Heavy metals in seafood – what is the risk to the consumer?

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Where do heavy metals come from?

Heavy metals, including mercury (Hg), cadmium (Cd) and arsenic (As) are present in the earth's crust and leach out into the terrestrial and aquatic environments, albeit at very low concentrations (Table 1). Transfer from the earth's crust to the surface environment can be aided by geothermal activity – e.g. Cd concentrations are higher in volcanic regions. In addition, they have, or have had important industrial and commercial applications and are, or have been, mined. Mining results in further release from their crust-sequestered sites which leads to artificial enhancement of their normally very low environmental concentrations (Barbour & Shaw, 1999). Further to this, some heavy metals are co-deposited in the earth's crust with useful metals that are valuable resources (e.g. Cd with zinc (Zn)) and so are commercially mined. The unwanted heavy metal contaminant (e.g. Cd) is then discarded with the mine tailings and leads to further environmental contamination. The use of fertilisers that might be contaminated with heavy metals (e.g. Cd) also adds to the environmental burden of these unwanted metals. Finally, the manufactured products incorporating heavy metals (e.g. Hg in long-life light bulbs) are returned to the earth (e.g. in landfill sites) at the end of their useful life which leads to further environmental contamination. Environmental concentrations of heavy metals are the result of addition of all, or some of these routes of contamination.

When heavy metals are present in the terrestrial environment they are continually leached by rain and watercourses eventually entering the marine environment (Table 1) where they might be incorporated into the food chain of sea creatures (e.g. fish and molluscs) used as human food.

Concentration (mg/kg)				
		Cd	As	Hg
Earth's crust	0.1	1.5	0.05	
Sea -	Surface	0.000001		
			0.0015	<0.00001
	Deep	0.0001		

Table 1. Concentrations of cadmium, arsenic and mercury in the earth's crust and marine environment, showing that the Cd concentration is higher at greater depth because it tends to form heavy silts (data from Cox, 1995).

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Bioaccumulation

Heavy metals occur in two forms in the environment – inorganic ions or organic complexes. Their organic complexes tend to be lipophilic and so bioaccumulate (e.g. methylmercury), whereas some heavy metal ions resemble biologically important ions and so are taken up by cells (e.g. arsenate); this will be dealt with in greater detail when the individual metals are discussed below.

Bioaccumulation means that heavy metal concentrations can be high in marine species eaten by humans because of the food chain concentrating effects. This concept is illustrated well by DDT (a very lipophilic pesticide; LogPow= 6.24); in a study in an east coast of the USA estuary (Woodwell et al, 1967) the concentration of DDT in the aquatic environment was only 5×10^{-5} mg/mL, but the levels in the top predator (heron) in this environment was 3.57 mg/kg body weight – this is a 71,000-fold food chain concentration.

Acceptable risk

When considering toxic chemicals in food it is important to decide at which point the health risk to the consumer becomes unacceptable. In food regulatory terms, this is usually the point at which regular consumption (e.g. every day for a lifetime – Acceptable Daily Intake (ADI)) of the food might be expected to lead to an adverse health effect on the consumer. However, this risk should be set in the context of benefit. For example, fish contaminated with mercury still provides its consumer with important nutrients and is enjoyable to eat – such benefits should be taken into account before declaring the risk too great. The issue of enjoyment as a benefit came to the fore during the UK's bovine spongiform encephalopathy (BSE; Mad Cow disease) epidemic in the mid 1980's to 1990's when the UK government banned beef on the bone because they decided that the risk of consumption of BSE prion in nervous tissue close to bones was too great. The public protested because they enjoyed eating beef on the bone and did not want to be told that the infinitesimally small risk was unacceptable. The UK government backtracked and allowed consumption of beef on the bone. Benefit in all of its forms – including enjoyment – must be considered as part of the risk-benefit equation.

Similarly fugu sashimi is a great delicacy to the Japanese, but fugu (a puffer fish) contains the potent toxin, tetrodotoxin (LD_{50} [mouse, oral] = 0.01 mg/kg). In fact, several people each year (between 2002 – 2006 there were 14 deaths (Hays, 2009)) die in Japan as a result of eating fugu. The Japanese government is far wiser than their UK counterpart; instead of banning fugu they introduced a training scheme for fugu sashimi chefs to minimise the risk of their sashimi containing a fatal dose of tetrodotoxin. This way forward was based solely on the enjoyment that some Japanese diners get from eating fugu sashimi despite its health risks.

These risk-benefit considerations are important when considering Hg-, Cd- or As-contaminated seafood in New Zealand.

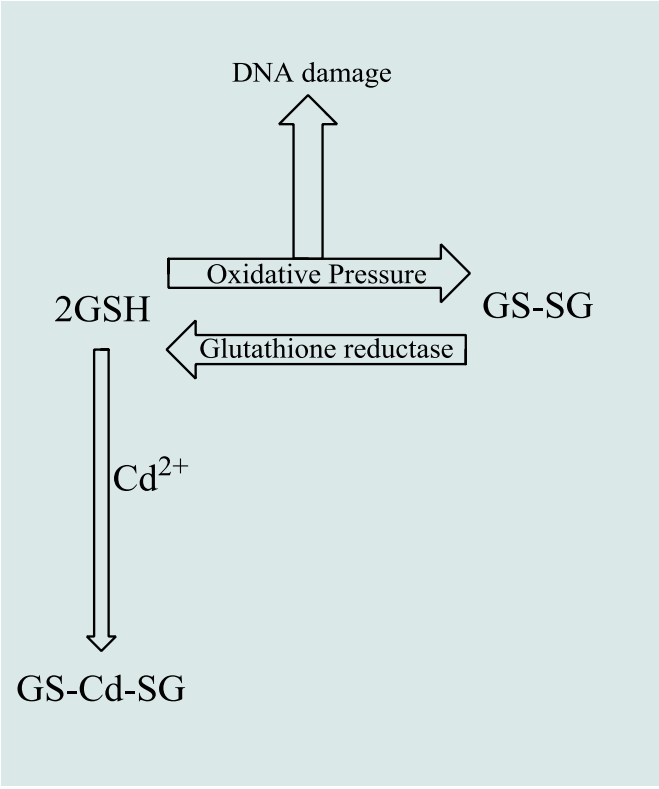

Figure 1. Glutathione (GSH) protects cells against oxidative pressure (e.g. $O_2^{\cdot -}$) by being oxidised itself to glutathione disulphide (GSSG). It is thought that Cd^{2+} depletes GSH by forming a Cd-GSH complex (GSCdSG) which in turn exposes DNA to attack by exogenous and endogenous mutagens that might initiate carcinogenesis.

Cadmium

Cadmium toxicity

Cd is a soft silver metal present at very low abundance (0.1 mg/kg; Table 1) in the earth's crust. It is usually present as Cd^{2+} (e.g. as $CdSO_4$). It is carcinogenic. Although its non-genotoxic mechanism of carcinogenesis is not understood, it is thought to involve epigenetic phenomena (Waalkes, 2003). On the other hand, depletion of cellular glutathione (GSH) by forming a glutathione Cd complex via GSH's sulfhydryl group might occur. Depletion of cell protective GSH means that other macromolecules in the cell (e.g. DNA) are more susceptible to attack by reactive chemical species (e.g. free radicals) generated by exogenous influences (e.g. by γ-rays forming $OH\cdot$ from H_2O) or endogenous processes (e.g. superoxide (O^{2-}) formed by xanthine metabolism). Reaction of highly reactive species with DNA might cause mutations that initiate carcinogenesis (Fig 1).

Exposure to Cd in New Zealand food and its toxicological significance

Cd is sequestered in the kidney cortex and liver and is accumulated by filter feeding bivalves. Kidney and liver are a particular problem in animals that are old at slaughter because they accumulate more Cd with age. For example, consumers of horse offals (e.g. in Italy) are at particularly high risk because horses are slaughtered for human consumption at a greater age than, for example, sheep. This is of no relevance to New Zealand because horse is not consumed. Liver is, however, relevant because lambs fries are eaten, however the sheep are slaughtered young and so do not accumulate significant Cd from their environment during their short lifetime. Despite this, New Zealand lamb's liver Cd levels are higher than in many other New Zealand foods (Table 2).

Food	[Cd] (mg/mL)	
	New Zealand	Overseas
Bread (white)	0.015	0.01
Bread (wholemeal)	0.018	0.015
Milk	0.0001	0.0004
Lamb's liver	0.103	0.084
Oysters	1.33	0.35
Potatoes	0.027	0.022

Table 2. Cd levels in New Zealand foods compared with food from overseas (data from NZTDS, 2009).

By far the most significant source of Cd in the New Zealand diet is oysters (Table 3). Oysters contribute approximately 44% of the Cd in the diet of 25+ year old New Zealand males (NZTDS, 2003/4). Cd levels are higher in oyster species that live in the marine sediment (e.g. Pacific oysters (*Crassostrea gigas*)) where higher levels of Cd are found (Table 1). Cultured oysters tend to have lower Cd levels because they are grown suspended rather than on the sea floor and so are not in direct contact with Cd-containing sediments.

Oysters are consumed infrequently by most people and therefore even though they represent a significant dietary source of Cd they are unlikely to contribute sufficient Cd to cause concern in most people. The modelled intake of Cd in 25+ year old oyster-eating males in New Zealand is 6.5 μg/kg body weight/month, whereas Cd intake from the same diet, but excluding oysters, is 5.0 μg/kg body weight/month (NZTDS, 2009). Clearly oysters make a considerable difference to Cd intake in the New Zealand diet.

The Provisional Tolerable Monthly Intake (PTMI) for Cd is 25 μg/kg body weight/month; therefore, the New Zealand Cd dietary exposure level is only of the order of 25% of the PTMI and so is not a cause for significant concern. However, it would not be advisable to consume oysters more than a few times a week for fear of approaching the PTMI. For most people this is not an issue.

Dietary exposure data is based, in this case, on levels of Cd in food and does not take account of bioavailability. Cd^{2+} has been shown to bind to metallothionein (Stillman et al, 1987). It is therefore possible that Cd in oysters is bound to metallothionein and that this affects Cd's bioavailability to the consumer. Interestingly, tissue metallothionein levels in Cd-exposed freshwater mussels (*Anodonta grandis*) correlates with Cd exposure levels (Couillard et al, 1993) suggesting that the mollusc adapts to Cd exposure by upregulating metallothionein expression. This might have favourable implications for the bioavailability of Cd to human consumers of shellfish.

Whether Cd^{2+} remains bound to the sulphydryl-based metal binding domain of metallothionein in food in the acidic environment of the stomach is an important consideration when assessing the importance of this mechanism of Cd's sequestration on bioavailability to the human consumer. It is likely that Cd^{2+} would be displaced by H^+ (Fig 2) and that metallothionein binding would have little, or no, beneficial effect in the context of food.

Metallothionein is a small (61 amino acid residues), cysteine-rich (20 cysteine residues) protein; Cd binds to the cysteine thiol groups in much the same way as it binds to GSH's cysteine residues (Fig 1). While it is possible that Cd is bound to metallothionein in oysters, when the oysters are eaten the very low pH in the stomach would almost certainly unfold metallothionein and release Cd from its cysteine thiol binding site (Fig 2). Therefore, in my opinion, the relevance of metallothionein sequestration of Cd as a human dietary bioavailability determinant is dubious.

The toxicity of Cd is modulated by selenium (Se); the Cd:Se ratio is more important than the Cd level *per se*. Dietary intakes of Se are higher in New Zealand's North Island than South Island (NZTDS, 2003/4) and thus, it would be expected that North Island consumers could tolerate higher dietary levels of Cd than their South Island counterparts. Since a high proportion of New Zealand's dietary Se is from wheat flour and Se levels in North Island flour are greater than in South Island flour it is possible to smooth out the potential geographically-based effects of dietary Cd by blending North and South island flour, or, perhaps importing Se-rich flour from other countries.

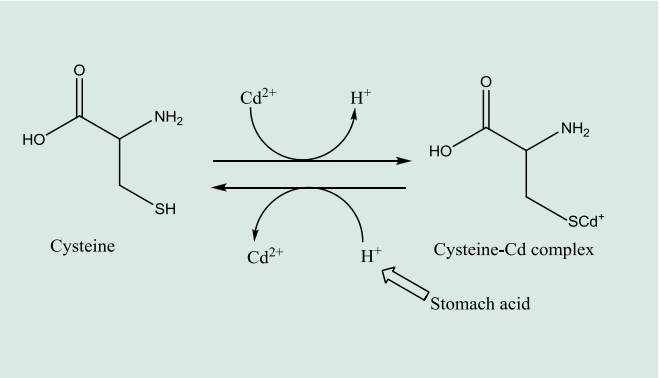

Figure 2 The possible formation of cysteine-Cd complex and likely reversal in the acid environment of the human stomach

Mercury

Mercury toxicity

Mercury occurs in nature as Hg^0, Hg^+, Hg^{2+}, and organic mercury (e.g. dimethylmercury, $(CH_3)_2Hg$; methylmercury cation CH_3Hg^+). All forms of Hg are toxic, but organic mercury is very much more toxic than its inorganic forms. Inorganic Hg is converted to organic mercury by microorganisms in marine and freshwater aquatic silts and since organic mercury is lipophilic it concentrates up the food chain attaining relatively high levels in high trophic level predators (e.g. tuna). This is illustrated well by the Minamata Bay case in Japan in the 1950s.

Minamata Bay took effluent from the Chisso factory which manufactured acetaldehyde with Hg catalysis. Inorganic (and some organic) mercury was contained in the factory effluent. The inorganic Hg was converted to organic Hg by microorganisms in Minamata Bay's sediment. The organic Hg was absorbed by plankton, etc. and concentrated up the Bay's food chain, concentrating in predatory fish. People living around the Bay utilised fish as a dietary staple. As a result of dietary intake of organic mercury (CH_3Hg^+) the Minamata Bay residents developed a characteristic neurological disorder termed itai itai disease – or Minamata disease. By 2001 there had been 2,265 Minamata disease cases and 1,785 deaths (MoE Japan, 2002; Kurland et al, 1960; Eto, 1997) – this was a serious issue.

Mercury is used in some industrial and household products (e.g. batteries) and industrial processes. Its use in fluorescent light bulbs is increasing as our desire to use energy efficient lighting increases. This will lead to an increase in Hg ore mining and disposal of Hg-contaminated waste to landfill.

Hg is neurotoxic. Organic Hg is very much more toxic that inorganic Hg because methylmercury cation binds to cystein forming methylmercurycysteinyl complex which mimics methionine and crosses the blood brain barrier on a methionine carrier (Fig 3) (Simmons-Willis et al, 2002).

The ultimate mechanism of toxicity of Hg compounds is thought to be via their interaction with thiol groups of cysteine residues in proteins which might cause protein conformational changes with concomitant changes in activity, or, if the cysteine residues are in enzyme active sites or ligand binding sites this might affect enzyme kinetics or ligand binding properties of receptors – all of which could have significant physiological effects.

Exposure to Hg in New Zealand food and its toxicological significance

The differential toxicities of organic and inorganic Hg is reflected in their provisional tolerable weekly intakes (PTWIs) which are 1.6 μg/

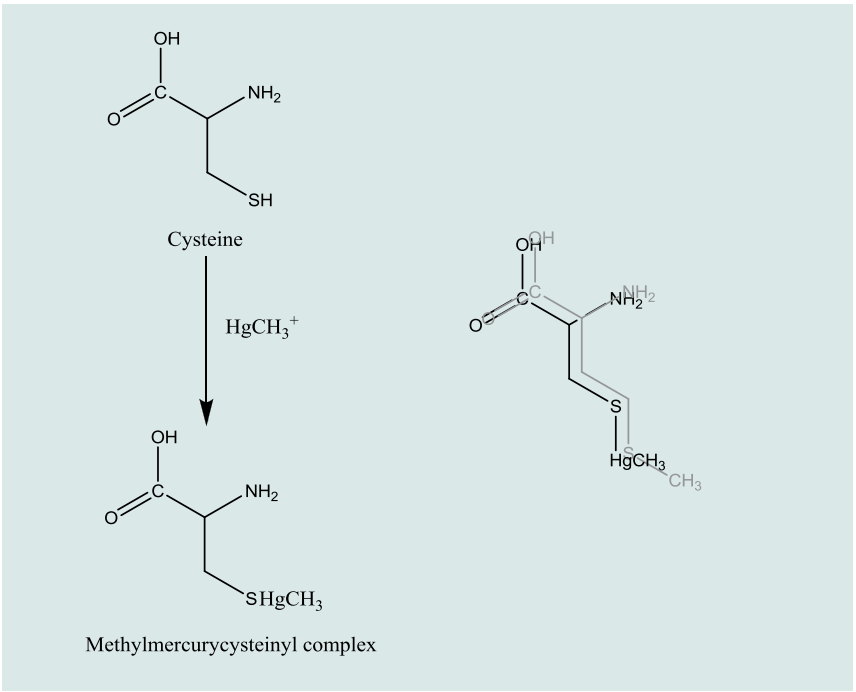

Figure 3 Left - Reaction of the amino acid, cysteine with methylmercury cation to form methylmercurycysteinyl complex. Right - Methylmercurycysteinyl complex (grey) shown superimposed on methionine (black) to show their structural similarities.

kg body weight for organic mercury and 4 μg/kg body weight for total mercury (WHO, 2007; WHO 2010). Dietary exposure to mercury in New Zealand is high (Table 4) compared to many other countries (approximately dietary exposures; New Zealand = 0.7, UK = 0.2, USA = 0.3 μg/kg body weight/month); this is probably because fish is a greater part of the New Zealand diet than it is in either the UK or USA. Other regions with high fish intake have correspondingly high mercury intakes (e.g. Basque country = 1.9 μg/kg body weight/month). Indeed, if a simulated New Zealand diet excludes fish the estimated inorganic mercury intake decreases by approximately 56% (Table 3). Fish is clearly an important source of dietary mercury.

Simulated diet	Estimated exposure (μg/kg body weight/week)	
	Inorganic mercury	Methyl mercury
Total	0.7	0.33
Excluding fish	0.2	
% PTWI [total diet]	5	21

Table 3 Estimated dietary exposure to methyl mercury and inorganic mercury in a simulated NZ diet for a 25+ year old male (NZTDS, 2009).

While 21% of the PTWI for organic mercury for a simulated New Zealand diet is not exceeding the tolerable intake it is getting close to the point that the risk of fish consumption in terms of organic mercury toxicity should be considered. The simulated diet is based on what is considered 'normal' fish consumption. Some consumers might eat more fish than average and thus would be at greater risk. To assess the risk of mercury in fish properly, any benefits of fish consumption must be taken into account; e.g. dietary Ω-3 fatty acids. Very recent studies have shown that the benefit of the Ω-3 fatty acids in fish outweigh the risk of its mercury content (FAO/WHO, 2011; Helleberg et al, 2012) and therefore it has been proposed that New Zealanders should not be advised to control their consumption of fish.

Arsenic

Arsenic toxicity

Arsenic is a metalloid found at low concentration in the earth's crust (Table 1), but is released by mining and geothermal activity. It is very toxic in its inorganic forms (e.g. AsO_3 LD_{50} [rat, oral] = 34.5 mg/kg body weight), but far less toxic in its organic forms (e.g. arsenobetaine LD_{50} [rat, oral] >10,000 mg/kg body weight); indeed, the lower the polarity of organic arsenic compounds the lower their toxicity (e.g. LD_{50}[rat, oral] CH_3As = 1,800; $(CH_3)_2As$ = 1,200; $(CH_3)_3As$ = 10,600 mg/kg body weight) (data from Kaise & Fukui, 1992). Both inorganic and organic arsenic occur in food, particularly seafood.

Inorganic arsenic's mechanisms of toxicity are based on its chemical properties. It binds strongly to thiol groups (e.g. cysteine) thus inhibiting the activity of cysteine-dependent enzymes and depleting GSH levels. In addition, arsenate has a striking resemblance to phosphate (Figure 4) and thus can interfere with cellular phosphate-based processes.

Arsenic is a carcinogen (Rossman, 2003). Its mechanism of carcinogenesis has not been fully elucidated, but it might involve GSH depletion (Thomas, 2009) which exposes DNA to reactive alkylating species or free radicals (e.g. superoxide generated by xanthine oxidase) which would normally be detoxified by GSH.

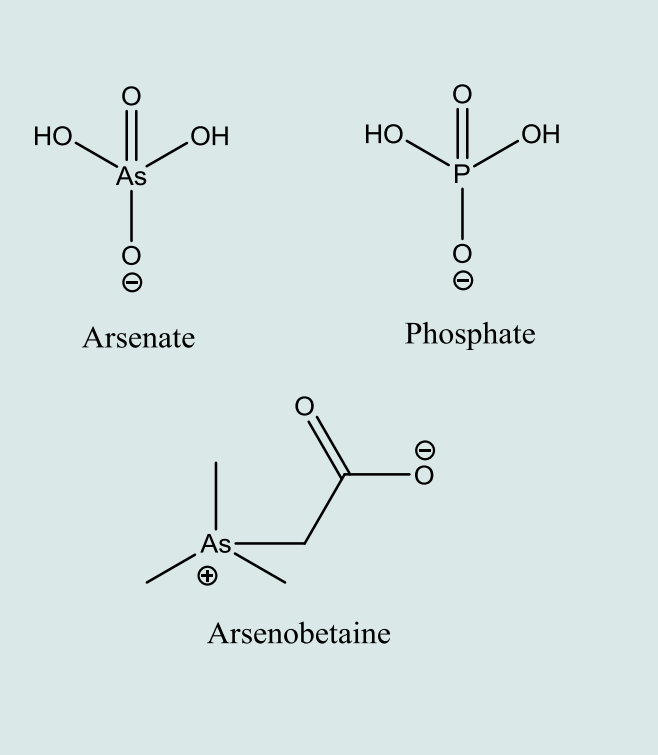

Figure 4 Phosphate, arsenate and arsenobetaine showing the structural similarities between phosphate and arsenate which explains why arsenate interferes with cellular phosphate-based processes.

Exposure to arsenic in New Zealand food and its toxicological significance

Arsenic (organic + inorganic) is found in fish products obtainable in New Zealand (Table 4) at concentrations ranging from 0.66 mg/kg (canned fish) to 3.99 mg/kg in fresh fish (NZTDS, 2009). There is no current WHO TWI or PTWI for inorganic arsenic because the previous value (15 μg/kg body weight (WHO, 1989) was withdrawn (WHO, 2010) because the PTWI was considered too close to the benchmark dose for a 0.5% increased incidence of lung cancer ($BMDL_{0.5}$ = 3.0 μg/kg body weight/day [21 μg/kg body weight/week]). Dietary exposure to total arsenic in New Zealand is approximately 13 μg/kg/week; the corresponding figure for inorganic arsenic is approximately 1.3 μg/kg/week of which approximately 92% is derived from fish (NZTDS, 2009) – this is about 6% of the $BMDL_{0.5}$. Therefore, dietary inorganic arsenic intake via fish is well below doses at which toxic effects would be expected; however, inorganic arsenic is carcinogenic and exposure to any carcinogen is undesirable, even at very low doses. Bearing in mind the Ω-3 fatty acid benefit argument discussed for organic mercury the risk associated with the dose of inorganic arsenic in fish is likely to be acceptable when set against the benefit of Ω-3 fatty acids.

Seafood	[As] (mg/kg)
Fresh fish	3.99
Battered fish	2.66
Oysters	2.38
Mussels	2.22
Fish fingers	1.02
Canned fish	0.66

Table 4 Arsenic concentrations in seafood purchased in New Zealand (NZTDS, 2009)

Overall conclusions

Dietary organic mercury intake (from fish) in New Zealand is approximately 21% of its PTWI, the corresponding figure for cadmium (from shellfish) is 25%, but since there is no PTWI for inorganic arsenic it is not possible to determine its intake in the same terms; however, the intake of inorganic arsenic (from fish) in New Zealand is 6% of the $BMDL_{0.5}$. These values clearly indicate a level of risk that is sufficient to warrant concern. On the other hand the benefits associated with seafood consumption are considerable. For example, Ω-3 fatty acids are present in seafood at higher concentrations than in many other foods: they are essential fatty acids and fish is clearly a good source. Although controversial, there is evidence for the importance of Ω-3 fatty acids in growth and development, particularly of the central nervous system and in preventing cardiovascular disease and depression. These benefits must be taken into account when assessing the risks associated with heavy metals in seafood. In this context, a risk/benefit assessment has been carried out for organic mercury in fish and falls firmly on the benefit side. It is likely if the same assessments were carried out for inorganic arsenic and cadmium that the same results

would be obtained. However, when assessing the weight of such risk/benefit assessments it is important to remember that the risk side of the equation is grounded in firm toxicological data whereas the benefit side is based on controversial, yet to be proved Ω-3 fatty acid benefit information. Perhaps there are still valid risk-based reasons not to over consume top of the food chain fish and oysters until the benefits of Ω-3 fatty acids are proved.

Hg, Cd and As all occur in seafood in New Zealand, and New Zealand consumers are likely to receive higher dietary doses of these heavy metals because of their greater concentrations in New Zealand marine environments than in many other parts of the world. This is in part due to New Zealand's volcanic nature and because heavy use of fertilisers (e.g. contaminated with Cd) is necessary to add phosphate to the country's phosphate-deficient soils. In view of this, the risk associated with consuming seafood derived from New Zealand marine environments is likely to be greater than seafood from many other countries where marine levels of heavy metals are lower. In a risk ranking context organic mercury poses the highest risk because its intake in New Zealand is a significant proportion (21%) of the PTWI.

However, it is the combined risk of Cd, As and Hg intakes that is important since they all occur in seafood, albeit at different concentrations in different seafoods. The balance of the combined risk in the context of the benefits of eating seafood is what is important. In my opinion, seafood should most definitely be part of a well balanced diet in New Zealand, but should not be overconsumed. The problem is that the 'jury is still out' re what constitutes 'overconsumption'.

Resources for heavy metal detection

The most common instrumentation for detection of heavy metals in food is Inductively Coupled Plasma Mass Spectrometers (ICPMS).

AsureQuality has two state of the art ICPMS instruments capable of detecting heavy metals at very low levels. Routinely up to 25 elements are simultaneously measured on these instruments. These include all the elements of concern in fish and shellfish such as mercury, arsenic, cadmium, lead, zinc, selenium, copper, chromium, nickel, cobalt, tin and iodine.

The Auckland laboratory's next generation ICPMS instrumentation offers a range of techniques to meet all analyses including very limited interferences; samples that require the removal of unknown interferences; and applications requiring the best performance with the lowest detection limits to meet various regulatory requirements.

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