres and major roads.

An older study examined lead in soils and pasture adjacent to a main road (Ward *et al.*, 1979). Lead in both soil and herbage decreased sharply with distance from the road, with surface soil lead concentrations decreasing from several hundred mg/kg to 50 mg/kg or less for distances greater than 10 metres from the road margins. A similar trend was seen with leaf and root lead concentrations. Since this study, lead additives have been removed from petrol available in New Zealand and the results of this study are likely to have limited relevance to the current situation.

Another circumstance of relevance is the use of shooting range or ex-shooting range land for animal grazing. A survey of selected clay target shooting ranges in Canterbury found soil concentrations of lead in excess of 10,000 mg/kg (Rooney, 2002). The New Zealand Clay Target Association has developed a code of practice to control risks to food safety and animal welfare associated with such land (New Zealand Clay Target Association, 2019).

A Norwegian study of sheep grazing on a shooting range concluded that there was little or no accumulation of lead in the pasture grass and the liver lead concentrations of grazing sheep were not significantly different to those of sheep grazed elsewhere (Johnsen *et al.*, 2019). The lead content of grass samples from control and shooting range locations were all less than 2 mg/kg dry weight, while soil lead concentrations were up to 7,200 mg/kg dry weight. The study also estimated the soil ingestion by sheep, using titanium as a tracer. The resulting estimates were extremely low for sheep (0.1-0.4%).

Investigation of an incident of cattle lead poisoning in Southland, due to cattle grazing on fodder beet on a gun club site, found high lead concentrations in the soil and plant tops (518 and 184 mg/kg dry weight, respectively) (Anonymous, 2014).

The European Union specifies a maximum content of lead in forage of 30 mg/kg (12% moisture basis) (EC, 2002).

4.3.5 Evidence of lead in New Zealand foods of animal origin

Dairy products and muscle meat in New Zealand generally contain very low concentrations of lead (<0.005 mg/kg). While lead can accumulate in livers and kidneys of livestock, concentrations of lead in these tissues are generally <0.1 mg/kg. The maximum permitted limit for lead in offal of any animal is 0.5 mg/kg, while the maximum permitted limit for meat is 0.1 mg/kg (MPI, 2016a). These limits are aligned with maximum limits specified in the Australia New Zealand Food Standards Code, Schedule 19.[8]

Table 3 summarises information on the concentration of lead in dairy and meat/offal products from recent NZTDSs.

Table 3. Concentration of lead in selected foods from NZTDSs

Food	Lead concentration (mg/kg) for NZTDS year, mean (range)[a]			
	2016	2009	2003/2004	1997/1998
Milk, 0.5% fat	(<0.001)	(<0.001)	(<0.001)	(<0.003-<0.006)
Milk, 3.25% fat	(<0.001)	(<0.001)	0.0006 (<0.001-0.001)	(<0.003-<0.006)
Milk, flavoured	0.001 (<0.001-0.002)	0.0007 (<0.001-0.001)	0.0008 (<0.001-0.002)	
Butter	(<0.01)	0.0088 (<0.01-0.035)	(<0.01)	(<0.014)
Cheese	(<0.01)	0.0017	(<0.01)	(<0.014)
Cream		(<0.002)	(<0.002)	
Dairy dessert	0.002 (<0.002-0.005)	0.0023 (<0.002-0.004)	(<0.002)	0.0053 (<0.007-0.007)
Ice cream	(<0.002)	(<0.002)	0.0013 (<0.002-0.003)	(<0.007)

[8] https://www.legislation.gov.au/Details/F2017C00333 Accessed 22 March 2019

Food	Lead concentration (mg/kg) for NZTDS year, mean (range)[a]			
	2016	2009	2003/2004	1997/1998
Infant/follow-on formula	(<0.01)	0.0009 (<0.001-0.002)	0.0012 (<0.001-0.005)	
Yoghurt	0.001 (<0.002-0.002)	0.0021 (<0.002-0.004)	0.0014 (<0.002-0.003)	(<0.007)
Beef, mince	0.001 (<0.002-0.002)	0.0042 (<0.002-0.012)	0.003 (<0.002-0.007)	(<0.007-<0.011)
Beef, rump	0.001 (<0.002-0.002)	0.0035 (<0.002-0.008)	0.0035 (<0.002-0.011)	(<0.007-<0.011)
Ham	0.005 (0.003-0.007)	0.0047 (<0.002-0.010)	0.0055 (0.003-0.009)	
Lamb/mutton	(<0.002)	0.0022 (<0.002-0.004)	0.0048 (<0.002-0.012)	(<0.007)
Lambs' liver	0.027 (0.01-0.054)	0.029 (0.011-0.053)	0.027 (0.016-0.040)	0.064 (<0.007-0.214)
Pork roast/chop	(<0.002)	0.0022 (<0.002-0.005)	0.0065 (<0.002-0.014)	(<0.007)

[a] References: 2016 (Pearson *et al.*, 2018), 2009 (Vannoort and Thomson, 2011), 2003/2004 (Vannoort and Thomson, 2005), 1997/1998 (Vannoort *et al.*, 2000)

Foods of terrestrial animal origin are only minor contributors to dietary lead exposure in New Zealand (Pearson *et al.*, 2018).

4.4 MERCURY

Mercury is concentrated in the earth's crust into a relatively small number of rich ore belts associated with volcanic activity (Clarkson, 1987). Both inorganic and organic forms of mercury are found in food. The level of mercury in foods is variable and reflects the levels of contamination in the area of cultivation. Livestock concentrate environmental mercury in the liver and kidney (WHO, 1991a; b).

4.4.1 Animal toxicity

There have been reports of experimentally-induced mercury poisoning in sheep (Stoev and Lazarova, 1998), goats (Pathak and Bhowmik, 1998) and pigs (Raszyk *et al.*, 1992). Effects were seen in a range of organ systems, including the gastrointestinal tract, kidneys, liver, spleen, heart and brain. The kidneys are the major site of deposition for mercury and appears to be the site of the most profound cytotoxic changes.

A retrospective analysis of toxic metal analyses in a veterinary diagnostic toxicology laboratory in Ontario, Canada noted that mercury poisoning was only reported for fish-eating raptors (Hoff *et al.*, 1998).

Mercury poisoning was diagnosed in four dairy heifers and was fatal in three cases (Simpson *et al.*, 1997). Clinical signs varied between animals and included salivation, excessive thirst, extreme depression and severe diarrhoea. Post-mortem examination revealed inflammation and ulceration of the alimentary tract, pulmonary and cardiac haemorrhages, pallor of the kidney cortices and peri-renal oedema. It was believed that the heifers were poisoned by ingesting soil contaminated with mercurous chloride.

In general, it would appear unlikely for pasture or forage to become contaminated with mercury at a sufficient level to cause intoxication.

4.4.2 Transfer of toxic agents to edible tissues and products

Hashemi (2018) found only very low concentrations of mercury in bovine muscle, liver and kidney, with mean concentrations of 0.003, 0.002 and 0.003 mg/kg wet weight, respectively. No correlations were found between tissue mercury concentrations and the concentrations in feed.

A Polish study found very similar results, with mean concentrations in muscle and liver of cattle and pigs and in bovine milk not exceeding 0.001 mg/kg wet weight (Szkoda *et al.*, 2013). The

maximum mercury concentration in muscle meat was 0.019 mg/kg and in milk was 0.005 mg/kg.

Transfer of mercury to tissues of lambs was examined after administration of a single dose of ^{203}Hg (Beresford *et al.*, 1999). Except for one animal, absorption of mercury was very low (<1%), with the majority excreted in faeces. After 181 days, 0.2% of the dose was present in muscle of a total of 0.5% retained in tissues.

4.4.3 Human toxicity

The adverse health effects due to mercury exposure show some variation, depending on the form of mercury and the route of exposure. Mercury may be present in foods as inorganic mercury or in organic forms, mainly methylmercury.

Mercury can present an acute health concern at higher levels, causing damage to the heart and blood supply, the kidneys and the gastrointestinal tract (JECFA, 2011c). However, the chronic toxicity of mercury is most relevant to public health. Chronic poisoning with inorganic mercury usually manifests as tremors, neuropsychiatric effects, such as delirium, impacts on emotions, insomnia and memory loss; and inflammation and lesions forming in the mouth and on the gums (JECFA, 2011c).

A range of neurological effects have been reported in children chronically exposed to inorganic mercury, including developmental delays and regression (JECFA, 2011c)

The organic form of mercury, methylmercury, presents the greater health hazard. Methylmercury is more readily absorbed from the diet and, unlike inorganic mercury, can readily cross the placental barrier to the developing foetus. Methylmercury exposure in the foetus is associated with developmental delays after birth, including potentially permanent impacts on motor skills, attention and cognition (EFSA, 2004).

4.4.4 Evidence of mercury in the New Zealand feed supply

No information was found on the mercury content of animal feed in New Zealand.

A study in the south of New Zealand reported low soil mercury concentrations, with a mean concentrations under pasture of 0.057 mg/kg (Martin *et al.*, 2017). Mercury concentrations in non-cultivated soils were higher (mean 0.082 mg/kg). This publication also gave a 'world' average for topsoil of 0.05 mg/kg.

A soil survey in the Auckland region reported mercury concentrations in the range <0.03-0.45 mg/kg (ARC, 1999). Higher soil mercury concentrations in this region would be expected due the volcanic origins of many of the soils (Adamse *et al.*, 2017).

The European Union specifies a maximum content of mercury in feed materials of 0.1 mg/kg (12% moisture basis) (EC, 2002).

4.4.5 Evidence of mercury in New Zealand foods of animal origin

Dairy products and muscle meat in New Zealand generally contain very low concentrations of mercury. In the 2016 NZTDS, lambs' liver was the only food of terrestrial animal origin to contain detectable concentrations of mercury (maximum 0.006 mg/kg) (Pearson *et al.*, 2018). The maximum permitted limits for mercury in animal products include 1.5 mg/kg in kidneys of wild animals, 1 mg/kg in pig kidneys, 0.1 mg/kg in pig and wild animal livers, 0.03 mg/kg in kidneys and livers of other animals and 0.01 mg/kg in mammalian meat (MPI, 2016a).

Foods of terrestrial animal origin are only minor contributors to dietary mercury exposure in New Zealand (Pearson *et al.*, 2018).

4.5 SELENIUM

Selenium is an essential dietary trace non-metal element. The selenium content of soil varies geographically and impacts on the selenium content of the food supply. In New Zealand, the selenium content of the soil is low, with about 30% of New Zealand soils classified as selenium deficient (Wichtel, 1998).

While selenium poisoning has been reported in New Zealand livestock, this has been solely associated with over-administration of selenium supplements (Clark, 1993).

Given this situation, further information on selenium toxicity has not been included in the current document.

4.6 COPPER

Copper is an essential trace element. However, it is also used as a fungicide, mainly in organic agriculture. Surveys of soil copper in New Zealand have shown mean concentrations in the range 3.6-44.5 mg/kg, depending on the soil type (ARC, 1999; Longhurst *et al.*, 2004). This appears similar to mean soil copper concentrations in the European Union, which were reported to be in the range 9.4-49.3 mg/kg, depending on land use type (Ballabio *et al.*, 2018) and the USA, with a reported mean copper content for agricultural soils of 30 mg/kg (Holmgren *et al.*, 1993). The US study also reported a geometric mean for 'world soils' of 60 mg/kg.

4.6.1 Animal toxicity

Both copper deficiency and copper toxicity have been reported in stock animals in New Zealand. While copper toxicity appears to primarily related to misuse of animal therapeutic products, toxicity has also been reported in relation to the feeding of palm kernel expeller in New Zealand (Anonymous, 2009; Varney and Gibson, 2008) and overseas (Chooi *et al.*, 1988). Overseas, copper toxicity in lambs has also been associated with feeding of sunflower meal (Garcia-Fernandez *et al.*, 1999). Copper toxicity has also been reported in sheep following copper sulphate treatment of fruit trees in the paddock in which they were feeding (Oruc *et al.*, 2009).

Copper accumulates in the liver, leading to necrosis, haemolysis and haemoglobinuria (Bozynski *et al.*, 2009; Mendel *et al.*, 2007). Intoxication may then progress to effects on the kidney, typically haemoglobinuric nephrosis (Castro *et al.*, 2007).

Sheep are particularly susceptible to copper poisoning, due to their high rate of hepatic copper accumulation and their low rates of excretion (Castro *et al.*, 2007).

Copper poisoning is exacerbated by low molybdenum intake and the presence in the diet of hepatotoxins, such as pyrrolizidine alkaloids (Bozynski *et al.*, 2009; Castro *et al.*, 2007).

4.6.2 Transfer of toxic agents to edible tissues and products

In a study carried out in Pakistan, a good correlation was found (Pearson correlation coefficient = 0.49) between copper in forage and copper in bovine milk (Batool *et al.*, 2016). The mean concentrations of copper in milk across 13 dairy farms were in the range 33-46 μg/L.

Analysis of soil, grass and milk samples from a polluted area in Romania allowed calculation of transfer factors for seven contaminant elements (Smical *et al.*, 2016). The calculated transfer factors are simple ratios of concentrations in the different matrices, rather than the actual proportion of the elements that is transferred. Transfer of copper from grass to milk was less than for lead, cadmium and zinc, but greater than for manganese, chromium and nickel.

A New Zealand study found an even stronger relationship (R^2 = 0.84) between herbage copper and copper accumulated in the livers of Romney sheep (Grace *et al.*, 1998). Liver copper concentrations reached as high as 450 mg/kg fresh weight, without any overt signs of toxicity in the sheep.

In contrast Hashemi (2018) found no significant correlation between copper in bovine feed and copper concentrations in tissues (muscle, liver and kidney). Copper concentrations in muscle meat (mean = 0.85 mg/kg wet weight, range 0.15-3.6 mg/kg) were appreciably lower than in liver (mean = 4.6 mg/kg wet weight, range 0.14-17.1 mg/kg) or kidney (mean = 2.7 mg/kg wet weight, range 0.18-7.6 mg/kg).

Cattle and buffalo received daily doses of copper equivalent to 80 mg/animal (Minervino *et al.*, 2009). Liver biopsy samples were taken on day 0, 45 and 105. Mean liver concentrations in cattle increased from 168 mg/kg on day 0, to 524 mg/kg on day 45 and 2620 mg/kg on day 105. In buffalo, liver copper concentrations increased from 262 mg/kg on day 0, to 649 mg/kg on day 45 and 1698 mg/kg on day 105.

4.6.3 Human toxicity

Copper is an essential trace element, but can be toxic at high levels of exposure. Copper intoxication in humans is rare in the absence of pathology such as Wilson's disease (National Health and Medical Research Council/Ministry of Health, 2006). As with animals, adverse effects are primarily related to accumulation of copper in the liver and resultant haemolytic crisis (Davis and Mertz, 1987).

4.6.4 Evidence of copper in the New Zealand feed supply

In an experimental study, application of copper fertiliser at rates in the range 0.4 to 4 kg/ha resulted in mean pasture (mixed ryegrass/clover) copper concentrations in the range 12.9 to 140 mg/kg dry weight (Grace *et al.*, 1998). Herbage copper concentrations were maximal 65 days post-application and had returned to pre-application levels by 374 days. The background mean concentration of copper in pasture was 8.1 mg/kg dry weight. This is largely consistent with a Pakistani study that reported mean forage copper concentration on 13 farms in the range 6.5-7.3 mg/kg (Batool *et al.*, 2016). Sunflower meal, associated with copper toxicosis in lambs, contained copper concentrations of 8.5-10 mg/kg (presumably wet weight basis) (Garcia-Fernandez *et al.*, 1999).

As part of an investigation of copper toxicity in a New Zealand dairy herd, copper concentrations were determined in samples from four pastures (Johnston *et al.*, 2014). Copper concentrations in three pastures were in the range 9-11 mg/kg dry weight, while in the fourth pasture the concentration was 17 mg/kg dry weight.

A survey of 398 agricultural and non-agricultural sites in New Zealand reported mean copper concentrations in soil, by soil type, ranging from 8.7 to 32.3 mg/kg (Longhurst *et al.*, 2004). Copper concentration in grass were in the range 8-12.5 mg/kg, while slightly higher concentrations (up to 18 mg/kg) were reported in legume and weed samples from the same sites.

Palm kernel expeller has been reported to contain greater than 20 mg/kg of copper, on a dry weight basis (Alimon, 2019; Varney and Gibson, 2008).

4.6.5 Evidence of copper in New Zealand foods of animal origin

Copper is an essential trace element for animal nutrition and concentrations in animals will be regulated by homeostatic mechanisms. Copper was last included in the NZTDS in 1990-1991 (Hannah *et al.*, 1995). Mean copper concentrations in mammalian muscle meats were in a fairly narrow range (1.0-1.9 mg/kg), while the mean concentration in lambs' liver was considerably higher (128 mg/kg). Dairy products had uniformly low mean copper concentrations (not detected to 0.3 mg/kg). These concentrations are very similar to findings

from the 2016 NZTDS (Andrew Pearson, MPI, personal communication) and are largely consistent with overseas findings (FSANZ, 2011; Rose *et al.*, 2010).

Foods of terrestrial animal origin are an important dietary source of copper in New Zealand (Hannah *et al.*, 1995).

4.7 NICKEL

Nickel is not considered to be essential to humans, but may be essential to some plants and bacteria.

4.7.1 Animal toxicity

There is little information on the toxicity of nickel to other than experimental animals.

Calves were administered 0, 62.5, 250 or 1000 mg/kg of nickel for eight weeks (O'Dell *et al.*, 1970). Animals in the highest dose group ate little and lost weight, but did not become emaciated. Calves receiving 250 mg/kg consumed 13% less food than controls and gained 11% less weight. No effect was seen in calves receiving 62.5 mg/kg nickel.

It has been suggested that these observations may have been due to decreased palatability of the feed, rather than due to a toxic effect.

4.7.2 Transfer of toxic agents to edible tissues and products

While not directly reporting on edible tissues, a Pakistani study reported a negative association between nickel in forage and nickel in the blood of rams consuming the forage (Khan *et al.*, 2013).

A Romanian study examined transfer of heavy metals from soil to vegetation and from vegetation to milk (Smical *et al.*, 2016). Of the seven metals considered, nickel showed the lowest rate of transfer from soil to vegetation and the third-lowest rate of transfer from vegetation to milk.

EFSA reviewed information on the transfer of feed nickel to milk and animal tissues (EFSA, 2015b). Studies summarised were consistent in concluding that supplementation of the animal diet with nickel had no impact on the nickel content of milk. Leeman *et al.* (2007) used literature data to derive a 95th percentile estimate of the transfer factor for transfer of nickel from feed to milk of 0.024. The same study estimated 95th percentile transfer factors for muscle, fat, liver and kidney of 0.58, 0.12, 0.70 and 0.70.

4.7.3 Human toxicity

Most of the information on the toxicity of nickel to humans comes from occupational studies, in which exposure is via inhalation, which are not relevant for dietary risk assessment purposes (FSANZ, 2008). Oral exposure to nickel has been shown to cause hypersensitivity in people previously sensitised via the dermal route to metallic nickel or nickel salts, with oral doses as low as 220 µg causing a positive response in some sensitive individuals (Casalegno *et al.*, 2015; EFSA, 2015a).

It has also been reported that oral nickel salt exposure may cause gastrointestinal effects (EFSA, 2015a; Nielsen, 1987). However, this appears to be due to local irritation, rather than systemic toxicity. Neurological effects (giddiness, headache, weariness) have also been reported in some cases (Casalegno *et al.*, 2015; EFSA, 2015a).

4.7.4 Evidence of nickel in the New Zealand feed supply

A survey of metal concentrations in soils in the Auckland region found elevated nickel concentrations in volcanic soils (mean = 87 mg/kg), while mean nickel concentrations in other soil types were in the range 2.7-9.0 mg/kg (ARC, 1999). This is consistent with a

survey of metal concentrations in topsoils from the Southland region (non-volcanic), with a mean of 8.0 mg/kg and a range of 1.8-54 mg/kg (Martin *et al.*, 2017).

In a study carried out in Canterbury a 'background' soil contained 7 mg/kg of nickel, while a sewage-treated soil contained 35 mg/kg of nickel (Gray and McLaren, 2005). In 11 rye grass cultivars grown on the two soils mean nickel concentrations were 1.0 and 42.6 mg/kg, respectively. It is unclear from this paper whether forage metal contents were reported on a fresh or dry weight basis.

A study in the Philippines reported a negative correlation between nickel in soil and nickel in forage grown on the soils (Khan *et al.*, 2016).

4.7.5 Evidence of nickel in New Zealand foods of animal origin

Nickel concentrations in New Zealand foods were examined as a component of the 2016 NZTDS. While the results of these analyses have not yet been published, nickel was only detected in two meat samples, one each of bacon and mince, both at concentrations of 0.02 mg/kg. Nickel was not detected in any dairy products above the LOD of 0.1 mg/kg (Andrew Pearson, MPI, personal communication).

The 22nd Australian Total Diet Study included analysis for nickel (FSANZ, 2008). Nickel concentrations in foods of animal origin were generally low (<0.03 mg/kg). The highest nickel concentrations were observed in peanuts (mean = 1.9 mg/kg), desiccated coconut (1.4 mg/kg) and avocado (1.0 mg/kg). Foods of animal origin made only a minor contribution to dietary nickel exposure.

4.8 CHROMIUM

Chromium is a transition metal ubiquitous in the environment from erosion of chromium-containing rocks. Chromium has a wide range of oxidation states from -2 to +6. The most stable and commonly occurring states are trivalent (chromium +3, Cr(III)), a form has been considered an essential element for humans and found in food; and hexavalent (chromium +6, Cr(VI)), which is toxic and a known carcinogen (EFSA, 2014a; b). The role of Cr(III) in the body and its classification as an essential element were reviewed by EFSA, who concluded that beneficial effects of Cr(III) intake were not observed in healthy populations, and therefore there is no evidence to suggest chromium is essential in the body (EFSA, 2014b).

4.8.1 Animal toxicity

While Cr(III) is generally considered to be beneficial to livestock, some cases of poisoning have been reported (EFSA, 2009c). Calves were accidentally poisoned with an unknown amount of Cr_2O_3 from dyestuffs. Animals became lethargic, with elevated respiratory and heart rates, diarrhoea and abdominal distress, paresis and paralysis. A high rate of mortality occurred. At necropsy, catarrhal enteritis, greenish faeces, liver and kidney degeneration, and cerebral oedema were found. Studies in cattle, pigs and horses have reported reduced weight gains in animals receiving chromium-supplemented feed, although findings from different studies are often contradictory (EFSA, 2009c)

4.8.2 Transfer of toxic agents to edible tissues and products

Most of the information available on transfer of chromium from feed to edible tissues and products is based on studies where chromium was added to feed, rather than on chromium naturally present in feed. It is uncertain what impact this would have on estimates of chromium transfer.

Holstein cows (3 groups of 5 animals) were administered 0.47, 1.5 or 4.7 g/day of chromium, as chromium (III) nicotinate for 40 days, respectively (Wang *et al.*, 2018). Chromium

concentrations remained relatively stable (about 0.1 mg/kg) for all dose groups, indicating little transfer from feed to milk through the course of the experiment.

These results are consistent with an earlier study in which chromium, as chromium-methionine, was supplemented into the diet of groups of Holstein cows at rates of 0, 0.03, 0.06 and 0.12 mg/kg bw for 56 days (Hayirli *et al.*, 2001). Mean milk chromium concentrations were virtually identical between treatment groups, with concentrations in the range 0.055-0.057 mg/L.

In beef cattle, supplementation of feed did not result in any consistent significant changes in the chromium concentration of muscle, liver or kidney (EFSA, 2009c). In pigs, the chromium content of muscle did not appear to be influenced by supplementation of feed with several inorganic and organic chromium (III) sources, at supplementation rates of 0.2 mg/kg. However, the chromium content of liver and kidney was increased by supplementation with chromium in the form of acetate, oxalate and picolinate. It is difficult to draw general conclusions across studies as the concentration of chromium in the muscles of unsupplemented pigs varied from <1.5 μg/kg to 96 μg/kg (EFSA, 2009c).

A Romanian study examined transfer of heavy metals from soil to vegetation and from vegetation to milk (Smical *et al.*, 2016). Of the seven metals considered, chromium showed the second-lowest rate of transfer from soil to vegetation and from vegetation to milk.

4.8.3 Human toxicity

While there are now doubts as to the essential requirement of chromium (III) for humans, there is little evidence for its oral toxicity. EFSA has reviewed information on the adverse effects in humans due to chromium (III) exposure (EFSA, 2014a). While there was some fragmentary evidence of adverse effects following inhalation and dermal exposure, no reports of adverse effects following oral exposure were included in the EFSA report.

Chromium (VI) compounds have been classified as carcinogenic to humans (Group 1) with respect to the cancer of the lung and also cancer of the nose and nasal sinuses based on evidence from occupational studies (IARC, 2012). Oral studies in humans have reported occurrence of oral ulcers, diarrhoea, abdominal pain, indigestion, vomiting, leukocytosis, and immature neutrophils (EFSA, 2014a).

4.8.4 Evidence of chromium in the New Zealand feed supply

A survey of metal concentrations in soils in the Auckland region found chromium concentrations in volcanic soils in the range 3-125 mg/kg (geometric mean = 48 mg/kg), while chromium concentrations in other soil types were in the range 2-55 mg/kg (geometric mean = 7.0-14 mg/kg depending on the soil type) (ARC, 1999). This is consistent with a survey of metal concentrations in topsoils from the Southland region (non-volcanic), with a mean of 14.1 mg/kg and a range of 3.7-72 mg/kg for pasture soils (Martin *et al.*, 2017).

A study in the Waikato indicated that land use may have an impact on soil chromium, with mean soil chromium concentrations ranging from approximately 10 mg/kg on dairy farms to 20 mg/kg on cropping farms (Taylor *et al.*, 2011). The authors of this study suggested that variation in chromium content of soils may be influenced by use of copper-chrome-arsenic (CCA) treated timber.

No information was found on the chromium content of pasture or other forage in New Zealand.

4.8.5 Evidence of chromium in New Zealand foods of animal origin

Chromium was examined in the 1982 and 1987/1988 NZTDSs (ESR/MoH, 1994; Pickston *et al.*, 1985). The 1982 NZTDS used a food composite approach, where a number of different foods are combined in the proportions they are consumed in the diet, to produce a single

analytical sample. For chromium, foods of animal origin (meat, fish, eggs and dairy products) contributed approximately one-third of the estimated dietary chromium exposure.

Table 4 summarises information on the concentration of chromium in dairy and meat/offal products from the 1987/88 NZTDS.

Table 4. Concentration of chromium in selected foods from 1987/88 NZTDS

Food	Chromium concentration (mg/kg) for 1987/88 NZTDS, mean[a]
Milk, 0.5% fat	0.04
Milk, 3.25% fat	0.02
Butter	<0.02
Cheese	<0.02
Ice cream	<0.02
Yoghurt	<0.02
Beef, mince	0.05
Beef, rump	0.02
Beef, topside roast	<0.02
Lamb, shoulder chops	<0.02
Lamb, leg roast	0.04
Lambs' liver	0.03
Pork pieces	0.03

[a] Reference: ESR/MoH (1994)

Chromium concentrations in foods were within a narrow range, with all but one food (bacon 0.15 mg/kg) having chromium concentrations in the range <0.02-0.05 mg/kg. While not yet published, the chromium results from the 2016 NZTDS were very similar to those from the 1987/88 NZTDS (Andrew Pearson, MPI, personal communication).

Chromium was analysed in Australian foods as part of the 22nd Australian Total Diet Study (FSANZ, 2008). Mean chromium concentrations in dairy products were in the range 0.005-0.038 mg/kg and in red meats were in the range 0.007-0.02 mg/kg.

While these two sources of information on the chromium content of food are in reasonably good agreement, other sources, such as the second French Total Diet Study, report chromium concentrations consistently an order of magnitude greater than those reported for New Zealand and Australia (Noël *et al.*, 2012).

5. ENVIRONMENTAL CONTAMINANTS

5.1 DIOXINS AND POLYCHLORINATED BIPHENYLS (PCBS)

Dioxins and PCBs are highly stable chlorinated cyclic organic compounds. The term dioxins is usually used to refer to polychlorinated dibenzo-*p*-dioxins (PCDDs) and dibenzofurans (PCDFs). PCDD/Fs have never been produced on an industrial scale and have no technological use. They are formed unintentionally in a number of industrial and thermal processes like the burning of some waste and the production of various chlorinated chemicals (EFSA, 2018a).

PCBs are a group of chlorinated compounds based on a biphenyl structure. Depending on the number of chlorine atoms (1–10) and their position on the two rings, 209 different compounds or congeners are possible. As a result of their physicochemical properties, such as non-flammability, chemical stability, high boiling point, low heat conductivity and high dielectric constants, PCBs were widely used in a number of industrial and commercial applications. PCBs were often used in transformers and as heat exchange fluids (EFSA, 2018a).

PCBs are commonly divided into two groups based on structural characteristics and toxicological effects. Dioxin-like PCBs (DL-PCBs) are 12 congeners that are non-ortho or mono-ortho chlorine substituted. Congeners in this group contain at least four chlorine substituents, can easily adopt a coplanar structure and show toxicological properties similar to dioxins. The other 197 PCB congeners are termed non-dioxin-like PCBs (NDL-PCBs) and include also non- or mono-ortho PCBs that contain less than four chlorines. The chemical structure and toxicity profile of NDL-PCB congeners differs from that of dioxins (EFSA, 2018a).

Due to the greater availability of information, this section will primarily discuss the dioxins and DL-PCBs.

5.1.1 Animal toxicity

EFSA reviewed information on dioxin and PCB exposure incidents involving cattle, sheep, goats and pigs, as well as companion and non-mammalian animals (EFSA, 2018a). While elevated exposure to dioxins and PCBs could be demonstrated, in most cases co-exposure to other environmental contaminants, such polycyclic aromatic hydrocarbons (PAHs) was probable. Effects reported included:

- Oxidative damage and reduced level of antioxidants in animal blood
- Increases in chromosomal aberrations
- Increases in sister chromatid exchange (SCE)

In all cases, EFSA concluded that the studies were not suitable for deriving a toxicological reference point.

5.1.2 Transfer of toxic agents to edible tissues and products

Due to their stability and lipophilicity, dioxins and PCBs accumulate in tissues of food-producing animals and can be excreted in fat-containing products such as milk (EFSA, 2018a). However, there are marked toxicokinetic differences between dioxin/PCB congeners and some congeners accumulate in the liver, rather than in fat, due to their binding to specific cytochrome P450 enzymes (EFSA, 2018a).

EFSA summarised transfer rates (TRs) for various dioxins and DL-PCBs (EFSA, 2018a). The transfer rate is defined as the amount excreted in milk as a percentage of the amount ingested. It should be noted that, as these compounds accumulate in fatty tissues or the liver, it is estimated that a steady-state relationship between exposure and excretion will only

be reached after several months. None of the studies summarised were conducted over such a time frame and the TRs should be viewed as indicative. Mean TRs across studies varied in the range 1-40%. Less chlorinated dioxins show higher TRs than more chlorinated congeners, due to their greater absorption from the gastrointestinal tract. However, considerable congener to congener variability was observed, with both absorption and metabolism contributing to TRs.

Less information is available on the transfer of dioxins and PCBs to meat. EFSA summarised information on studies in cattle, sheep, goats and pigs (EFSA, 2018a). Most of the studies summarised considered the distribution of residues to back fat, liver and muscle. In general, lipid-based levels in muscle were greater than in adipose tissues, while those in the liver were greater again. However, when contaminated feed is replaced by clean feed, levels in muscle decrease more quickly than those in adipose tissue.

5.1.3 Human toxicity

EFSA reviewed the epidemiological information examining associations between dioxin and/or DL-PCB body burden and various health endpoints (EFSA, 2018a).

Chloracne[9], observed in accidental, occupational and unresolved poisoning cases with dioxins and DL-PCBs, is the adverse health effect with the strongest evidence for a causal relationship, with children appearing to be particularly sensitive. However, chloracne only occurs after high exposures (resulting in serum levels >20,000 pg/g fat). There is insufficient information with respect for an association between DL-PCBs exposure and chloracne, independent of dioxin exposure.

There is consistent evidence for an association between post-natal exposure to dioxins and impaired semen quality in males. Again, this association is not independently apparent for DL-PCBs.

While associations to other developmental and reproductive effects in males (cryptorchidism) and females (endometriosis, pubertal development, menstrual cycle characteristics, ovarian function, time to pregnancy, uterine leiomyoma and age at menopause) have been examined in some studies, EFSA concluded that there was insufficient evidence to conclude a causal association.

A relationship between high dioxin exposure in fathers and a low male to female ratio in offspring was seen consistently in three cohort studies and was considered to be likely to be causal. However, associations with other birth outcomes were considered to be inconclusive.

An association between childhood exposure to dioxins and tooth enamel hypomineralisation was considered to be likely to be causal.

Other endpoints for which the evidence was considered to be inconclusive were thyroid disease and function, type 2 diabetes and obesity, cardiovascular mortality, hepatic or digestive diseases, immune system effects, neurodevelopmental outcomes, and specific cancer types.

Adverse effects associated with NDL-PCBs have also been considered (JECFA, 2016). Studies are complicated by the fact the exposure to NDL-PCBs is generally accompanied by co-exposure to DL-PCBs. Potential health effects associated with exposure to NDL-PCBs

[9] Chloracne is a persistent cystic and hyperkeratotic skin malady. The most important features are non-inflammatory alterations of keratinisation of the pilosebaceous glands resulting in initial erythema followed by comedones, cysts, pustules and abscesses that lead to scarring.

include changes in thyroid hormone homeostasis, neurodevelopmental effects, immunological effects and some types of cancer. Associations with cancer appear to be strongest for associations between NDL-PCB exposure and melanoma.

5.1.4 Evidence of dioxins and PCBs in the New Zealand feed supply

A survey of organochlorine compounds in New Zealand soils reported that mean dioxin levels, expressed as international toxic equivalents, were lowest in agricultural land, compared to indigenous forest and grasslands, and provincial and metropolitan centres (Buckland *et al.*, 1998a). A similar pattern was seen for the sum of PCB congeners. However, the dioxin and PCB content of New Zealand soils was reported to be "consistently lower than concentrations reported in soils collected from Europe and North America". Incidents of feed contamination overseas have generally been due to the contamination of compound feed material by a contaminated ingredient or additive (Malisch and Kotz, 2014). Three examples from Europe are:

- Contamination of citrus pulp pellets, used as a component of compound feed for dairy cattle, with contaminated lime
- Contamination of fat used in the product of animal feed
- Contamination of poultry feed with a dioxin-containing clay, used as a flowing agent.

While there is no information to provide confirmation, it appears highly unlikely that forage material in New Zealand would be highly contaminated with dioxins or PCBs.

The European Union specifies a maximum content of dioxins (PCDDs and PCDFs) in feed materials of plant origin of 0.75 ng Toxic Equivalent Quotient (TEQ)/kg (12% moisture basis) (EC, 2002). A maximum content of 1.25 ng TEQ/kg is also specified for the sum of dioxins and PCBs and a maximum content of 10 μg/kg for the sum of six NDL-PCBs in feed materials of plant origin.

5.1.5 Evidence of dioxins and PCBs in New Zealand foods of animal origin

A diet study was conducted as part of the Ministry for the Environment's organochlorines programme (Buckland *et al.*, 1998b). The highest concentrations of dioxins, expressed as international toxic equivalents (I-TEQ) were detected in fat from fish (0.41-1.82 ng I-TEQ/kg) and fat from cereal products and bread (0.19-0.66 ng I-TEQ/kg). Given the highly lipophilic nature of these compounds, levels in fat from meat and meat products (0.072-0.57 ng I-TEQ/kg) and fat from dairy products (0.056-0.26 ng I-TEQ/kg) were modest. A similar pattern of residues was seen for the sum of PCB congeners, with the highest concentrations in fat from fish. Dietary exposure estimates for dioxins and PCBs were reported to be low by international standards.

Maximum permitted limits for coplanar PCBs mammalian or avian meat and fat in New Zealand is 0.5 ng TEQ/kg (MPI, 2016a). The Australia New Zealand Food Standards Code, Schedule 19 gives maximum limits for total PCBs of 0.2 mg/kg in mammalian fat and milk and milk products.[10]

During 2014-2016, 12 raw milk samples and 10 dairy products (butter, cheese, cream, anhydrous milk fat) were tested for dioxins and PCBs (MPI, 2017b). While concentrations of individual chemicals were not reported, it was concluded that "these results, in association with New Zealand's geographical isolation and relatively low level of industrialisation, support the conclusion that dairy cattle within New Zealand are not significantly exposed to dioxins and PCBs and that any levels in dairy products manufactured from New

[10] https://www.legislation.gov.au/Details/F2017C00333 Accessed 22 March 2019

Zealand raw milk are unlikely to pose any concern relative to international action levels and/or limits".

5.2 POLYBROMINATED DIPHENYL ETHERS (PBDE)

Brominated flame retardants (BFRs) are chemicals added to commercial items that contain foams, fabrics and plastics to reduce the likelihood of fires. A major class of BFRs, polybrominated diphenyl ethers (PBDEs) has emerged, over the past fifteen years, as persistent environmental contaminants of health concern, now commonly reported in biomonitoring studies worldwide, including New Zealand ('t Mannetje *et al.*, 2013). These compounds occur globally in the environment due to the production of three commercial products; pentabromodiphenyl ether (pentaBDE), octabromodiphenyl ether (octaBDE), and decabromodiphenyl ether (decaBDE). The pentaBDE and octaBDE products have been either banned or restricted in use, leaving only the decaBDE formulation being actively produced in some areas. The three commercial products are mixtures of PBDE congeners that are commonly found in biological and environmental matrices. Of the 209 theoretical congeners possible, the congeners most commonly encountered in environmental or human sampling include BDE-28, BDE-47, BDE-99, BDE-100, BDE-138, BDE-153, BDE-154, BDE-183, and BDE-209 (EFSA, 2011b).

5.2.1 Animal toxicity

No information was found on the toxicity of PBDEs to livestock. Some information was found on animal poisoning by polybrominated biphenyls (PBBs), however, the presence of the ether linkage in PBDE suggests the chemistry of these two groups of compounds will be sufficiently different that it would be unwise to extrapolate from the toxicity of PBBs to PBDEs.

5.2.2 Transfer of toxic agents to edible tissues and products

While a number of studies have determined the concentrations of PBDEs in foods of animal origin, very few have considered animal feed and the rate of transfer.

The fate of higher-brominated PBDEs was examined in lactating cows fed silage naturally contaminated with hepta- to deca-brominated PBDEs (Kierkegaard *et al.*, 2007). Deca-brominated PDE209 was the predominant congener in feed, organs, adipose tissues and faeces, but not milk. In contrast to lower-brominated PBDEs, the hepta- to deca-brominated PBDEs were present in adipose tissues at concentrations 9-80 times higher than in milk fat. While adipose tissue only accounts for about 15% of the live weight of the cows, over 90% of the PBDE burden was contained in these tissues. This suggests that for higher-brominated PBDEs, meat, rather than milk, may be an important source of human exposure.

A mass-balance approach was taken to examine the distribution and excretion in milk of tri- to hexabrominated PBDEs in lactating cows (Kierkegaard *et al.*, 2009). Analysis of tissue and milk samples suggested that PBDEs were fairly uniformly distributed in the lipid component of these materials. Gastrointestinal absorption of PBDE congeners decreased with increasing degree of bromination, from 88% for tetra-brominated BDE49 to 35% for hexabrominated BDE154. Gastrointestinal absorption was negatively associated with the compound log octanol-water partition coefficients. For the predominant PBDE congeners (BDE47, 99, 100, 153 and 154) transfer rates were in the range 15-34%. It was noted that the degree of PBDE transfer was less than that reported for PCB congeners.

Excretion kinetics of two PBDEs (BDE47 and 99) and PCBs was examined in goats exposed to contaminated soil (5% in feed) (Ounnas *et al.*, 2010). PCBs varied widely in their rate of transfer to milk, with transfer rates in the range 6-62%. The two PBDEs reached steady state transfer rates of about 30%.

5.2.3 Human toxicity

Human toxicity data for PBDEs, individually or as mixtures, has been assessed by EFSA (EFSA, 2011b).

Consistent, but not universal, associations have been seen in epidemiological studies between PBDE exposure and clinical or subclinical hyperthyroidism (elevated serum levels of T_3 and T_4 and decreased levels of TSH).

Inconsistent associations have been reported between *in utero* exposure to PBDEs and measures of neurodevelopment. Only one of the three studies reported controlled for concurrent exposure to other halogenated contaminants.

There was equivocal evidence for associations between PBDE exposure and various cancers (non-Hodgkins lymphoma, testicular, breast and pancreatic). It was noted that measures of exposure assessed current exposure, not exposure during the likely period of cancer initiation.

While some studies have found associations between BDE153 exposure and diabetes and/or metabolic syndrome, the lipophilicity of PBDEs and the known role of obesity as a risk factor for these conditions suggests that further evidence for an association would be required.

Effects of PBDEs on reproductive indices have been examined, although EFSA noted that most of the associations between exposure to PBDEs and effects on fertility or offspring are either based on one single study or are inconsistent through studies.

The JECFA assessment of PBDEs provided no additional information (JECFA, 2006).

5.2.4 Evidence of PBDEs in the New Zealand feed supply

No information was found on PBDEs in New Zealand forage or soils.

A survey of foods and feeds in the UK included analysis of composite feeds for livestock, oilseeds and cereals and grasses (Fernandes *et al.*, 2016). Results were expressed as the sum of 17 PBDEs or the sum of 10 European Commission priority PBDEs. Expressed as the sum of 17 PBDEs, concentrations in grasses were in the range 0.56-1.5 μg/kg, oilseeds and cereals 0.11-0.82 μg/kg and composite feeds 0.19-9.63 μg/kg. The highest mean concentrations were detected in fish and fish feed.

Deposition of PBDEs on the leaves of maize (*Zea mays*) to be used for silage production in Italy was examined (Brambilla *et al.*, 2015). Concentrations of the sum of eight PBDEs were in the range 2.7-6.2 μg/kg.

In another Italian study, PBDE concentrations were determined in soil and grass from an alpine pasture (Parolini *et al.*, 2012). PBDE concentrations, expressed as the sum of 13 PBDEs, were in the range 1.7-8.2 μg/kg dry weight, with the dominant congeners being BDE47 and 99. Concentrations in vegetation were several times higher than concentrations in soil, suggesting that the majority of contamination in vegetation was from atmospheric deposition.

5.2.5 Evidence of PBDEs in New Zealand foods of animal origin

As part of a study into the potential impact of grazing dairy cattle on land used for bioremediation of solid waste from petrochemical mining, bulk tank milk was sampled from 17 affected farms and three control farms (MPI, 2014b). PBDEs were detected in milk from two affected farms, with one sample containing BDE99 (2.3 ng/kg or 0.0023 μg/kg), while the other contained BDE99 (2.0 ng/kg or 0.002 μg/kg), BDE47 (3.7 ng/kg or 0.0037 μg/kg) and BDE100 (0.5 ng/kg or 0.0005 μg/kg).

FSANZ conducted a survey of PBDEs in Australian composite food samples (FSANZ, 2007). The highest mean concentrations (sum of 26 congeners, lower bound) were in bacon (0.51 μg/kg), eggs (0.91 μg/kg) and pork chops (0.69 μg/kg); all products of intensive agriculture, suggesting that compound feed may be a source of PBDE contamination. Beef steak (0.19 μg/kg) and sheep liver (0.35 μg/kg) contained lower concentrations of PBDEs, while PBDEs were not detected in full fat or reduced fat milk. The analytical method used in this study was less sensitive than that used in the New Zealand study described in the previous paragraph and the congener concentrations seen in New Zealand milk would not have been detected in the FSANZ study.

5.3 PERFLUOROALKYLATED SUBSTANCES (PFAS)

Perfluorinated or perfluoroalkylated substances (PFASs) are highly fluorinated aliphatic compounds with high thermal and chemical stability, as well as high activity as surfactants. PFASs are used in a range of industrial and chemical applications, including textiles, paper, packaging materials, paint and varnish, and fire-extinguishing liquids (EFSA, 2012a). Several PFASs are recognised as environmentally persistent organic pollutants. Diet is considered the main source of exposure to PFASs. Primary international interest has to date focussed on perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA).

5.3.1 Animal toxicity

No information was found on the toxicity of PFAS in livestock animal species.

5.3.2 Transfer of toxic agents to edible tissues and products

A pilot study was carried out of the toxicokinetics of PFOS/PFOA in dairy sheep fed naturally-contaminated corn silage (Kowalczyk *et al.*, 2012). The feed contained higher concentrations of PFOS (90 μg/kg dry weight) than PFOA (33 μg/kg dry weight). PFOS transferred into ovine milk to a greater extent than PFOA, with mean concentrations in milk of two sheep over 21 days of contaminated feed administration of 3.4 and 8.9 μg/L for PFOS and 0.2 and 0.7 μg/L for PFOA. Over the 21 day feeding period, 1-2% of ingested PFOS was excreted in milk, while 0.3-0.4% of ingested PFOA was excreted in milk. PFOS also accumulated in tissues to a greater degree than PFOA, with highest concentrations seen in the liver (885 and 1172 μg/kg) followed by the kidney (172 and 286 g/kg) and muscle tissue (24 and 35 μg/kg). PFOA concentrations in these tissues did not exceed 5 μg/kg. Approximately half the ingested PFOA was excreted in urine, while >90% of PFOS was not excreted.

The same research group carried out a similar study on a wider range of perfluorinated compounds in Holstein cows (Kowalczyk *et al.*, 2013). This study also included consideration of perfluorohexane sulfonate (PFHxS) and a short-chain precursor, perfluorobutanesulfonyl fluoride (PFBS). As with dairy sheep, PFOS was the main PFAS excreted in milk, with 4.7-14.1% of the ingested dose excreted. PFHxS was also excreted in milk (1.5-2.5%), but the remaining two compounds were barely excreted in milk (≤0.1%). The highest PFOS concentrations were determined in liver (3000-4000 μg/kg, 17.9-20.7% of ingested dose). Although the greatest proportion of the ingested PFOS dose (43-46%) was in muscle tissue, the concentrations (145-178 μg/kg) were substantially lower than those in liver. Approximately 2-9% of PFHxS was deposited in muscle tissue. PFOA and PFBS did not transfer to tissues to any great extent.

A study in beef cattle found a somewhat different pattern of distribution and excretion in three Lowline Angus steers receiving a single oral dose of PFOS (Lupton *et al.*, 2014). At 28 days after dose administration, approximately 36% of the dose was measured in blood, 4.3% in muscle and 5.7% in carcass remainder. The major route of excretion was via the faeces (11%), with minimal urinary excretion (0.5%). It is uncertain whether the differences between

these results and those from the study of Kowalczyk *et al.* (2013) were due to differences in experimental design or differences in animal physiology.

5.3.3 Human toxicity

PFOS and PFOA have been considered by EFSA (EFSA, 2008b). EFSA derived a tolerable daily intake (TDI) for PFOS of 0.15 μg/kg bw/day from the no observed adverse effect level (NOAEL) in a subchronic study in cynomolgus monkeys, with lipid (HDL) and thyroid hormone effects seen at doses above the NOAEL. While lipid and thyroid hormone effects have also been reported in occupationally exposed humans, thyroid hormone (T_3) levels increased in human occupationally exposed to PFOS, while in the study in cynomolgus monkeys T_3 levels decreased. There is some evidence of an increased risk of bladder cancer in workers occupationally exposed to PFOS, although the study reporting a significantly increased risk was based on only three bladder cancer cases. The study was further complicated as workers were also exposed to other chemicals.

EFSA derived a tolerable daily intake (TDI) of 1.5 μg/kg bw/day for PFOA, based on the NOAEL for a subchronic study in rats, with hepatocellular hypertrophy and increased liver weight seen at doses above the NOAEL (EFSA, 2008b).

EFSA reassessed PFOS and PFOA in 2018 and derived updated tolerable intakes, based on human epidemiological studies (EFSA, 2018b). For PFOS, increases in serum total cholesterol in adults, and decreases in antibody response at vaccination in children were identified as the critical effects. For PFOA, increases in serum total cholesterol was the critical effect. After benchmark modelling of serum levels of PFOS and PFOA, and estimating the corresponding daily intakes, EFSA established tolerable weekly intakes (TWI) of 13 ng/kg bw/week for PFOS and 6 ng/kg bw/week for PFOA. EFSA noted that, due to scientific uncertainties and the implications of other scientific work that is currently in progress, the scientific opinion on PFOS and PFOA and the associated TWIs should be considered as provisional, with a review expected by December 2019.

FSANZ considered the human health risk of PFAS in 2017, in response to environmental concerns related to their use in firefighting foams.[11] FSANZ derived a TDI of 20 ng/kg bw/day for PFOS, based on the NOAEL for decreased parental and offspring body weight in a reproductive toxicity study in rats, Pharmacokinetic modelling was used to convert the NOAEL to a human equivalent dose (HED), with an uncertainty factor of 30 (3 x inter-species, 10 x intra-species) was applied. For PFOA, the TDI was based on foetal toxicity in a developmental and reproductive toxicity study in mice. Following the same adjustment to a HED and application of a 30-fold uncertainty factor, a TDI of 160 ng/kg bw/day was derived. These TDIs are substantially lower than the former EFSA limits, but substantially higher than the most recent EFSA limits.

A number of epidemiological studies have focussed on cancer, reproductive and neurobehavioural (e.g. attention deficit hyperactivity disorder) endpoints (Sunderland *et al.*, 2019). Reproductive and neurobehavioural studies have generally not shown significant associations between PFOS body burden and the selected endpoints. Studies of cancer incidence have shown significant risks associated with some PFAS, but not always PFOS.

The US Agency for Toxic Substances and Disease Registry (ATSDR) has reviewed information related to PFAS and concluded that there were consistent findings for associations of serum PFOA and PFOS with increases in serum lipid levels, decreases in

[11] https://www.health.gov.au/internet/main/publishing.nsf/content/ohp-pfas-hbgv.htm#FSANZ Accessed 31 May 2019

birth weight, increases in uric acid levels, and alterations in biomarkers of liver damage (ATSDR, 2015). Evidence for an association with cancer endpoints was considered to be equivocal.

5.3.4 Evidence of PFAS in the New Zealand feed supply

No information was found on PFAS in New Zealand forage or soils, with the exception of soils in the vicinity of New Zealand Defence Force facilities where PFAS-containing fire-fighting foams had been used (PDP, 2018a; b; c).

Laboratory and field studies have demonstrated the ability of a range of plants to take up PFOA and PFOS from contaminated soils (Kowalczyk *et al.*, 2012; Stahl *et al.*, 2009). In controlled experiments, PFOA was taken up to a greater extent than PFOS in maize, oats, wheat and perennial ryegrass (Stahl *et al.*, 2009). Uptake was correlated with the amount added to soil and concentrations in plant material were substantially greater in straw than in grains (not applicable to ryegrass).

5.3.5 Evidence of PFAS in New Zealand foods of animal origin

As part of an ongoing investigation into PFAS contamination in the vicinity of New Zealand Defence Force facilities where PFAS-containing fire-fighting foams had been used, PFAS, reported as total PFOS + PFHxS, were detected in two sheep meat samples (concentrations not reported, and in two of three cattle meat sample (0.28 and 0.38 μg/kg) (PDP, 2018a; c). PFAS were not detected in an associated goats milk sample.

MPI analysed selected food samples from the 2016 New Zealand Total Diet Study for a range of PFAS (Pearson, 2018). Samples analysed were beef rump, butter, cheese, egg, fresh fish, plain hamburger, lamb/mutton, lettuce, mussels, pork roast, potato (skin on) and sausages. One PFAS (perfluorohexanoic acid) was detected in one beef rump sample at a concentration of 0.42 μg/kg.

PFOS and PFOA were analysed in retail foods as part of the 24th Australian Total Diet Study (FSANZ, 2016). PFOA was not detected in any samples, while PFOS was detected in two individual samples of fresh fish and beef sausages, at concentrations of 1.0 and 0.2 μg/kg, respectively.

6. RADIONUCLIDES

Radionuclides are radioactive forms of elements (isotopes). Radionuclides undergo radioactive decay by the emission of energy in the form of ionising radiation (gamma radiation, electrons or alpha or beta particles). Radioactive decay results in formation of other radioisotopes, referred to as 'daughters' of the original isotope. While some radionuclides are naturally occurring, other predominantly occur as the result of human activities, including nuclear fission.

The most commonly occurring radionuclides in foods are potassium (^{40}K), radium (^{226}Ra) and uranium (^{238}U), although the radionuclides present in foods may vary with food type and geographic location (WHO/FAO, 2011). Radionuclides generated in nuclear installations that could enter the food chain include; radioactive hydrogen (^{3}H), carbon (^{14}C), technetium (^{99}Tc), sulphur (^{35}S), cobalt (^{60}Co) strontium (^{89}Sr and ^{90}Sr), ruthenium (^{103}Ru and ^{106}Ru), iodine (^{131}I and ^{129}I), uranium (^{235}U) plutonium (^{238}Pu, ^{239}Pu and ^{240}Pu), caesium (^{134}Cs and ^{137}Cs), cerium (^{144}Ce), iridium (^{192}Ir), and americium (^{241}Am).

6.1.1 Animal toxicity

In addition to direct irradiation, animals may be exposed to radionuclides through inhalation of radioactive material, absorption of radioactive material through the skin or ingestion of feed contaminated with radioactive material. The latter route of exposure is of interest in the current study. Dermal absorption of radionuclides is generally considered to make a negligible contribution to exposure.

Most radionuclides are not extensively absorbed during passage through the gastrointestinal tract and are excreted in the faeces (Morris, 1988). Absorbed radionuclides may be distributed widely within the body or concentrated in particular organs, depending on the chemistry of the element. For example, ^{137}Cs was shown to be widely distributed in the bodies of dairy cows, while ^{131}I was concentrated in the thyroid, in the same manner as stable iodine. Sheep and cattle have been shown to be reasonably resistant to thyroid and reproductive effects of ionising radiation, although exposure of embryos during the critical stage of limb bud formation (gestation days 32-34 in cattle and 22-24 in sheep) can result in a high proportion of bone deformities in offspring.

6.1.2 Transfer of toxic agents to edible tissues and products

The International Atomic Energy Agency (IAEA) has published consolidated information on the transfer of radionuclides from the diets of livestock to milk and edible tissues (IAEA, 2010). The IAEA report consolidated data in terms of the fraction absorbed and the feed transfer coefficient. The feed transfer coefficient is the concentration in the animal tissue or product (Bq/kg or Bq/L)[12] divided by the daily intake of the radionuclide (Bq/day). The resulting units for the coefficient (days/kg or days/L) are not intrinsically meaningful, but a greater value of the coefficient can be taken to indicate greater transfer of the radionuclide to the specified tissue or product.

The greatest fractional absorption for radionuclides are for iodine (0.98), sodium (0.90), chloride (0.90), caesium (0.80) and phosphorus (0.67). The highest transfer coefficients for transfer to milk are phosphorus>sodium>calcium>sulphur>iodine>caesium>selenium for bovine milk, phosphorus>iodine>sodium>caesium>nickel for goats' milk, and phosphorus>nickel>iodine~calcium>sulphur>sodium for sheep milk. For muscle meat, transfer coefficients were in the order zinc>phosphorus>caesium>chloride>sodium for beef,

[12] Bq = Becquerel, the SI unit of radioactivity

caesium>sodium>zinc>iodine>cobalt for mutton, caesium>yttrium>strontium>tellurium for goat meat, and selenium>caesium>zinc>uranium>iodine for pork.

While these figures are dependent on available information, it is notable that caesium, which is an output from nuclear industry activities and distributes widely in the body, is present in all lists.

Non-pregnant ewes fed an experimental diet containing ^{137}Cs showed greater accumulation of radionuclides in muscle than pregnant ewes (Beresford *et al.*, 2007b). The differences were even more pronounced between non-pregnant and lactating ewes, presumably due to radiocaesium excretion in milk.

Saltmarsh vegetation from the environs of the Sellafield nuclear plant in the UK was found to be contaminated with a range of radionuclides, with highest activities of ^{106}Ru and ^{137}Cs (means 2370 and 1500 Bq/kg, respectively) (Beresford *et al.*, 2007a). Ewes and lambs were fed the vegetation for eight weeks. The highest radionuclide activities in muscle were for ^{137}Cs (12 Bq/kg fresh weight in lambs and 9.5 Bq/kg in ewes), Caesium activities were also the highest in liver, lung and kidney. Steady accumulation of ^{137}Cs in milk was also demonstrated across the study period, with an activity of 12 Bq/L reached after eight weeks.

Following the Chernobyl nuclear incident there was heavy deposition of radionuclides in alpine pastures in Austria, used for dairy cow grazing (Lettner *et al.*, 2007). Nine alpine pastures were monitored, with mean ^{137}Cs activities in the range 70-1132 Bq/kg dry weight and ^{90}Sr activities in the range 15-37 Bq/kg dry weight. Milk from cows grazing these pasture contained mean ^{137}Cs activities in the range 7-139 Bq/L and ^{90}Sr activities in the range 0.2-0.6 Bq/L.

6.1.3 Human toxicity

The major human health effect associated with radionuclides and the ionising radiation they produce is cancer (WHO, 2013). Population-based cancer risk estimates come primarily from the Japanese atomic bomb survivor Life Span Study (LSS) cohort data. Increased radiation-related risks have been observed in the LSS for leukaemia, and for a large number of solid cancer sites, including oral cavity, bone, oesophagus, stomach, colon, liver, lung, non-melanoma skin cancer, female breast, ovary, urinary bladder, brain/central nervous system and thyroid (Douple *et al.*, 2011).

Some non-cancer adverse health effects may also be observed after moderate or high radiation dose exposures. These include thyroid diseases (nodules, dysfunction), visual impairment (lens opacities, cataracts), circulatory diseases, reproductive dysfunctions, teratogenic effects and heritable effects (WHO, 2013). However, these effects are unlikely to be relevant in the context of the current document.

6.1.4 Evidence of radionuclides in the New Zealand feed supply

Uranium (^{238}U) occurs as a contaminant in phosphate rocks from Christmas Island and Nauru and New Zealand manufactured superphosphate has been shown to contain 8-37 mg/kg of uranium. Use of superphosphate was shown to increase the uranium content of a New Zealand hill farm soil, with concentrations increasing over a 23 year period for application rates of 30, 50 and 100 kg/ha/year of phosphorus (Schipper *et al.*, 2011). At the highest fertilisation rate, soil uranium increased from 1.26 mg/kg to 2.80 mg/kg between 1983 and 2006.

A study carried out in the Bay of Plenty determined uranium concentrations in topsoil from land under a range of uses (Guinto, 2011). Mean concentrations under dairy pasture (1.51 mg/kg), maize cropping (1.02 and 1.15 mg/kg), sheep/beef pasture (0.80 mg/kg), deer pasture (1.00 mg/kg) and kiwifruit orchard sites (1.29 mg/kg) were elevated compared to topsoils in indigenous forest sites (0.52 mg/kg). While there was some evidence of temporal

increases in topsoil uranium on agricultural land during the period 2000-2010, the trends are nowhere near as pronounced as those in the controlled study of Schipper *et al.* (2011).

6.1.5 Evidence of radionuclides in New Zealand foods of animal origin

The Ministry of Health funds an annual monitoring programme of environmental radioactivity in New Zealand.[13] In addition to air, rainwater and seawater testing the programme includes analysis of milk powder samples from Waikato, Taranaki and Westland for ^{131}I, ^{134}Cs and ^{137}Cs. In 2017/18, only ^{137}Cs was detected, with about half of the monthly samples containing detectable radioactivity (Thomas, 2018). Mean activities were 0.5, 1.1 and 0.3 Bq/kg in milk powders from Waikato, Taranaki and Westland, respectively. Mean radioactivity levels in milk powders from these three sites are quite consistent from year to year.

Pearson *et al*. (2016) analysed samples of 40 food types for a range of radionuclides. The foods were mostly sampled in Christchurch and Wellington, with the exception of wild pork, which was sampled in North Canterbury. Foods of relevance to the current study were beef steak, cows' milk, lambs' liver, pork chop and wild pork. Radiocaesium (^{137}Cs) was only detected above the minimum detectable concentration (MDC) in five fish samples, with a maximum concentration of 0.44 Bq/kg. Indicative concentrations (below the MDC) were reported for two milk, one pork chop, one lambs' liver and two wild pork samples. Indicative concentrations were in the range 0.05-0.16 Bq/kg fresh weight. While the naturally occurring radionuclide ^{40}K was detected in all samples, other gamma emitters (^{134}Cs, ^{131}I, ^{60}Co and ^{241}Am) were not detected in any foods of relevance to the current study. The beta emitter ^{90}Sr was not detected in any New Zealand produced food included in the study.

Alpha emitters (^{238}U, ^{234}U and ^{210}Po)[14] were analysed in composite samples of each food type. The highest concentrations of these radionuclides were detected in shellfish, spices and tuna (^{210}Po only). However, livestock meat contained elevated concentrations of all three radionuclides compared to plant-based products. Concentrations of the three radionuclides were 0.024, 0.024 and 0.031 Bq/kg in beef steak, 0.067, 0.087 and 0.643 Bq/kg in lambs' liver, 0.021, 0.016 and <0.016 Bq/kg in pork chops and 0.016, 0.018 and 0.182 Bq/kg in wild pork, respectively.

The Codex *General Standard for Contaminants and Toxins in Food and Feed* includes guideline levels (GLs) for nuclear industry related radionuclides in foods.[15] However, these GLs are applicable to "foods destined for human consumption and traded internationally, which have been contaminated following a nuclear or radiological emergency". Consequently, the GLs have little relevance in a non-emergency situation and have not been reproduced here.

[13] https://www.health.govt.nz/our-work/radiation-safety/environmental-radioactivity-monitoring-programme/environmental-radioactivity-monitoring-current-programme Accessed 14 March 2019

[14] ^{210}Po is the penultimate daughter of ^{238}U and decays to stable ^{206}Pb.

[15] http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCODEX%2BSTAN%2B193-1995%252FCXS_193e.pdf Accessed 12 March 2019

7. CONCLUSIONS

Two primary issues were addressed in relation to chemical contaminants of animal forage in New Zealand:

- The potential for hazards to elicit adverse health outcomes in food-producing animals; and
- The potential for hazards to be transferred to the human food chain and contribute markedly to human exposure.

With respect to the first of these issues, adverse health effects in animals in New Zealand have predominantly been caused by ingestion of unintended plant material (e.g. acorns, ragwort) or intended plant material containing unexpected levels of inherent toxic constituents (e.g. brassicas). A second class of feed-associated exposures causing harm in livestock animals are fungal contaminants of feed, with toxins produced by *Claviceps purpurea* and *Pithomyces chartarum* of particular note. Occasional cases of contaminant element intoxication have been reported in New Zealand, although some of these are related to non-feed sources (e.g. cattle eating old car batteries). There is no evidence of adverse health effects in New Zealand livestock from exposure to environmental contaminants or radionuclides and contamination levels of these hazards in the feed supply appear to be low.

There is little evidence that plant toxins are transferred to foods of animal origin to any great extent. Similarly, for most mycotoxins, only a small proportion of the animal exposure dose is transferred to tissues or products used as animal foods. The exception is aflatoxins, where 2-6% of ingested AFB_1 may be excreted in milk as AFM_1. However, New Zealand livestock will only be exposed to AFB_1 through consumption of imported supplementary feed material.

Levels of contaminant elements in foods of animal origin will generally reflect levels in feed and pasture soil. There is potential for food of animal origin to contribute to human exposure to contaminant elements if the feed environment is contaminated. Soil concentrations of cadmium are known to be elevated, due to long-term use of phosphate fertilisers based on material from Nauru Island. This mainly impacts on the cadmium content of offal (liver and kidney) and appears to have little impact on the cadmium content of muscle meat and milk.

While lipophilic environmental contaminants can transfer into the fatty component of foods of animal origin at quite high rates, where the information is available, levels of contamination in the New Zealand feed environment are low by world standards. Similarly, levels of contamination of the New Zealand environment with radionuclides are generally considered to be low.

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