DETOXIFICATION: HEAVY METALS

Toxic heavy metals are considered major environmental pollutants, with lead, mercury, cadmium and arsenic being the most important metal toxins for human health.[1] Heavy metals are widely used in the industrialised world and human exposure to their contamination has dramatically increased over the past 50 years.[1,2] Heavy metals are non-degradable, so they persist in the environment, with exposure posing bio-accumulative hazardous health risks. Heavy metals can affect a variety of body tissues and organs, such as the nervous, renal, hepatic, cardiovascular, respiratory, reproductive and immune systems.[1-3] Heavy metals disrupt cellular events including growth, proliferation, differentiation, damage-repairing processes and apoptosis.[3] These toxic heavy metals increase production of free radicals and oxidative stress and cause endocrine disruption, direct DNA damage and enzymatic inhibition. They can also cause damage to cell walls and the mitochondria, as well as malfunction of cellular processes and homeostasis.[1-3]

Table 1: Key heavy metals

Arsenic	Arsenic exposure has been shown to lead to dermal changes, such as pigmentation, hyperkeratosis, ulceration and skin lesions and to result in CNS and neurological damage, fatigue, weakness and headache. Arsenic has also been shown to cause gastrointestinal damage, diarrhoea, hepatomegaly and liver damage, renal damage and cardiovascular dysfunction, including peripheral vascular disease. Arsenic toxicity is associated with negative reproductive health and increased risk of birth defects, as well as an increased risk of some cancers.[1-6]
Cadmium	Cadmium exposure increases the risk of osteoporosis and skeletal damage, hypertension, diabetes and insulin resistance, some cancers, as well as an increased rate of miscarriage. Cadmium is a significant renal toxicant and causes renal damage. The concentration of cadmium in the kidney tissue of smokers is twice that of non-smokers, increasing the risk of renal tissue damage.[1-6]
Lead	Chronic lead toxicity has been associated with the risk of developing neurological conditions such as Parkinson's disease, Alzheimer's disease, decreased cognition, as well as neuro-behavioural dysfunction and a decline in the function of the peripheral nervous system. Lead toxicity may also lead to renal dysfunction, anaemia and hypertension. Infertility and an increased risk of miscarriages have also been associated with lead toxicity.[1-6]
Mercury	Mercury toxicity primarily affects the central nervous system and brain, kidneys, liver and lungs. It has been associated with disruptions to the nervous system, damage to brain function, damage to DNA and chromosomes, allergic reactions, tiredness, headaches and has been shown to negatively affect reproductive health.[1-6]

Strategies to support detoxification of heavy metals

Antioxidants are important to help reduce the deleterious effects of heavy metals. Heavy metal toxicity generates reactive oxygen and nitrogen species, with many of the toxic manifestations of these metals being caused primarily by oxidative stress and an imbalance between pro-oxidant and antioxidant homeostasis.[1-3,6-8] Heavy metals can also bind to sulfhydryl groups of proteins and deplete glutathione, which is an important endogenous antioxidant.[6] Management of heavy metal toxicity often involves chelation therapy.[1,7] Studies show that supplementation of antioxidants along with a chelating agent prove to be a better treatment regimen than monotherapy with chelating agents.[6,7]

Other important strategies to reduce the negative health impact of heavy metals include supporting detoxification processes, supporting immune system health and function and ensuring adequate intake of key nutrients. Some nutrients are required to support detoxification and heavy metal elimination. Heavy metal toxicity may also lead to an increased demand for certain nutrients to support normal physiological processes.

Figure 1: Management of heavy metal exposure

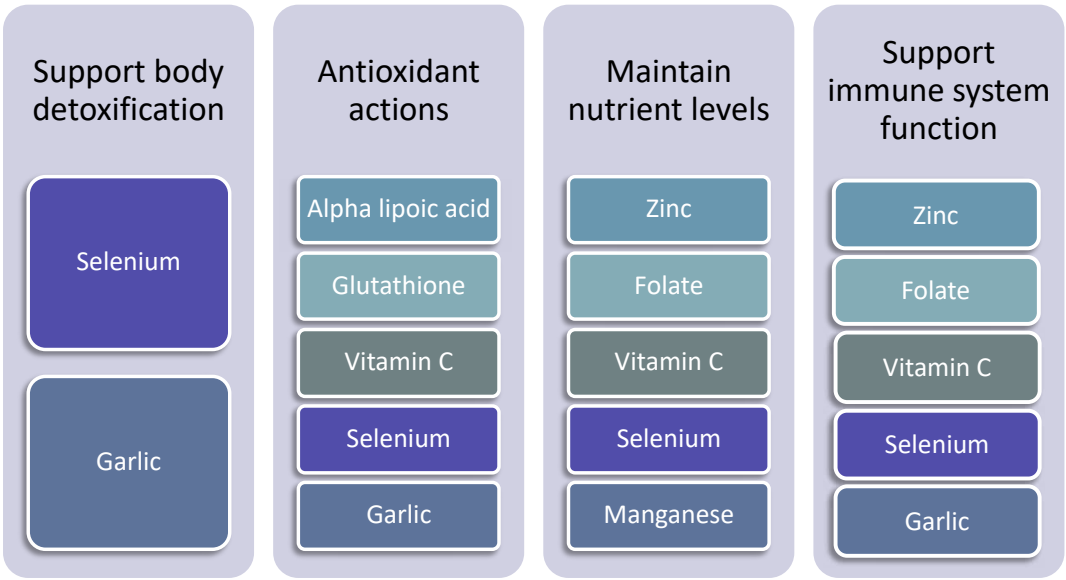

Table 2: Reducing the health impact of heavy metals

Nutrients	Actions and evidence
Alpha lipoic acid	• Alpha lipoic acid is both a water and a fat-soluble antioxidant produced naturally in the body.[9] It can regenerate endogenous antioxidants, such as vitamin E, vitamin C and glutathione and help prevent oxidative damage.[9] Alpha lipoic acid may protect against heavy metal poisoning according to *in vitro* and animal studies: • Alpha lipoic acid may protect against arsenic-induced toxicity in the liver and kidneys,[10,11] neurotoxicity,[12,13] haematological abnormalities[14] and male reproductive health.[15] • Alpha lipoic acid may protect against cadmium-induced neurotoxicity and inhibit neuronal apoptosis and injury,[16] cadmium-induced hepatoxicity and mitochondrial damage[17] and cadmium-induced nephrotoxicity and renal oxidative stress.[18] • Alpha lipoic acid may protect against lead-induced biochemical alterations in neurological, immunological and reproductive organs.[19]

Garlic	• Garlic supports natural detoxification pathways, and preliminary animal and *in vitro* research suggests that garlic may aid in heavy metal detoxification and reduce heavy metal accumulation in organs.[5,20-27] • Heavy metals have a high affinity for sulphur-containing peptides and it has been proposed that the sulphur-based constituents of garlic, such as allicin, provide protective effects by combining with heavy metals and promoting excretion.[5,20] • Garlic also has important antioxidant properties and may help to reduce metal-induced oxidative stress.[21,22,28-30]
Glutathione	• Glutathione is the major endogenous antioxidant produced by cells and participates directly with neutralisation of free radicals.[31] Glutathione protects cells from reactive oxygen species associated with heavy metal toxicity.[2, 20] • It is also a potent physiological chelator involved in cellular response, transport and excretion of heavy metal cations and is a biomarker for toxic metal overload.[20] *In vitro* evidence suggests that glutathione has potential to reduce the toxic effects of mercury.[33]
Folate	• Folate plays a critical role in methylation reactions.[34] Low folate status, whether due to poor dietary intake or genetic variations, may impede arsenic methylation and urinary excretion, and exacerbate or increase the risk of arsenic toxicity.[34] Conversely, methylation of arsenic has been shown to reduce arsenic toxicity.[34] • A Cochrane review reported that folic acid or folate supplementation (≥ 400 mcg daily) reduces blood arsenic concentration and improves urinary excretion of arsenic in adults exposed to arsenic, compared to placebo.[34]
Manganese	• Manganese is a component of metalloenzymes and plays an antioxidant role as part of manganese superoxide dismutase, which helps prevent lipid peroxidation by superoxide radicals.[35] Manganese also provides direct free radical scavenging activity.[35] Pharmaceutical chelation therapy may deplete manganese due to a relative lack of specificity.[36]
Selenium	• Maintaining adequate selenium levels may help to protect against mercury toxicity.[37] Evidence suggests that selenium and selenoproteins may be the primary targets for mercury poisoning, leading to a mercury-induced selenium deficiency state.[37] Mercury binds to the selenium site on selenoproteins, especially in the thioredoxin system, permanently inhibiting their function and disrupting the intracellular redox environment and regeneration. This increases the concentration and deleterious effects of intracellular reactive oxygen species leading to mitochondrial damage, lipid peroxidation, impaired protein repair and apoptosis and dysregulation of calcium homeostasis.[37] This has been associated with an increased risk of neurotoxicity, as well as other physiological damage.[37] • Selenium supplementation (100 mcg Se daily from Se-rich yeast) increased mercury excretion and reduced urinary markers of oxidative stress in a 3-month clinical study conducted in a population suffering from elevated mercury exposure.[38] • Population-based studies in Canadian Inuits also suggest that high dietary intake of selenium may be protective against mercury toxicity and oxidative stress.[39] • Selenium has also been shown to have protective and detoxifying actions against renal toxicity induced by mercury, lead and cadmium.[40]

Vitamin C	• Vitamin C may help mitigate oxidative damage caused by heavy metals and shows chelating properties.[2,36,41] • In a small human study in adult smokers, vitamin C (1000 mg daily for a week), significantly decreased lead levels, which was attributed to its chelating properties and by inhibiting intestinal lead absorption.[41] • Vitamin C has also been reported to act as a chelating agent of lead, with similar potency to that of EDTA in an animal model.[36] • In another small study conducted in healthy individuals, a correlation was found between higher serum ascorbic acid levels and lower blood lead levels.[42] • Vitamin C may also reduce blood cadmium concentrations in cigarette smokers by decreasing intestinal absorption.[43] Cigarette smoking significantly increases exposure to cadmium and is associated with blood cadmium concentrations being 28% higher in smokers compared to non-smokers.[43] Population studies suggest smokers may have lower dietary intake of vitamin C-containing foods such as fruits and vegetables.[43] Vitamin C supplementation may also improve sperm quality in heavy smokers.[44] • Vitamin C deficiency has been reported to enhance sensitivity towards cadmium and lead toxicity, and supplementation has been shown to reduce toxicity of both these metals in human and animal studies.[36] • In animal studies, vitamin C has also been shown to provide protective effects against oxidative damage caused by cadmium, [2,36,45-47] lead toxicity,[2,36,48,49] arsenic toxicity[50-52] and mercury toxicity.[45,46]
Zinc	• Maintaining adequate zinc status may help to protect against heavy metal toxicity and oxidative stress.[36] • Zinc has been shown to alleviate oxidative stress caused by exposure to lead and cadmium, due to its role as a cofactor of the antioxidant enzyme copper zinc-superoxide dismutase.[36] • Studies in both humans and animals have reported that zinc deficiency can lead to greater absorption and toxicity of both lead and cadmium.[36] Zinc has similar physical and chemical properties to lead and cadmium and competes for the binding sites of metal absorptive and enzymatic proteins.[36] • Zinc intake also induces the synthesis of metallothionein, a low molecular weight protein that has a high affinity for cadmium and leads to its detoxification by binding to cadmium.[36] • Zinc supplementation effectively preserves the activity of a zinc-dependent enzyme that is very sensitive to lead toxicity in the blood.[36]

**References available on request*