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Supporting document 1

Risk and technical assessment – Application A1329

Exclusion of Blacklip Rock oysters farmed in the Northern Territory from the ML for cadmium in molluscs

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Executive summary

The Department of Agriculture and Fisheries, Northern Territory (NT) Government of Australia (DAF NT), has applied to amend Schedule 19 of the Australia New Zealand Food Standards Code (the Code) to exempt Blacklip Rock oysters (*Saccostrea spathulata*) from the maximum level (ML) of 2 mg/kg for cadmium in molluscs.

Concentrations of cadmium in Blacklip Rock oysters vary across aquaculture sites in the NT. FSANZ assessed cadmium concentrations of 398 Blacklip Rock oysters farmed at 4 aquaculture sites (approximately 100 per site) in the NT sampled by DAF NT to derive the mean cadmium concentrations of market size oysters (≥70 mm length). Approximately half of the samples tested exceed the current ML of 2 mg/kg.

FSANZ conducted a risk assessment to evaluate any risks to public health and safety that could arise from 2 scenarios:

- The exclusion of Blacklip Rock oysters farmed in the NT from the ML for cadmium in molluscs of 2 mg/kg.
- The introduction of an alternative ML for cadmium in Blacklip Rock oysters farmed in the NT of 3 mg/kg, considered to be the level as low as reasonably achievable in the catchment areas.

The Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) identified renal tubular dysfunction as the critical effect of cadmium in humans. JECFA established a Provisional Tolerable Monthly Intake (PTMI) of 25 µg/kg bw for cadmium, based on a meta-analysis of urinary β2-microglobulin concentrations in 30,000 individuals exposed to cadmium across 35 epidemiological studies. The health-based guidance value (HBGV) was expressed on a monthly basis due to the long half-life of cadmium in humans of 10–33 years.

Based on the evaluated epidemiological and toxicological evidence, FSANZ has determined that a Tolerable Monthly Intake (TMI) of 25 µg/kg bw remains appropriate for cadmium.

A dietary exposure assessment was conducted to estimate exposures to cadmium for the Australian population as the intended market for Blacklip Rock oysters is primarily domestic

Australian markets. Overall, consumption of Blacklip Rock oysters farmed in the NT is unlikely to be of public health and safety concern for Australian consumers based on the available cadmium concentration data.

For the worst-case scenario assessed, approximately 194 g of Blacklip Rock oyster meat could be consumed per month (equivalent to approximately 38 Blacklip Rock oysters per month) before exceeding the TMI for cadmium of 25 µg/kg bw. This estimate is representative of a consumption pattern of eating approximately one dozen oysters (12) per day, 3 times per month. For the worst-case exposure assessment based on longer term oyster consumption amounts (mean of 33 g/day and 90th percentile (P90) of 45 g/day) and the frequency of oyster consumption (3 times per month), the estimated mean and P90 total dietary exposures to cadmium are 65% and 85% of the TMI respectively, for the Australian population aged 2 years and above.

FSANZ considers the worst-case exposure assessment based on longer term oyster consumption to be conservative and likely an overestimate of the mean and P90 total dietary exposures to cadmium. The longer-term consumption scenario assumes Blacklip Rock oysters would be consumed throughout the year. However, the harvesting season for Blacklip Rock oysters would be restricted to the dry season in the NT (from May to October). Furthermore, the mean cadmium concentration included in the calculations for the worst-case dietary exposure assessment was the highest mean concentration across the 4 sampled aquaculture sites.

Higher cadmium concentrations may occur in Blacklip Rock oysters than those evaluated in the risk assessment. Thus, FSANZ assessed the public health and safety risks of an alternative ML of 3 mg/kg for cadmium for Blacklip Rock oysters farmed in the NT, considered to be the lowest level reasonably achievable in the catchment areas.

For the scenario of a ML of 3 mg/kg, the amount of oyster meat that could be consumed before exceeding the TMI is more than double that estimated using the worst-case scenario dietary exposure estimate based on concentration data of oysters sampled from 4 aquaculture sites in the NT (approximately 429 g per month, equivalent to approximately 67 oysters per month). The estimated long-term P90 total dietary exposure to cadmium would be reduced to 55% of the TMI for the Australian population aged 2 years and above.

FSANZ concludes that setting a ML of 3 mg/kg for cadmium in Blacklip Rock oysters would provide greater assurance of public health and safety than an exclusion from the ML for the species and is consistent with as establishing a ML as low as reasonably achievable in the catchment area.

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1 Introduction

The Department of Agriculture and Fisheries, Northern Territory (NT) Government of Australia (DAF NT), has applied to amend Schedule 19 of the Australia New Zealand Food Standards Code (the Code) to exempt Blacklip Rock oysters (*Saccostrea spathulata*) from the maximum level (ML) of 2 mg/kg for cadmium in molluscs.

DAF NT has assessed sources of pollution within the catchment area of shellfish harvest sites across the NT and determined cadmium uptake in Blacklip Rock oysters to be naturally occurring and not derived from anthropogenic sources. It has been suggested that elevated concentrations of cadmium in Blacklip Rock oysters may result from the accumulation of cadmium derived from annual phytoplankton (algal) blooms, specifically *Trichodesmium erythraeum* (Munksgaard et al. 2017). Decay of phytoplankton biomass releases cadmium in seawater and sediment, which may increase its bioavailability and contribute to episodic elevations in uptake by Blacklip Rock oysters.

Concentrations of cadmium in Blacklip Rock oysters vary across aquaculture sites in the NT. FSANZ assessed cadmium concentrations of 398 Blacklip Rock oysters farmed at 4 aquaculture sites (approximately 100 per site) in the NT sampled by DAF NT to derive the mean cadmium concentrations of market size oysters (≥70 mm length). Approximately half of the samples tested exceed the current ML of 2 mg/kg.

The 4 aquaculture sites currently operate as research sites and are expected to transition to commercial farms under NT licensing and regulatory frameworks. Samples of Blacklip Rock oysters included in the risk assessment were grown under research trial conditions, some for longer than the expected growth period to market size (18–24 months). Therefore, measured cadmium concentrations may not be representative of commercially harvested, market-size Blacklip Rock oysters farmed in the NT, expected to be lower than 3 mg/kg across aquaculture sites in the catchment areas.

Blacklip Rock oysters were selected as candidates for aquaculture due to the short growth period to market size, tolerance to variable environmental conditions, and consumer acceptance. The expected market product for Blacklip Rock oysters farmed in the NT is whole, fresh oysters from hatchery-produced stock grown and harvested in the NT. The intended market is primarily the domestic Australian market, with a production target of 1 million Blacklip Rock oysters per aquaculture site each year, equivalent to approximately 2% of national production. A small volume of Blacklip Rock Oysters is also produced in Queensland, with 12,000 oysters sold in 2017 (Nowland et al. 2020). The cadmium concentrations in Blacklip Rock Oysters produced in Queensland is not within the scope of this application.

2 Risk to public health and safety

FSANZ conducted a risk assessment to evaluate any risks to public health and safety that could arise from 2 scenarios:

- The exclusion of Blacklip Rock oysters farmed in the NT from the ML for cadmium in molluscs of 2 mg/kg.
- The introduction of an alternative ML for cadmium in Blacklip Rock oysters farmed in the NT of 3 mg/kg, considered to be the level as low as reasonably achievable in the catchment area.

The following questions were considered in the toxicological and epidemiological assessment:

- Are there any public health and safety concerns with exempting Blacklip Rock oysters farmed in the NT from the current ML for cadmium in molluscs of 2 mg/kg?
- Are there any vulnerable sub-populations that would be adversely affected by exempting Blacklip Rock oysters farmed in the NT from the current ML for cadmium in molluscs?

The scenario of an alternative ML for cadmium in Blacklip Rock oysters farmed in the NT was considered in the dietary exposure assessment, as shown in section 0.

Evaluations of cadmium by the Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) were available (JECFA 2011). FSANZ has used these safety assessments as the basis of its evaluation and conducted a literature review to determine whether there is any new information that would require a revision of the JECFA conclusions.

2.1 JECFA evaluations

The safety of cadmium has been evaluated by JECFA on several occasions, most recently at the 73rd meeting in 2010 (JECFA 2011).

A provisional tolerable weekly intake (PTWI) of 7 µg/kg body weight (bw) was first established by JECFA at the 33rd meeting (WHO 1988). The PTWI was established on the basis of the concentration of cadmium in the kidney associated with no observed increase in urinary β2-microglobulin (β2MG) concentration, a biomarker of renal tubular dysfunction (WHO 1988).

A revised provisional tolerable monthly intake (PTMI) of 25 µg/kg bw was established at the 73rd meeting following a re-evaluation of the safety of cadmium. The PTMI was derived from a meta-analysis of the dose-response relationship of urinary β2MG and cadmium concentrations conducted by the European Food Safety Authority (EFSA 2009b). JECFA considered that a health-based guidance value (HBGV) expressed on a monthly basis was more appropriate than a weekly value, given the long half-life of cadmium in humans of 10–33 years.

2.1.1 Toxicokinetics

Absorption

Dietary cadmium is absorbed at low levels in the gastrointestinal tract, ranging from 1–10%

in humans (≤5% in males and ≤10% in females) and 0.5–3% in experimental animals. *In vivo* studies in animals have shown an interaction between cadmium absorption and dietary composition, including fibre, protein, carbohydrate and mineral nutrients. Zinc, iron and calcium are antagonistic to cadmium absorption, as they bind the same intestinal transporters. Dietary deficiencies in these mineral nutrients are associated with a 10-fold increase in the absorption of cadmium in rats (Reeves and Chaney 2008). JECFA commented that the increase in cadmium absorption in iron-deficient mice may be attributable to an increase in the expression of the divalent metal transporter 1 (*DMT1*) and metal transporter protein 1 (*MTP1*) in the duodenum (Kim et al. 2007).

In humans, significant increases in concentrations of cadmium in the urine and kidney have been observed in iron-deficient females (serum ferritin concentration below 30 µg/L), irrespective of zinc status. The effect of low serum ferritin stores on cadmium absorption in females was estimated to be higher than the effect of 10 pack-years of smoking or a 10-year increase in age, which are key contributors to the body burden of cadmium (Barregard et al. 2010).

Distribution

Following absorption, cadmium binds to metallothionein and is distributed to the kidney, liver and placenta through systemic circulation. In humans, 50–75% of the body burden of cadmium is found in the kidney and liver, while 20% is found in muscle tissue and a minor quantity is detected in bone (JECFA 2011).

Elimination

The apparent half-life of cadmium ranges from 200–700 days in mice and rats and up to 2-years in monkeys. In humans, cadmium is slowly excreted following absorption, with an estimated biological half-life of 10–33 years. JECFA noted that an apparent half-life of kidney cadmium of 11.6 years (standard deviation 3.0 years) was observed in a 20-year cohort study of Swedish women aged 56–70 years (Amzal et al. 2009).

2.1.2 Toxicological data

Chronic toxicity and carcinogenicity

JECFA concluded that renal effects observed in experimental animals following low-level, long-term exposure to cadmium were the toxicological endpoints of most relevance to dietary exposure in humans.

Histopathological changes in the kidney (including epithelial cell damage in the proximal tubules, tissue degeneration, apoptosis, tissue atrophy, interstitial fibrosis, glomerular sclerosis, and tissue necrosis) in rabbits, rats, and monkeys were associated with cadmium concentrations in the kidney of 200–300 µg/g in long-term exposure studies.

The no observed adverse effect level (NOAEL) for renal effects of cadmium chloride administered in drinking water ranged from 0.8–2.6 mg/kg bw/day in rats and 0.4 mg/kg bw/day in monkeys. Low molecular weight proteinuria, glucosuria, and amino aciduria were identified as biomarkers of early renal damage in animals.

Cadmium has been shown to be carcinogenic in experimental animals treated by injection or inhalation. In rats, exposure to cadmium caused a range of tumours, including malignant tumours at the site of injection and in the lungs after inhalation. Oral cadmium exposure has been associated with proliferative lesions of the ventral lobe of the prostate gland in rats with adequate dietary zinc intake. In contrast, dietary zinc deficiency in rats was found to inhibit

tumour development associated with cadmium exposure. JECFA commented that these findings are of limited relevance to the potential carcinogenicity of cadmium in humans due to the anatomical differences in the prostate gland in rodents and humans.

Developmental toxicity

Previous JECFA evaluations concluded that decreased fetal weight, skeletal malformations, and increased fetal mortality were common findings of developmental toxicity studies of cadmium, usually in combination with maternal toxicity (JECFA 2004). However, developmental neurobehavioral effects, including decreased locomotor and exploratory activity and certain electrophysiological changes, have been observed in the absence of overt symptoms of maternal toxicity.

In a repeated-dose oral toxicity study evaluated at the 73rd JECFA meeting, pregnant female rats were administered cadmium chloride (10 mg/L) in drinking water from day 0–21 of gestation. Significant increases in cadmium concentrations were detected in dam blood (13-fold), foetal blood (2.5-fold), placenta (17-fold), and foetal brain (3-fold), compared to controls (Benitez et al. 2009). Average foetal weight at the end of the dosing period was 20% lower in the treatment group, compared to controls. A NOAEL was not determined in the study.

Genotoxicity

Previous JECFA evaluations concluded that equivocal results have been obtained in mutagenicity studies in a variety of prokaryotic or mammalian cells (JECFA 2004). JECFA noted that cadmium induces chromosomal aberrations in human and rodent cells, however, evidence suggests the mechanism is not direct genotoxicity.

JECFA noted that cadmium is not a redox-active metal and therefore, induces deoxyribonucleic acid (DNA) damage through indirect pathways, including through the induction of oxidative stress and inhibition of DNA repair mechanisms.

An *in vitro* genotoxicity study in human cell lines evaluated at the 73rd JECFA meeting showed dose-dependent inhibition of a DNA repair mechanism (excision repair of bulky DNA adducts) at non-cytotoxic concentrations of cadmium chloride and particulate cadmium oxide, via disruption of the assembly and disassembly of nucleotide excision repair proteins (Schwerdtle et al. 2010).

In an *in vivo* micronucleus assay evaluated at the 73rd JECFA meeting, a significant increase in micronuclei in peripheral blood was observed in male rats administered cadmium chloride (15 mg/kg bw/day) via oral gavage for 60 days, compared to controls (Celik et al. 2009). A significant increase in micronuclei in bone marrow associated with cytotoxicity was further shown in the single-dose group in the study.

2.1.3 Observations in humans

Renal effects

Epidemiological studies have established an association between urinary excretion of cadmium and biomarkers of renal function, including N-acetyl-β-glucosaminidase (NAG), β2MG, α1-microglobulin, and retinol-binding protein (RBP). However, as non-specific biomarkers of renal damage, the health significance of increases in urinary concentrations of low molecular weight proteins is uncertain at a population level.

Low molecular weight proteinuria may indicate potentially adverse effects, making the kidneys more susceptible to other stressors, or may only indicate an early renal response to

cadmium which may be adaptive or reversible. Alternatively, increases in urinary concentrations of low molecular weight proteins may reflect co-excretion with cadmium, rather than a causal relationship.

Cadmium tubulopathy has been observed at early stages of low molecular weight proteinuria (defined as urinary excretion of β2MG or RBP at 300–1000 µg/g creatinine). JECFA concluded low molecular weight proteinuria in itself does not appear to give rise to any subjective symptoms or objective disease and is, in its early stage, not accompanied by any histological changes. Occupational studies show reversal of modest increases in low molecular weight proteins after cessation of workplace exposure. In contrast, irreversible tubular proteinuria has been observed at higher levels of urinary excretion of β2MG or RBP (>1000–10000 µg/g creatinine). This stage of low molecular weight proteinuria may be associated with an accelerated age-related decline of glomerular filtration rate (GFR). Cadmium nephropathy (typically associated with a decreased GFR) has been observed at urinary excretions of β2MG or RBP >10000 µg/g creatinine.

In a cross-sectional study (*n*=14778) of the US National Health and Nutrition Examination Survey (NHANES) evaluated at the 73rd JECFA meeting, blood cadmium concentrations were identified as a risk factor for the prevalence of albuminuria (≥30 mg/g creatinine), including after adjustment for the effect of smoking (Navas-Acien et al. 2009). No association was observed between blood cadmium concentration and decreased GFR among non-smokers.

Skeletal effects

JECFA identified fracture incidence as the critical effect of cadmium on bone. Chronic exposure to cadmium is associated with an increased risk of osteomalacia, attributed to changes in calcium, phosphorous and vitamin D metabolism as a secondary effect of renal tubular dysfunction. Itai-itai disease (defined as osteomalacia and osteoporosis with severe pain) emerged as a severe health effect of population-level cadmium poisoning from the environmental contamination of water and rice crops in Japan. An inverse association between urinary cadmium excretion and bone mineral density (and an increased risk of osteoporosis) has been observed in epidemiological studies of human exposure to cadmium at levels lower than those linked to itai-itai disease.

In a cross-sectional study of adults exposed to high environmental levels of cadmium in Belgium evaluated at the 73rd JECFA meeting, urinary cadmium concentrations were associated with increased bone resorption (measured as decreased bone mineral density, increased serum calcitonin (calciuria), and decreased serum parathyroid hormone) in the absence of renal tubular dysfunction (Schutte et al. 2008b). However, these findings have not been reproduced in the absence of renal tubular dysfunction in subsequent epidemiological studies. JECFA concluded that it is not established whether the association between urinary cadmium and decreased bone mineral density is secondary to renal tubular dysfunction, and the available data for bone mineral density is not suitable to conduct a dose-response analysis to establish a direct effect of cadmium on bone.

Cardiovascular disease

JECFA concluded the epidemiological evidence for an association between cadmium exposure and cardiovascular outcomes is limited, based on studies evaluated at the 73rd JECFA meeting. In cross-sectional analyses of US NHANES data, urinary cadmium concentrations were associated with an increased risk of cardiovascular diseases, including myocardial infarction, stroke, and heart failure (Everett and Frithsen 2008; Peters et al. 2010). In adults exposed to high environmental levels of cadmium in Belgium, urinary cadmium concentrations were associated with changes in physiological markers of

cardiovascular function (pulse wave velocity, arterial pulse pressures and arterial compliance and distensibility) (Schutte et al. 2008a). Blood cadmium concentrations have been associated with an increased risk of hypertension in study populations from South Korea and the US (Eum et al. 2008; Tellez-Plaza et al. 2008).

Cancer

The International Agency for Research on Cancer (IARC) classified cadmium as carcinogenic to humans (group I), based on sufficient evidence of increased risk of lung cancer (and limited evidence of an increased risk of kidney, liver and prostate cancer) associated with the inhalation of cadmium in occupational settings (IARC 1993). Case-control studies evaluated at the 73rd JECFA meeting showed increases in the risk of bladder and breast cancer associated with human exposure to cadmium (McElroy et al. 2006; Kellen et al. 2007; Vinceti et al. 2007).

In adults exposed to high environmental levels of cadmium in Belgium, urinary cadmium concentrations were associated with an increase in overall cancer incidence, with excess cases of lung cancer attributable to residence in the environmental exposure area (Nawrot et al. 2006). In a prospective cohort study of postmenopausal women in Sweden evaluated at the 73rd JECFA meeting, dietary cadmium exposure (mean 1.5 µg/kg bw/week) was associated with an increased incidence of endometrial cancer. JECFA concluded that further epidemiological evidence was required to confirm the potential estrogenic effects (including hypertrophy and hyperplasia of the endometrial lining) of cadmium and any associated increased risk of hormone-related cancers (Åkesson et al. 2008).

Mortality

Prospective cohort studies in the US and Belgium evaluated at the 73rd JECFA meeting showed an association between urinary cadmium excretion and an increased risk of all-cause mortality and cancer mortality. In a 9-year cohort study of the US NHANES (baseline 1988–1994) data, doubling of urinary cadmium level (0.64 versus 0.32 µg/g creatinine) was associated with a 28% increased risk of all-cause mortality and 55% increased risk of cancer mortality in men, after control for confounding (including for the effect of smoking) (Menke et al. 2009). A 21% increased risk of mortality from cardiovascular disease was further observed for men in the cohort. In a 20-year cohort study of adults exposed to high environmental levels of cadmium in Belgium, the risk of all-cause mortality, non-cardiovascular disease mortality, and cancer mortality increased (20%, 44% and 43%, respectively) in association with a doubling of baseline urinary cadmium level (1.36 versus 0.68 µg/g creatinine) (Nawrot et al. 2008). The increased risk of mortality to cadmium exposure was observed in the absence of renal dysfunction (measured by urinary RBP and serum creatinine concentrations) in the study.

In Japan, significant increases in mortality risk have been attributed to increases in urinary cadmium concentration above 3 µg/g creatinine, particularly among females (Nakagawa et al. 2006). In a 20-year cohort study of adults exposed to high environmental levels of cadmium, urinary β2MG concentrations ≥1000 µg/g creatinine were associated with a 41% increased risk of all-cause mortality (Arisawa et al. 2007). The authors concluded that renal dysfunction associated with cadmium exposure was a significant predictor of mortality. In a 15-year cohort study of another population in Japan exposed to cadmium contamination (based on the 1974–1975 health impact survey in the Kakehashi River basin), urinary β2MG concentrations above 1000 µg/g creatinine were further associated with a significant increased risk of all-cause mortality in males and females (27% and 46%, respectively) (Nishijo et al. 2006). An increased risk of mortality from cardiovascular diseases was observed (ischemic stroke in males and heart failure in females) at urinary β2MG concentrations of 300–1000 µg/g creatinine in the study.

2.1.4 Dietary exposure

JECFA calculated a mean cadmium exposure for adults of 2.2–12 µg/kg bw/month, based on national estimates of dietary exposure for Australia, China, Japan, Chile, Lebanon, the Republic of Korea, the US, and the EU. Dietary exposure to cadmium for children (0.5–12 years) ranged from 3.9–20.6 µg/kg bw/month (based on data reported for Australia and the US). Exposure for vegetarians was estimated to be 23.2 µg/kg bw/month, based on data reported by EFSA.

Updated dietary exposure assessments for cadmium have been conducted by JECFA at subsequent meetings, most recently in 2021 for the evaluation of cadmium in chocolates and cocoa-derived products.

2.1.5 Dose-response analysis

Biomarker studies

JECFA identified impaired tubular reabsorption in the renal cortex as the primary toxic effect associated with chronic exposure to cadmium in humans. Increased excretion of low molecular weight proteins and solutes were identified as biomarkers of decreased tubular reabsorption. However, JECFA commented that urinary concentrations of low molecular weight proteins may not be indicative of an adverse effect. Increased excretion of high molecular weight proteins and decreased serum clearance of creatinine were noted as clinical biomarkers of progressive renal damage associated with chronic exposure to cadmium.

JECFA considered a meta-analysis of urinary β2MG and cadmium concentrations conducted by EFSA as the pivotal study to derive a HBGV, which reduced the potential bias associated with selection of a single key study.

Pivotal study: Meta-analysis of dose-effect relationship of cadmium for benchmark dose (BMD) evaluation (EFSA 2009b)

In 2008–2009, EFSA conducted a systematic review to inform the development of a database for BMD analyses of cadmium exposure and cut-off points associated with clinical changes in target organs. The systematic review was conducted in accordance with Cochrane review guidelines and included scientific peer-reviewed publications from 1966–2008. Renal effects were the most frequently studied health outcome in epidemiological studies of human exposure to cadmium.

Urinary β2MG was selected as the biomarker of effect for inclusion in the meta-analysis, as the most investigated low molecular weight protein in relation to human exposure to cadmium. EFSA concluded there was insufficient evidence of an effect of cadmium on bone, due to limited published epidemiological and clinical studies, and the heterogeneity of results reported across published studies. EFSA further concluded that limited evidence was available for the inclusion of other non-renal outcomes (including cardiovascular, carcinogenicity, reproductive, and neurotoxicity effects) in the BMD evaluation.

EFSA developed a database of 30,000 individuals (93.5% of Asian descent) exposed to cadmium based on data from 35 epidemiological studies, including 34 cross-sectional analyses and one cohort study. The database included 165 matched pairs of group means of urinary cadmium and β2MG concentrations. EFSA conducted a Bayesian meta-analysis and hierarchical modelling to calculate the overall dose-effect relationship. A mixed-effects model was used to adjust for the large inter-study heterogeneity (due to uncontrolled confounding) and inter-individual variability within studies. The model was restricted to subjects more than

50-years old and excluded the occupational exposure subgroup due to the potential for a different dose-response to be observed in relation to occupational exposure. The final sample population included in the model was primarily comprised of females, which EFSA identified as the most vulnerable population at risk of adverse health outcomes associated with cadmium exposure. However, the effect of gender on urinary cadmium and β2MG concentrations was determined to be minor.

The BMD evaluation determined a breakpoint urinary cadmium concentration of 5.24 (5^{th}–95^{th} percentiles 4.94–5.57) µg/g creatinine, after which there is a marked increase in urinary ß2MG concentrations in association with increases in urinary cadmium concentrations.

Toxicokinetic modelling

JECFA characterised a linear association between dietary cadmium exposure and urinary cadmium concentration based on a one-compartment model published by Amzal et al. (2009). The simplified one-compartment model performed sufficiently and accounted for population variability, compared to a complex 8-compartment model. The model included toxicokinetic and statistical parameters based on the half-life of cadmium, including measures of individual variability. The outcome of the model was expressed as the population distribution (cumulative population frequency) of the ratio of urinary (µg/g creatinine) to dietary (µg/kg bw/day) cadmium.

Dose-response relationship between urinary cadmium excretion and dietary cadmium exposure

Population percentiles of dietary cadmium exposure were estimated from a 2-dimensional Monte Carlo simulation of the variability and uncertainty in the breakpoint. A dietary cadmium exposure of 1.2 (5^{th}–95^{th} percentiles 0.8–1.8) µg/kg bw/day (equivalent to 36 (5^{th}–95^{th} percentiles 24–54) µg/kg bw/month) was estimated as equal to the breakpoint urinary cadmium concentration of 5.24 (5^{th}–95^{th} percentiles 4.94–5.57) µg/g creatinine.

2.1.6 Conclusions of JECFA evaluation

JECFA identified renal tubular dysfunction as the most sensitive toxicological endpoint associated with human exposure to cadmium. JECFA considered a meta-analysis of β2MG and cadmium excretion in urine as a pivotal study to derive a HBGV. JECFA concluded that as the apparent half-life of cadmium is about 15 years, steady state would be achieved after 45–60 years of exposure. A BMD analysis of the group mean data from individuals who were 50 years of age and older showed a breakpoint urinary cadmium concentration of 5.24 (5^{th}–95^{th} percentiles 4.94–5.57) µg/g creatinine. Higher urinary cadmium concentrations were associated with marked increases in β2MG excretion.

Based a one-compartment toxicokinetic model, JECFA determined a corresponding dietary exposure of 1.2 µg/kg bw/day, with a lower bound value (associated with the 5^{th} population percentile of dietary cadmium exposure) of 0.8 µg/kg bw/day.

JECFA established a PTMI for cadmium of 25 µg/kg bw based on the lower bound value of dietary cadmium exposure to ensure the value was protective for susceptible individuals within the population. JECFA withdrew the previous PTWI of 0.7 µg/kg bw and concluded the HBGV should be expressed on a monthly basis due to the long half-life of cadmium in humans.

2.2 Additional studies

Five studies published since the 73^{rd} JECFA meeting containing information relevant to the

safety assessment of cadmium were identified in a literature search.

Systematic review of adverse health effects associated with oral cadmium exposure (Schaefer et al. 2022)

In 2020–2022, the US Food and Drug Administration (FDA) conducted a systematic review of critical adverse health effects associated with dietary intake of cadmium to inform the selection or development of a HBGV, based on assessments by other regulatory agencies[1]. The systematic review was conducted in accordance with the Office of Health Assessment and Translation Systematic Review framework developed by the US National Toxicology Program and included scientific peer-reviewed publications to January 2020. In total, 207 studies (103 animal studies; 105 human studies) were selected for inclusion in the systematic review. Based on a risk of bias assessment of 49 studies, the most toxicological and epidemiological evidence was available for renal (tubular degeneration) and bone (decreased bone mineral density) effects in association with oral cadmium exposure (Appendix 1). The review selected (based on low risk of bias and high study quality) 7 studies (5 animal studies; 2 human studies) to inform the development of a HBGV (Table 1)

[1] The French Agency for Food, Environmental and Occupational Health & Safety (ANSES), US Agency for Toxic Substance and Disease Registry (ASTDR), EFSA, and JECFA.

Table 1. Summary of toxicological and epidemiological studies selected to inform the development of a HBGV for the US FDA (Schaefer et al. 2022).

Endpoint	Species	Reference	Summary
Kidney	Rat	(Mitsumori et al. 1998)	Sub-chronic study. Doses[1] of 0 ppm (control), 8 ppm, 40 ppm, 200 ppm, and 600 ppm (equivalent to 0, 0.8, 4, 20 and 60 mg/kg bw/day, respectively) administered in feed, with 24 animals/group (female only; 5-week-old[2]). NOAEL: 40 ppm (tubular lesions)
Kidney	Rat	(Shibutani et al. 2000)	Sub-chronic study. Doses[1] of 0 ppm (control), 8 ppm, 40 ppm, 200 ppm, and 600 ppm (equivalent to 0, 0.8, 4, 20 and 60 mg/kg bw/day, respectively) administered in feed, with 50 animals/group (female only). LOAEL: 200 ppm (tubular degeneration)
Bone	Rat	(Brzóska et al. 2005)	Chronic study. Doses of 0 (control), 1, 5, and 50 mg/L (equal to 0, 0.06–0.22, 0.24–1.01 and 2.25–9.65 mg/kg bw/day, respectively) administered in drinking water, with 40 animals/group (female only; 3-week-old[2]). LOAEL: 1 mg/L (bone mineral density; tibia)
Bone	Rat	(Brzóska and Moniuszko-Jakoniuk 2005)	Chronic study. Doses of 0 (control), 1, 5, and 50 mg/L (equal to 0, 0.06–0.22, 0.24–1.01 and 2.25–9.65 mg/kg bw/day, respectively) administered in drinking water, with 40 animals/group (female only; 3-week-old[2]). LOAEL: 1 ppm (bone mineral density; total)
Kidney	Rat	(Groten et al. 1994)	Chronic study. Doses[1,3] of 0.3 ppm, 3 ppm, 30 ppm, 90 ppm (equivalent to 0.03, 0.3, 3 and 9 mg/kg bw/day, respectively) administered in feed, with 20 animals/group (male only). NOAEL: 3 ppm[1] (histopathological changes; urinary enzymes)
Bone	Human	(Engström et al. 2011)	Cross-sectional study. Swedish females aged 56–69 years (*n*=2673; *n*=1243 never-smokers). NOAEL: 0.5–0.75 µg/g urinary creatinine (bone mineral density; total) for never-smokers
Kidney	Human	(Åkesson et al. 2005)	Cross-sectional study. Swedish females aged 53–64 years (*n*=820). LOAEL: 0.5–<0.75 µg/L (0.79 µg/g urinary creatinine) (tubular degeneration: NAG)

ppm: Parts per million.
[1] Dose of cadmium chloride ($CdCl_2$).
[2] Age at the start of dosing.
[3] Dose of cadmium-metallothionein (CdMt).

An assessment of sensitivity biomarkers for urinary cadmium burden (Li et al. 2020)

In a cross-sectional study of adults aged ≥50 years old (*n*=1595) residing in villages in China potentially exposed to cadmium from smelting operations, more than half of participants had a urinary cadmium concentration higher than 5 µg/g creatinine[2]. Urinary β2MG concentration was identified as a more sensitive biomarker for renal dysfunction than urinary NAG concentration. Applying a benchmark dose response (BMR) value of 10%, a BMD (lower confidence limit) (BMDL)[3] of 2.51 µg/g creatinine for males and 2.24 µg/g creatinine for females was established as the level of urinary cadmium associated with renal dysfunction.

Dose-response evaluation of urinary cadmium and kidney injury biomarkers in Chinese residents and dietary limit standards (Qing et al. 2021)

Based on a systematic review and meta-analysis of 158 epidemiological studies of cadmium, urinary β2MG and NAG concentrations were determined as the most sensitive biomarkers of renal injury, compared to urinary microalbumin and RBP concentrations. Applying a BMR value of 5%, a BMDL of 3.07 µg/g creatinine based on β2MG and 2.98 µg/g creatinine based on NAG were calculated as the levels of urinary cadmium associated with renal injury. A tolerable daily intake (TDI) of 0.28 µg/kg bw (equivalent to 16.8 µg/day based on bw of 60 kg) was established based on toxicokinetic modelling of NAG. The average dietary cadmium intake of 30.6 µg/day in the Chinese population exceeded the TDI proposed by the authors.

Estimation of urinary cadmium BMD thresholds for preschool children in a cadmium-polluted area based on Bayesian model averaging (Du et al. 2024)

In a cross-sectional study of pre-school children aged 3–5 years (*n*=518) exposed to environmental contamination in China, urinary NAG concentration was identified as the most sensitive biomarker of early renal damage associated with cadmium exposure. Applying a BMR value of 5%, a BMDL of 2.76 µg/g creatinine (1.92 µg/g creatinine for males and 4.12 µg/g creatinine for females) was determined as the level of urinary cadmium associated with renal impairment in children, lower than reported for adults.

The Validity of Benchmark Dose Limit Analysis for Estimating Permissible Accumulation of Cadmium (Satarug et al. 2022)

From a retrospective analysis of adults (*n*=534) in Thailand who had resided in a high-exposure area for cadmium for ≥30 years and controls (*n*=200) from a low-exposure area, a BMD analysis was conducted for 3 renal endpoints: urinary β2MG and NAG concentrations and a decrease in estimated glomerular filtration rate (eGFR). Urinary NAG concentrations were identified as the most sensitive biomarker of renal damage associated with cadmium exposure, compared to urinary β2MG concentration and eGFR. Applying a BMR value of 5%, a BMDL value of 0.67 ng/L filtrate was determined as the level of urinary cadmium associated with kidney tubular cell injury. These effects were observed at lower levels of cadmium exposure than the level of 5.24 µg/g creatinine established by JECFA. However, the results may be limited by residual confounding due to the higher prevalence of chronic

[2] The national standard threshold level, defined as the urinary cadmium concentration at which an individual would be classified as at risk according to clinical standards.

[3] BMDL is defined as the lower limit of the confidence interval of a BMD analysis and used as reference point or point of departure (PoD) for risk characterisation.

kidney disease and smoking in the high-exposure group, compared to controls[4].

2.3 Assessments by other regulatory agencies

2.3.1 EFSA

The Scientific Panel on Contaminants in the Food Chain (CONTAM) Panel established a tolerable weekly intake (TWI) for cadmium in 2009 (EFSA 2009a). The HBGV was developed based on the EFSA meta-analysis of the dose-response relationship of urinary β2MG and cadmium concentrations, also selected by JECFA to derive a HBGV (JECFA 2011).

The CONTAM Panel classified cadmium as primarily toxic to the kidney in humans, concluding that accumulation of cadmium in the kidney causes renal dysfunction resulting in a decreased GFR and progressive renal failure. The Panel determined a BMDL5 for urinary cadmium of 4.0 µg/g creatinine. A chemical-specific adjustment factor of 3.9 was applied to account for inter-individual variation in urinary cadmium concentrations within studies, resulting in a value of 1.0 µg/g creatinine.

The Panel conducted an updated dietary exposure assessment for cadmium based on 140,000 new data points of cadmium in various food commodities collected from 2003–2007 across 20 Member States. Based on the EFSA Concise European Food Consumption Database, the estimated mean dietary exposure[5] to cadmium was 2.3 (range 1.9–3.0) µg/kg bw/week for adults across Europe. High dietary exposure[6] was estimated to be 3.0 (2.5–3.9) µg/kg bw/week.

The Panel characterised the association between dietary cadmium exposure and urinary cadmium concentration based on a one-compartment model of data from the Swedish Mammography Cohort study (females aged 58–70 years). The Panel concluded that the average daily dietary intake of cadmium should not exceed 0.36 µg/kg bw in order for urinary cadmium concentrations to remain below 1 µg/g creatinine in 95% of the population at age 50. Based on this value, the Panel established a TWI for cadmium of 2.5 µg/kg bw. The Panel identified that certain population subgroups (including vegetarians and children) may exceed the TWI by 2-fold and concluded that exposure to cadmium at the population level should be reduced across Europe.

The HBGV was adopted prior to the JECFA assessment of cadmium in 2010. The Panel retained the TWI in a subsequent safety assessment of cadmium in 2012 (EFSA 2012) .

2.3.2 US FDA

The US FDA established an oral toxicological reference value (TRV) for cadmium based on the systematic review by Schaefer et al. (2022) of the critical adverse health effects associated with dietary intake of cadmium (Schaefer et al. 2023).

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[4] Within the high-exposure group, 15.3% of males and 10.7% of males had chronic kidney disease. No control participants were diagnosed with chronic kidney disease. Smoking rates differed between the groups, with a higher prevalence in the high-exposure group of 81.5% for males and 32.8% for females, compared to 47% males in the control group. No females in the control group were smokers.

[5] Mean dietary exposure was defined as the median of mean exposure for whole population for individual countries across Europe.

[6] High dietary exposure was defined as the sum of the 95th percentile for the 2 main contributors of dietary exposure (cereals and vegetables) and mean exposure for whole population.

A range of oral TRVs was derived from 3 critical effects of cadmium: decreased bone mineral density, renal tubular degeneration, and accumulation of cadmium in the proximal tubular cells of the renal cortex. Based on 2 key epidemiological studies (selected based on low risk of bias and high study quality), the FDA concluded that the effects of cadmium exposure on the bone and kidney result in equivalent PoDs of approximately 0.50 µg/g creatinine for females aged 50–60 years (Åkesson et al. 2005; Engström et al. 2011). The FDA further identified a PoD of 0.50 µg/g creatinine based on the estimated renal cortical cadmium concentration in the US population at 50 years of age from NHANES data. To develop the TRV, the FDA applied a reverse dosimetry human physiologically based pharmacokinetic (PBPK) model (adapted from a previous publication) to human data for each critical effect (Kjellström and Nordberg 1978). The model included creatinine excretion, body weight, and kidney weight models for the US population based on NHANES data and intervals of uncertainty for mean populational estimates. A TRV range of 0.21–0.36 µg/kg bw/day was derived from both bone and kidney endpoints based on the PoDs of 0.50 µg/g creatinine. The FDA concluded the oral TRV range was biologically plausible based on additional BMD modelling of kidney and bone (decreased bone mineral density and bone mineral concentration) effects in animal studies, which showed a TRV range of similar magnitude (0.63–1.8 µg/kg bw/day).

2.4 Studies on cadmium exposure from high oyster consumption in New Zealand

Two studies containing information specific to cadmium intake from high levels of oyster consumption in New Zealand were identified in a literature search. One additional study reporting on cadmium intake from oyster consumption in New Zealand was provided by the applicant. No studies of the Australian population were identified in a literature search or provided by the applicant.

These studies report investigations of human exposure to cadmium among a single cohort of Dredge (Bluff) oyster farmers in Bluff, New Zealand during the 1981 season (March–August) (Sharma et al. 1983; McKenzie-Parnell et al. 1988). The level of selected elements in Dredge oysters in the season was measured as: 5.7 mg cadmium and 51 mg zinc per kg wet weight, for an average wet weight of 6 g per oyster (McKenzie-Parnell et al. 1988). Higher cadmium content in Dredge oysters compared with other oyster species is associated with non-anthropogenic sources in New Zealand. Across these studies, limited quantitative data are reported for measurements of cadmium concentrations and human health outcomes.

Cadmium in blood and urine among smokers and non-smokers with high cadmium intake via food (Sharma et al. 1983)

Cadmium concentrations in blood and urine were measured in 78 oyster farmers (59 males and 19 females) aged 20–75 years. Whole blood and urine samples were measured one-week prior to the commencement of the season (pre-season) and in the final week of the season (end-season), with a subgroup of 18 participants measured in mid-season. Participants were categorised into 4 groups based on average oyster consumption patterns throughout the season and compared to a control group of 17 people who were not regular oyster consumers and had no oyster intake for 4 weeks prior to the sampling period.

Blood cadmium concentrations were significantly higher (P <0.01) in oyster consumers at pre-season (mean 2.85 µg/L), mid-season (mean 4.33 µg/L), and end-season (mean 3.97 µg/L), compared to controls (mean 0.9 µg/L) measured at pre-season. Among non-smokers, a dose-response relationship was observed between average oyster consumption and mean cadmium blood concentrations at pre-season and end-season (Table 2).

Mean urinary cadmium concentrations were significantly higher in oyster consumers, compared to controls measures at pre-season. However, no dose-response relationship was identified for mean urinary cadmium concentrations in association with average oyster consumption levels (Table 2).

Table 2. Mean concentrations of cadmium in whole blood and urine samples of non-smokers associated with dietary cadmium intake from Bluff oysters in the 1981 season, New Zealand (Sharma et al. 1983).

Intake category	Mean consumption[1] (oysters/day)	Pre-season		End-season	
		Mean blood cadmium ± SD (µg/L)	Mean urinary cadmium ± SD (µg/L)	Mean blood cadmium ± SD (µg/L)	Mean urinary cadmium ± SD (µg/L)
Control	0	0.9 ± 0.28	0.62 ± 0.34	NM	NM
I (Low)	0.8	1.26 ± 0.35	NR	1.87 ± 1.16	1.49 ± 1.28
II (Low–mid)	2.5	1.46 ± 1.03	NR	1.76 ± 0.61	1.66 ± 1.32
III (Mid–high)	4.2	1.79 ± 0.79	NR	2.75 ± 1.02	1.50 ± 1.35
IV (High)	9.7	3.16[2]	NR	3.70	1.74

NM: Not measured; NR: Not reported in publication; SD: Standard deviation.
[1] Mean consumption of oysters per day based on the combined estimate for smokers and non-smokers for each intake category.
[2] SD not applicable (*n*=1).

Unusually high intake and faecal output of cadmium, and faecal output of other trace elements in New Zealand adults consuming Dredge oysters (McKenzie-Parnell et al. 1988)

Faecal outputs (3-day collection) of cadmium and dietary minerals were measured in 75 oyster farmers (56 males and 19 females) aged 18–76 years who showed a dietary intake of cadmium at pre-season comparable to the New Zealand general population. A significant linear correlation (r=0.369, P<0.01) was observed between end-season faecal outputs of cadmium and average oyster intakes reported in a dietary history questionnaire (Table 3). Increases in faecal concentrations of zinc were also observed for high consumers of oysters, compared to individuals with a lower oyster intake.

Table 3. Mean concentrations of cadmium in fecal samples associated with dietary cadmium intake from Bluff oysters in the 1981 season, New Zealand (McKenzie-Parnell et al. 1988).

Intake category	Mean consumption (oysters/day)	Pre-season	End-season
		Mean fecal cadmium ± SD (µg/day)	Mean fecal cadmium (µg/day)
I (Low)	0.7	12 ± 7	15 (Reference)
II (Low–mid)	1.9	11 ± 5	84
III (Mid–high)	5.2	12 ± 7	129 *
IV (High)	18.2	12 ± 8	233 *

* P<0.05.

Cadmium intake via oysters and health effects in New Zealand: Cadmium intake, metabolism and effects in people with a high intake of oysters in New Zealand (McKenzie et al. 1986)

Concentrations of cadmium and dietary minerals were measured in blood, urine and hair samples of 78 oyster farmers (57 males and 19 females) aged 20–75 years. Whole blood and urinary cadmium concentrations were reported by Sharma et al. (1983). Hair cadmium concentrations showed no association with oyster consumption and no changes were observed between pre- and end-season (results not reported). Blood cadmium and zinc concentrations showed no correlation (results not reported). No renal damage in association with cadmium intake was observed among study participants, based on measurements of

urinary protein (proteinuria), including β2MG, and glucose (glycosuria) (results not reported).

2.5 Hazard characterisation

Intake of cadmium from food is the main source of human exposure in the general population among non-smoking adults, contributing approximately 90% of exposure (EFSA 2009a). Following exposure, cadmium has a biological half-life in the human body of 10–33 years, accumulating in the liver and kidneys. Long-term exposure to cadmium is associated with adverse health outcomes (Satarug et al. 2023).

2.5.1 HBGV selection

Based on the reviewed evidence, FSANZ has concluded that the JECFA PTMI of 25 µg/kg bw remains appropriate as the HBGV for cadmium, based on the following considerations:

- The JECFA PTMI was derived from a meta-analysis of 35 epidemiological studies of 30,000 individuals exposed to cadmium. The selection of a meta-analysis of urinary β2MG and cadmium concentrations as a pivotal study to derive a HBGV by JECFA reduced the potential bias associated with selection of a single key study.

- Since the latest JECFA evaluation in 2010, there have been no published BMD analyses based on updated systematic reviews or meta-analyses of renal dysfunction associated with human exposure to cadmium.

- JECFA established a PTMI for cadmium of 25 µg/kg bw based on the lower bound value of dietary cadmium exposure to ensure the value was protective for the general population including susceptible individuals.

2.5.2 Absorption of oyster-derived cadmium

Dietary minerals (zinc, iron and calcium) compete with cadmium for absorption in the gastrointestinal tract and therefore, oyster-derived cadmium may be absorbed at lower levels than cadmium from other foods due to the high content of iron and zinc in oysters.

In a study of cadmium exposure in a cohort of Dredge Oyster farmers in New Zealand, a linear correlation was observed between the faecal output of cadmium and average oyster consumption, indicating increases in excretion of cadmium associated with dietary intake. A dose-response relationship was observed between average oyster consumption and mean blood cadmium concentrations, representative of recent exposure history (approximately 100 days) (Nordberg et al. 2018). However, a dose-related increase in urinary cadmium concentrations was not observed for average oyster consumption categories.

Similarly, an epidemiological study of oyster farmers (*n*=61) in Canada reported significant increases in blood cadmium concentrations associated with oyster consumption among non-smokers; however, no association was observed for urinary cadmium concentrations and recent or long-term oyster consumption (Copes et al. 2008).

Despite the high iron and zinc content of oysters, iron-deficient individuals may remain a vulnerable sub-population under this exposure scenario. Copes et al. (2008) identified serum iron concentration as a predictor of variance in blood cadmium concentrations associated with a protective effect. Significantly higher blood (63%) and urinary (24%) cadmium concentrations have also been observed in females with plasma ferritin levels <20 µg/L who consumed a high-shellfish diet, compared to females with the same iron store levels who consumed a mixed-diet (Vahter et al. 1996).

While the hypothesis that oyster-derived cadmium may be absorbed at lower levels than cadmium from other foods due to the high content of iron and zinc is plausible or even likely mechanistically for individuals, there is insufficient evidence to quantify the extent to which this effect occurs in humans consuming oysters, including in potentially sensitive sub-populations such as iron-deficient individuals. Given the lack of evidence, a different exposure scenario could not be applied in a dietary exposure assessment.

3 Dietary exposure assessment

The dietary exposure assessment provides an estimate of the magnitude, frequency and duration (where appropriate) of exposure to cadmium in Blacklip Rock oysters. As confirmed by the applicant during the assessment, only fresh farmed Blacklip Rock oysters were considered for this assessment.

The dietary exposure assessment aimed to answer the following questions:

- What are the estimated mean and 90th percentile (P90) consumption amounts of fresh oysters for the Australian population aged 2 years and above?
- What are the estimated mean and P90 dietary exposures to cadmium from Blacklip Rock oysters for the Australian population aged 2 years and above, and how do these exposures compare to the HBGV?
- What are the estimated mean and P90 dietary exposures to cadmium from all food sources, including Blacklip Rock oysters, for Australian population 2 years and above, and how do these exposures compare to the HBGV?
- What is the contribution from Blacklip Rock oysters to the total exposure to cadmium for the Australian population aged 2 years and above?
- What amount of Blacklip Rock oysters can be consumed before total dietary exposure to cadmium exceeds the HBGV?
- Is the ML of 2 mg/kg for cadmium in molluscs specified in the Code appropriate?
- What are the estimated mean and P90 total dietary exposures to cadmium, if mean cadmium concentration in Blacklip Rock oysters is 3 mg/kg (the alternative ML), for the Australian population aged 2 years and above, and how do these exposures compare to the HBGV? (see Appendix 2 for details).

A separate dietary exposure assessment for the New Zealand population was not considered for this assessment[7] as the intended market for Blacklip Rock oysters is primarily domestic Australian markets. A summary of the general FSANZ approach to conducting dietary exposure assessments is on the FSANZ website. A detailed discussion of the FSANZ methodology and approach to conducting dietary exposure assessments is set out in *Principles and Practices of Dietary Exposure Assessment for Food Regulatory Purposes* (FSANZ 2024). Additional dietary exposure information related to the proposed risk management options are provided in Appendix 2 of this report.

3.1 Consumption of oysters

Oyster consumption data reported in the 2011-12 Australian National Nutrition and Physical Activity Survey (2011-12 NNPAS) (Australian Bureau of Statistics 2015) was used to estimate consumption of Blacklip Rock oysters for the Australian population aged 2 years and above using FSANZ's dietary modelling computer program Harvest. The design of this nutrition survey and the key attributes, including survey limitations, are set out on the FSANZ website. The two days of dietary survey data from the 2011-12 NNPAS were used in different

[7] The New Zealand population was considered for the alternative ML scenario only as the ML will also apply to New Zealand if included in the Code.

ways.

Whilst data from the 2023 NNPAS has been released by the ABS, only summary consumption statistics at the food group level have been published to date. At the time of this assessment the raw data from the survey that allows extraction of consumption for specific foods was not available to FSANZ, therefore the 2023 NNPAS data were not able to be used for this assessment.

The results show that;

- On any single day the mean consumption amount of oysters for consumers is 78 g and P90 is 180 g (median is 90 g). The Harvest nutrient model was used for this estimation that considers oysters reported consumed as is; no consumption of oysters from mixed dishes or foods, commercially processed oysters (frozen or canned) and oyster sauces were included. Day one consumption data were used for this estimate, which is provides an indication of portion sizes of oysters that are consumed. The ratio of consumers to survey respondents is less than 1%.

- Over a longer period of time mean consumption is 33 g/day and P90 is 45 g/day. The Harvest raw commodity model was used for this estimation that considers oysters reported consumed as is and oysters from homemade mixed dishes or foods (e.g. soup). No consumption of commercially processed oysters[8] (e.g. canned oysters) and oyster sauces were included. An average of 2 days consumption data were used for this estimate, which is more representative of longer term consumption. The ratio of consumers to survey respondents is less than 1%.

3.2 Estimated dietary exposures to cadmium

Dietary exposure assessments require data on the concentrations of cadmium in Blacklip Rock oysters and other food sources (background exposure), and consumption data for the foods that have been collected through a national nutrition survey.

The estimations were based on:

- Mean cadmium concentrations (raw data, Confidential Commercial Information-CCI under section 114 of *Food Standards Australia New Zealand Act 1991*) in the Blacklip Rock oysters sampled from 4 aquaculture sites in the NT provided by the applicant. FSANZ derived the mean cadmium concentration levels from raw data of market size oysters (≥ 70 mm length[9]) for each site and all sites together.

- Background dietary exposure to cadmium at the mean for the general Australian population (2 years and above); 2.5-6.6 µg/kg bw/month for consumers of cadmium from the 25th Australian Total Diet Study (ATDS) (FSANZ 2019). The upper bound exposure was used for the calculation to reflect the worst-case scenario.

- Longer term oyster consumption amounts (mean of 33 g/day and P90 of 45 g/day) estimated as explained in section 3.1 above.

[8] The battered and marinated oyster foods were assumed not to be processed.

[9] Oysters that are smaller than the market size (60-69 mm) were also used for the mean cadmium calculation for one of the sites to ensure sufficient raw data points (n ≥40).

- It was assumed that the frequency of Blacklip Rock oyster consumption is 3 times per month. According to food consumption frequency data reported in the 1995 Australian National Nutrition Survey (ABS 1995), 'other seafood' including oysters are consumed 3 times per month or less by around 95% of the Australian population aged 12 years and above.

- Contaminant HBGV; Tolerable Monthly Intake (TMI) for cadmium is 25 µg/kg bw/month.

Table 4 shows estimated mean and P90 dietary exposures to cadmium from Blacklip Rock oysters and the total dietary exposures from all food sources including Blacklip Rock oysters for the Australian population based on mean cadmium concentrations in Blacklip Rock oysters and their mean meat weights in 4 aquaculture sites in the NT.

Table 4. Estimated dietary exposures to cadmium from Blacklip Rock oysters and the total dietary exposures from all food sources including Blacklip Rock oysters for the Australian population.

Aquaculture site[10]	Exposure- µg/kg bw/month*				Exposure-% HBGV			
	Exposure from Blacklip Rock oysters		Total exposure[$]		Exposure from Blacklip Rock oysters		Total exposure[$]	
	Mean	P90	Mean	P90	Mean	P90	Mean	P90
A	10.1	15.2	16.7	21.8	40	60	65	85
B	4.8	7.3	11.4	13.9	20	30	45	55
C	1.8	2.7	8.4	9.3	7	10	35	35
D	2.3	3.5	8.9	10.1	9	15	35	40
Four sites together	4.6	7.0	11.2	13.6	20	30	45	55

* As the HBGV is expressed on a monthly basis (TMI), estimated daily dietary exposures were multiplied by the assumed frequency of Blacklip Rock oyster consumption per month to derive the estimate of monthly dietary exposures. The assumed frequency of Blacklip Rock oyster consumption was 3 times per month.
[$] Total exposure equals the combined exposure from Blacklip Rock oysters and all other food sources (background exposure-6.6 µg/kg bw/month).

The mean and P90 dietary exposures to cadmium from Blacklip Rock oysters in different aquaculture sites range from 1.8 to 10.1 µg/kg bw/month (7-40% HBGV) and 2.7 to 15.2 µg/kg bw/month (10-60% HBGV) respectively. The mean and P90 total dietary exposures to cadmium from all food sources including Blacklip Rock oysters range from 8.4 to 16.7 µg/kg bw/month (35-65% HBGV) and 9.3 to 21.8 µg/kg bw/month (35-85% HBGV) respectively.

According to the 25th ATDS (FSANZ 2019), the contribution of molluscs to the estimated total dietary cadmium exposure is 3% for the Australian population aged 2 years and above[11]. For the estimates presented in Table 4, the contribution of Blacklip Rock oysters to the total estimated dietary exposure to cadmium for consumers of the oysters ranges from 21-60%[12].

[10] The codes: A, B, C and D have been assigned to each site for identification and reporting purposes.

[11] Contributors were based on lower bound mean scenario using cadmium at 0.2 mg/kg in mussels. The maximum concentration of cadmium in mussels in a composite sample was 0.26 mg/kg.

[12] Based on mean exposures.

3.3 Estimating amount of Blacklip Rock oysters that can safely be consumed

The theoretical maximum allowable level (TMAL) for a specific commodity or food group is the concentration of a food chemical which a high consumer of that commodity or food group would need to be exposed to, in order to have a dietary exposure equal to, but not exceeding, the HBGV (FAO/WHO 2020). The calculation considers contributions to total dietary exposure from all other foods consumed at a population average level as well, if applicable.

The TMAL back calculation method is also commonly used to estimate the amount of a food that can be consumed before the HBGV is exceeded, based on a known concentration of a chemical in the food and considering the level of dietary exposure to that chemical from all other foods (FAO/WHO 2020). FSANZ used this methodology for this assessment.

Back calculation equation:

Amount of food (kg) =

$$\frac{\text{(HBGV (units/kg bw) – mean respondent exposure from all other foods (units/kg bw))} \times \text{mean population body weight (kg)}}{\text{concentration of chemical in the food (units/kg food)}}$$

For this assessment, the calculation was based on:

- The HBGV, background dietary exposure to cadmium, and the mean cadmium concentration in Blacklip Rock oysters as explained in section 3.2 above. For this calculation mean cadmium concentration in Blacklip Rock oysters (not the maximum as a worst case) was used given the chronic nature of the HBGV and the fact that over time consumers are likely to be consuming an average concentration of cadmium in the oysters.

- Mean body weight of the population group; 70 kg for the Australian population aged 2 years and above from the 2011-12 NNPAS (Australian Bureau of Statistics 2015).

- Mean meat weight (raw data, CCI) of the Blacklip Rock oysters sampled from 4 aquaculture sites in the NT provided by the applicant. FSANZ derived the mean meat weights from raw data of market size oysters (≥ 70 mm length[13]) for each site and all sites together.

Table 5 shows the estimated amount of Blacklip Rock oysters, as grams of meat weight per month and number of oysters per month that can safely be consumed by the Australian population.

Table 5. Estimated meat weight and number of Blacklip Rock oysters that can safely be consumed by the Australian population.

Aquaculture site	Oyster meat weight (g) per month	Number* of oysters per month
A	194	38
B	406	44

[13] Oysters that are smaller than the market size (60-69 mm) were also used for the mean meat weight calculation for one of the sites to get required raw data points (n ≥40).

C	1109	175
D	852	165
Four sites together	421	65

* Meat weight of market size oysters ranges from 5 to 9 g approximately.

According to this calculation, for the worst-case scenario (site A), the meat weight of Blacklip Rock oysters that can be consumed before exceeding the HBGV, is approximately 194 g per month (equivalent to approximately 38 oysters per month). If relevant frequency of oyster consumption data (3 times per month) (Australian Bureau of Statistics 1995) is applied to this scenario, this estimate is representative of a consumption pattern of eating approximately one dozen oysters (12) per day 3 times per month.

3.1 Assessment of the current ML of cadmium for molluscs in the Code

The assessment of the current ML of cadmium for molluscs in the Code was conducted using the TMAL method described above in section 3.3.

TMAL equation:

TMAL =

$$\frac{\text{(HBGV (units/kg bw) – mean respondent exposure from all other foods (units/kg bw))} \times \text{mean population body weight (kg)}}{90^{\text{th}} \text{ percentile consumption amount for commodity or food group of interest (kg)}}$$

Apart from the variables used in the back calculation above, this calculation was based on:

- A mean consumption amount for molluscs of 21 g/ consumer/day from the 25th ATDS (FSANZ 2019). As the HBGV is for a chronic endpoint, and the food group is only consumed occasionally, a consumption amount around the middle of the distribution (mean/median) was used as a better reflection of a high level of consumption over a long period of time. The determination of 'occasionally consumed' was based on 1995 Australian National Nutrition Survey data showing 'other seafood' where oysters are captured are only consumed 3 times per month or less by around 95% of the population aged 12 years and above (Australian Bureau of Statistics 1995).

- As the HBGV is expressed on a monthly basis (TMI), the estimated mean dietary exposure was multiplied by 30 to derive the estimate of monthly dietary exposure.

Based on the Australian national consumption data, the maximum concentration of cadmium which could be present in molluscs including oysters before the estimated dietary exposure for oyster consumers exceeds the HBGV (TMI of 25 µg/kg bw/month) is 2 mg/kg. This is equivalent to the ML of cadmium for molluscs (excluding Dredge (Bluff) oysters and Queen scallops) currently in the Code.

4 Risk characterisation

Concentrations of cadmium in Blacklip Rock oysters vary across aquaculture sites in the NT. FSANZ assessed cadmium concentrations of 398 Blacklip Rock oysters farmed at 4 aquaculture sites (approximately 100 per site) in the NT sampled by DAF NT to derive the mean cadmium concentrations of market size oysters (≥70 mm length). Approximately half of the samples tested exceed the current ML of 2 mg/kg.

FSANZ conducted a risk assessment to evaluate any risks to public health and safety that could arise from 2 scenarios:

- The exclusion of Blacklip Rock oysters farmed in the NT from the ML for cadmium in molluscs of 2 mg/kg.
- The introduction of an alternative ML for cadmium in Blacklip Rock oysters farmed in the NT of 3 mg/kg, considered to be the level as low as reasonably achievable in the catchment area.

The safety of cadmium has been evaluated by JECFA on several occasions, with renal tubular dysfunction identified as the critical effect in humans (JECFA 2011). JECFA established a PTMI of 25 µg/kg bw for cadmium, based on a meta-analysis of urinary β2-microglobulin concentrations in 30,000 individuals exposed to cadmium across 35 epidemiological studies. The HBGV was expressed on a monthly basis due to the long half-life of cadmium in humans of 10–33 years. FSANZ evaluated toxicological and epidemiological evidence published since the JECFA assessment and did not identify any new information that would warrant a change to the HBGV.

A dietary exposure assessment was conducted to estimate exposures to cadmium for the Australian population as the intended market for Blacklip Rock oysters is primarily domestic Australian markets. FSANZ concludes that consumption of Blacklip Rock oysters farmed in the NT is unlikely to be of public health and safety concern for Australian consumers based on the available cadmium concentration data.

For the worst-case scenario assessed, approximately 194 g of Blacklip Rock oyster meat could be consumed per month (equivalent to approximately 38 Blacklip Rock oysters per month) before exceeding the TMI for cadmium of 25 µg/kg bw/month. This estimate is representative of a consumption pattern of eating approximately one dozen oysters (12) per day 3 times per month.

For the worst-case exposure assessment based on longer term oyster consumption amounts (mean of 33 g/day and 90th percentile of 45 g/day) and the assumed frequency of oyster consumption (3 times per month), the estimated mean and P90 total dietary exposures to cadmium are 65% and 85% of the TMI for the Australian population aged 2 years and above. These estimates are 70% and 90% of the TMI respectively, if the exposure from commercially processed oysters (e.g. canned oysters) were also considered for this scenario.

FSANZ considers the worst-case exposure assessment based on longer term oyster consumption to be conservative and likely an overestimate of the mean and P90 total dietary exposures to cadmium. The longer-term consumption scenario assumes Blacklip Rock oysters would be consumed throughout the year. However, the harvesting season for Blacklip Rock oysters would be restricted to the dry season in the NT, limiting the availability of fresh, farmed Blacklip Rock oysters to a 6-month period annually (from May to October). Furthermore, the mean cadmium concentration included in the calculations for the worst-

case dietary exposure assessment (site A) was the highest mean concentration across the 4 sampled aquaculture sites. The Blacklip Rock oyster meat that could be consumed per month before exceeding the TMI is approximately 2 to 5–fold higher for oysters farmed at other aquaculture sites in the NT (sites B, C and D).

Minor and transient exceedances in the TMI for cadmium would not be associated with an increased risk of adverse health outcomes. Renal damage is associated with chronic dietary intake at a population level. Cadmium bioaccumulates in the human body and is slowly eliminated. For chemicals with a long half-life, body burden reflects cumulative exposure over time. Under a chronic dietary exposure scenario, the effect of short periods of increased intake (in this case, above the TMI) on body burden is inversely associated with the half-life of the chemical (Renwick 1999). For an increased exposure a chemical to result in an equivalent increase in the steady state body burden, exposure at the increased level would need to continue for 4–5 times the half-life of the chemical (Renwick and Walker 1993). Therefore, if an individual exceeded the TMI for cadmium for a short period in relation to the half-life, the magnitude of excess intake would not result in a proportional increase in body burden (Renwick 1999). Short-term, periodic intake above the TMI for cadmium is unlikely to change overall human health risk if average intake over time remains below the TMI.

Dietary cadmium exposure from all food sources is expected to remain below the TMI in Australia in the absence of a ML for the species. However, it is not known whether Blacklip Rock oysters farmed at new or existing aquaculture sites in the NT could have higher cadmium concentrations than those evaluated in the risk assessment due to environmental conditions, specifically the frequency and severity of seasonal algal blooms in the region. Thus, FSANZ assessed the public health and safety risks of an alternative ML of 3 mg/kg for cadmium in Blacklip Rock oysters farmed in the NT, considered to be the level as low as reasonably achievable in the catchment area.

For the scenario of a ML of 3 mg/kg, the meat weight of Blacklip Rock oysters that could be consumed before exceeding the TMI was estimated to be approximately 429 g per month (equivalent to approximately 67 oysters per month). This amount is more than double the worst-case scenario estimate of 194 g per month (site A). Based on longer term oyster consumption amounts and frequency of oyster consumption, the estimated mean and P90 total dietary exposure to cadmium are 45% and 55% of the TMI, respectively, for the Australian population aged 2 years and above.

Conclusion

Overall, consumption of Blacklip Rock oysters farmed in the NT is unlikely to be of public health and safety concern for Australian consumers. The estimated long-term total dietary exposure to cadmium is 85% of the TMI for high consumers in the Australian population.

However, higher cadmium concentrations may occur in Blacklip Rock oysters than those evaluated in the risk assessment. FSANZ concludes that setting a ML of 3 mg/kg for cadmium in Blacklip Rock oysters farmed in the NT would provide greater assurance of public health and safety than an outright exclusion from the ML for the species and is consistent with as establishing a ML as low as reasonably achievable in the catchment area.

For the scenario of a ML of 3 mg/kg, the amount of oyster meat that could be consumed before exceeding the TMI is more than double that estimated using the worst-case scenario dietary exposure estimate based on concentration data of oysters sampled from 4 aquaculture sites in the NT. The estimated long-term total dietary exposure to cadmium would be reduced to 55% of the TMI for high consumers in the Australian population.

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Appendix 1

Summary of toxicological and epidemiological evidence reported in US FDA review

Table 4. Summary of qualitative assessment of toxicological and epidemiological evidence of critical adverse health effects associated with oral exposure to cadmium (Schaefer et al. 2022).

Endpoint	***Toxicological data*** **Evidence rating[1] and conclusion**	***Epidemiological data*** **Evidence rating[1] and conclusion**
Bone	High (*n*=21 studies) Effect on mechanical strength of bone: Increase in risk of osteopenia, osteoporosis and fractures. Effect on skeletal development associated with *in utero* exposure. Increase in risk in females than males. LOAEL: 1 ppm (decreased bone mineral density; rat)	Mid–High (*n*=14 studies) Decrease in bone mineral density and increase in risk of osteoporosis. Limited studies of fractures and other markers of bone health. Bias: Unadjusted confounding, temporality, and consistency of findings.
Kidney	High (*n*=15 studies) Renal tubular dysfunction and changes in urinary/serum proteins (sub-chronic and chronic studies). LOAEL: 5 ppm (24-month study; rat) and 0.3 ppm (sub-acute study; rat)	Mid–High (*n*=41 studies) Increase in excretion of low molecular weight proteins. Urinary β2MG concentration was most frequently studied biomarker of effect (*n*=24 studies; 92% cross-sectional). Bias: Unadjusted confounding, temporality, and consistency of findings.
Cardiovascular	Mid–High (*n*=12 studies) Potential increase in systolic blood pressure from change in red blood cell morphology and increase in inflammation.	Low–Mid (*n*=14 studies) Limited evidence. Potential increase in systolic and diastolic blood pressure, and increase in risk of adverse cardiovascular outcomes, including ischemic stroke, myocardial infarction, and atherosclerotic plaques. Bias: Unadjusted confounding, temporality, consistency of findings, and limited studies.
Tissues	Mid–High (*n*=11 studies) Accumulation primarily in the kidney.	NR
Haematology and pathology	Mid–High (*n*=6 studies) Decreased haemoglobin at exposure >28 ppm: Increase in risk of anaemia. Effect on haematology associated with *in utero* exposure. Dose-response relationship observed at high exposure levels.	Low–Mid (*n*=2 studies) Limited evidence. Potential increase in risk of iron-deficient anaemia. Bias: Unadjusted confounding, temporality, consistency of findings, and limited studies.

Endpoint	*Toxicological data* **Evidence rating[1] and conclusion**	*Epidemiological data* **Evidence rating[1] and conclusion**
Developmental	Mid–High (*n*=2 studies) Skeletal malformations and adverse pathology outcomes associated with *in utero* exposure observed in 2 generation studies.	*Neurodevelopmental* Low–Mid (*n*=2 studies) Limited evidence. Potential decrease in performance neurocognitive delays in children. Bias: Unadjusted confounding, temporality, and consistency of findings.
Neurological	Mid–High (*n*=11 studies) Altered locomotion activity associated with *in utero* exposure and/or lactation (sub-acute). Pathology changes (rather than behavioural changes) observed in adults.	NR
Reproductive	Low–Mid (*n*=18 studies) Limited evidence. Potential decrease in sperm, pathological changes in male reproductive organs and increase in estrogen production in females. Implantations, litter size, and fertility associated observed at high exposure levels.	Low–Mid (*n*=5 studies) Limited evidence. Potential decrease in birth weight associated with maternal exposure. Bias: Unadjusted confounding, temporality, and consistency of findings.
Immune and skin	Low–Mid (*n*=6 studies) Limited evidence of effect on immune function and skin sensitisation. LOEL: 3 ppm (positive antinuclear antibody test; mouse)	NR
Oxidative stress	Low–Mid (*n*=5 studies) Effect on redox potential from decrease in SOD, GSH and Cyt-C-Ox. LOAEL: 5 ppm (monkey)	NR
Cancer	Low–Mid (*n*=4 studies) Limited evidence. Low study quality.	Low–Mid (*n*=23 studies) Limited evidence of an increase in risk in various types of cancer, including endometrial, melanoma, prostate, bladder, gastric, pancreatic, and breast. Bias: Unadjusted confounding, temporality, mixed results, and limited studies.
Gastrointestinal and metabolism	Low–Mid (*n*=3 studies) Limited evidence.	NR

Cyt-C-Ox: Cytochrome *c* oxidase; GSH: Glutathione; LOAEL: Lowest observed adverse effect level; NR: Not reported; ppm: Parts per million; SOD: Superoxide dismutase.
[1] Evidence rating scored out of 4: High=4; Mid-High=3; Low-Mid=2; Low=1.

Appendix 2

Additional dietary exposure related information to support risk management options

Estimating amount of Blacklip Rock oysters that can safely be consumed if the mean cadmium concentration is 3 mg/kg (the alternative ML)

For this scenario, using the same assumptions and methodology as explained in section 3.3 of this report and a mean cadmium concentration of 3 mg/kg, the meat weight of Blacklip Rock oysters that could be consumed before exceeding the HBGV was estimated to be approximately 429 g per month (equivalent to approximately 67 oysters per month[14]). This amount is more than double the worst-case scenario estimate of 194 g per month as presented in section 3.3 of this report.

Estimating dietary exposures if the mean cadmium concentration in Blacklip Rock oysters is 3 mg/kg (the alternative ML)

For this scenario, using the same assumptions and methodology as explained in section 3.2 of this report and a mean cadmium concentration level of 3 mg/kg, the estimated mean and P90 total dietary exposures to cadmium are 45% and 55% of the HBGV respectively for the Australian population aged 2 years and above. These exposures are lower than the estimated mean and P90 (65% and 85% of the HBGV respectively) for the worst-case scenario presented in section 3.2 of this report (see Table 4).

The New Zealand population was considered for the alternative ML scenario only to assess any potential public health and safety concerns as the ML will also apply to New Zealand if included in the Code. For the New Zealand adult population (aged 15 years and above)[15], using the same assumptions and methodology as explained in section 3.2 of this report, a mean cadmium concentration level of 3 mg/kg and consumption amounts for the New Zealand population, the estimated mean and P90 total dietary exposures to cadmium are 45% and 90% of the HBGV respectively.

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[14] Mean meat weight of market size oysters was considered 6.4 g for this estimation.

[15] Oyster consumption data (day one) from the 2008–09 New Zealand Adult Nutrition Survey (aged 15 years and above). https://www.health.govt.nz/statistics-research/surveys/past-surveys/nutrition

The higher P90 dietary exposure estimate for the New Zealand adult population (90%) than the Australian population (55%) is because only one day of food consumption data are used to estimate dietary exposures for the New Zealand adult population. Where dietary exposures can be averaged using 2 days of food consumption data or more, the tails of the exposure distribution are narrowed resulting in lower P90 dietary exposure values, as demonstrated with the results for Australia.

There are not sufficient oyster consumers in the 2002 New Zealand National Children's Nutrition Survey to calculate reliable exposure estimates for New Zealand children (aged 5-14 years). https://www.health.govt.nz/statistics-research/surveys/past-surveys/nutrition