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REVIEW

Toxicity of mercury

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A ruling by the European Union heralds the demise of those useful clinical instruments, the mercury thermometer and the mercury sphygmomanometer. The new laws have been passed because of worries about mercury poisoning. Yet you can drink metallic mercury and come to no harm. What does it all mean? There are three forms of mercury from a toxicological point of view: inorganic mercury salts; organic mercury compounds; and metallic mercury. Inorganic mercury salts are water soluble, irritate the gut, and cause severe kidney damage. Organic mercury compounds, which are fat soluble, can cross the blood brain barrier and cause neurological damage. Mercury metal poses two dangers. It can be vaporised: the vapour pressure at room temperature is about 100 times the safe amount, so poisoning can occur if mercury metal is spilled into crevices or cracks in the floorboards. Dentists are occasionally poisoned this way. Mercury easily crosses into the brain, and causes tremor, depression, and behavioural disturbances. A second danger from metallic mercury is that it is biotransformed into organic mercury, by bacteria at the bottom of lakes. This can be passed along the food chain and eventually to man. It was this process that led to the Japanese tragedy at Minimata Bay in the late 1950s when over 800 people were poisoned. It is the need to reduce mercury contamination of the environment which should encourage us to cut the usage of metallic mercury. However, much more metallic mercury is spilled as waste by the chemical industry than is dropped on the floor in the clinic.

Keywords: mercury; toxicity; thermometer; sphygmomanometer

Toxicity of mercury

A new European Union directive[1] will prohibit the use of mercury in sphygmomanometers and clinical thermometers. We review here the toxic effect of mercury and its compounds and discuss their relevance to the environment and to modern medicine.

The Chinese used mercury (II) sulphide 1000 years before the birth of Christ as the red dye pigment vermilion. It was used similarly in the Graeco-Roman world, with both Hippocrates and Galen recording its toxic effects. Since then its toxicity has become well known in metalworkers, miners, felt-hat manufacturers, dyers and paint manufacturers. Despite this, mercury has been incorporated into the treatment of man's maladies from ancient times. Its main use has been to treat syphilis, from its first appearance in the West in the 15th century up to World War II.[2] Mercury and its salts have at various times been used as antiseptics, skin ointments, laxatives, diuretics, bowel washouts for the treatment of colorectal cancer, and scabicides. It is still used today as a solvent for the silver-tin amalgams used in dental fillings. So how toxic is mercury?

The hazards of mercury

There are substantial differences in toxicity of elemental mercury metal, inorganic mercury salts, and organometallic mercury compounds and we review each form separately.

Metallic mercury

Metallic mercury (liquid mercury, quicksilver, hydrargyrum (hence Hg), elemental mercury), is a silver white metal which melts at –38.7°C. Mercury is best known as a liquid metal, having a vapour pressure (a measure of the amount of vapour 'given off') of 0.002 mm Hg at 25°C. This approximately doubles for every 10°C increase in temperature, so that heating metallic mercury greatly increases the associated risks, as inhalation is the usual route of toxicity. Inhaled mercury vapour accumulates in the body, and in particular the central nervous system, which is the site of its major toxic actions. Orally ingested elemental mercury rarely causes acute toxic effects, as gastro-intestinal absorption is low—less than 0.01% of the dose.[3] For practical purposes, ingestion of oral elemental mercury as a single dose poses a negligible risk of severe toxicity. The oral LD_{10} is reported to be 1429 mg/kg (in man), or approximately 100 g for a 70 kg adult. Percutaneous absorption is also low (approximately 2% of the rate of uptake by the lung).[4]

Absorption by inhalation readily occurs, as mercury vapour freely crosses the alveolar membrane[5] with nearly 100% bioavailability.[6] Once absorbed, a proportion of mercury is taken up by the red blood cell, whilst some remains in the bloodstream, allowing its rapid distribution around the body, including the central nervous system. Within the red blood cells, liver, and central nervous system the

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metal is oxidised via the catalase-peroxide pathway to mercury (II) oxide. The rate at which this reaction occurs is limited in the presence of catalase inhibitors and competitive substrates such as ethanol. Mercury excretion from the body starts almost immediately after absorption, following a variety of routes, though principally by the kidneys.[7] Minor routes of excretion include the gastro-intestinal tract and saliva into which mercury is actively secreted, as well as from the lungs, in the nails and the hair and also from sweat glands. There is a relatively fast initial phase, during which a third of the inhaled mercury is rapidly concentrated in the liver and kidneys, and excreted in the bile or urine. This phase has an estimated half-life of 2–16 days. A still slower second phase, reliant on renal accumulation and probably responsible for the excretion of the majority of the body's mercury load via the urine, has a half-life of 30–60 days.[8] A slower third phase of excretion, via the kidney, has been postulated accounting for ~15% of the mercury load.[9] Mercury deposited within the brain has an elimination half-life that may exceed several years.[10] In workers with high lifetime exposure to elemental mercury, deposits of mercury were found in the brain at autopsy, even though exposure to mercury had ceased years previously.[11] In rats, the highest concentrations of mercury were found in the Purkinje cells of the cerebellum and in certain neurons of the spinal cord and midbrain.[12]

The toxicity of mercury vapour is dose-dependent. Exposed patients may initially complain of a metallic taste. Three to 5 h after a high acute exposure, cough, dyspnoea, chest tightness, lethargy, restlessness, fever and signs of pneumonitis can develop. If the exposure levels are sufficient, and especially when accumulation occurs after repeated exposures, then central nervous symptoms and signs arise, with tremor, and erethism (behavioural disturbances).[13] Vasomotor disturbances may also occur with excess perspiration and blushing. Other oral changes include ulceration, bleeding gums and loosening of the teeth.[14]

Chronic poisoning markedly affects the central nervous system and kidney. Tremor, initially involving facial muscles and eyelids, is present at rest, but aggravated by intention. It gradually becomes more pronounced and also starts to affect the limbs. Handwriting becomes illegible, with omission of letters and eventually whole words; erethism is manifest as excessive shyness, loss of confidence, vague fears, irritability, insecurity, and suicidal melancholia. The patient becomes unable to perform simple tasks such as dressing.[10] Renal problems are relatively rare considering that the major route of elimination is via the kidneys. The commonest signs are of proteinuria-reflecting glomerular damage. With high doses a frank nephrotic syndrome can develop, that has been seen both in industry and medicine.[15,16]

Inorganic mercury salts

Inorganic mercury salts are present in nature in various colours ranging from the white oxides to the browns and blacks of the sulphide compounds. They are also commonly used in industry. They have been used in medicine in teething powders, skin-lightening creams and as preservatives in certain medicines—particularly as eyedrops. Mercury (I) chloride (calomel) was widely used as a purgative in the form of the 'blue pill'.

The toxicity of mercury salts varies with their solubility. Usually mercury (I) compounds are of low solubility and significantly less toxic than mercury (II) compounds. Inorganic mercury salts present a far greater hazard than elemental mercury if ingested orally, owing to their greater water solubility.[17] For mercury (II) chloride, the lethal dose may be as small as 0.5 g, compared with 100 g mercury metal. Mercury salts are usually non-volatile solids, so poisoning by inhalation is rare, though toxicity may arise if aerosols are deposited in the lungs. Once adsorbed, the mercury (I) form will readily react with the thiol groups of amino acids such as cysteine. The protein metallothionein, functions as a natural chelator, preventing damage by mercury and other transitional metals to thiol-containing proteins. Once metallothionein proteins are saturated, other structurally related proteins can be damaged. Inorganic mercury salts are not lipid soluble, and so do not cross the blood brain barrier in significant amounts. The majority of the dose of an ingested inorganic mercury salt accumulates either in the liver, where it is excreted in the bile, or in the kidney, where it is excreted in the urine.

The symptoms and signs of inorganic mercury poisoning arise in two phases. Very soon after ingestion, there is burning pain in the chest, rapid discolouration of the mucous membranes (secondary to precipitation of proteins in the mucosal lining), and gastro-intestinal pain from direct local trauma due to the salts' corrosive nature. There can be vomiting and a profuse bloody diarrhoea which can in extreme cases lead to hypovolaemic shock and death. If the patient survives the initial effects of the poison, the systemic effects predominate, with mercurial stomatitis (glossitis, ulcerative ginigivitis, hypersalivation, and a metallic taste), loosening of the teeth, and renal damage. The renal damage arises secondary to accumulation of the mercury salt in the proximal convoluted tubules, causing a transient polyuria, proteinuria (in severe cases a nephrotic syndrome), haematuria, anuria and renal acidosis.

Chronic inorganic mercury poisoning often occurs in combination with elemental mercury poisoning, where the central nervous system effects predominate. Chronic poisoning from pure inorganic mercury salt is rare. Its symptoms, though previously described in children as acrodynia or 'Pink Disease', were only formally attributed to inorganic mercury compounds in 1951 by Warkany and Hubbard[18] following a study of mercury containing substances used in teething powders, worm pills, ammoniated mercury ointment, and mercury (II) chloride. It is characterised by severe leg cramps, irritability, paraesthesia (a sensation of pricking in the skin), pink extremities and exfoliation of skin.

Organic mercury compounds

Organic mercury compounds are an important cause of poisoning. Mass outbreaks have occurred throughout the world, either inadvertently secondary to pollution, or via direct ingestion of organic mercury compounds. In the developed world, exposure is most commonly via the aquatic food chain, where micro-organisms convert elemental mercury to organic mercury before being eaten by larger invertebrates and so on up the chain, ending with man.

The organic mercury compounds are very lipid soluble: 90–100% of an oral dose is absorbed. The exact distribution within the body is uncertain. A large proportion of a dose is transformed to inorganic compounds. This however fails to explain the characteristic central nervous system pattern of toxicity. Specific damage is seen in the cerebellum and visual cortex. The excretion of organic mercury compounds is initially in the bile via the liver.[19] However they undergo enterohepatic recirculation, leading to reabsorption and uptake into the red blood cells where they are metabolised, forming inorganic salts and follow pathways previously discussed.

The toxicity of organic mercury exposure may be delayed for weeks to months, with predominant gastro-intestinal and central nervous system effects.[20] The gastro-intestinal effects include nausea, vomiting and abdominal pain; higher doses can cause diarrhoea and an exposure-related colitis. Other symptoms include the discolouration of the gums (similar to poisoning with inorganic compounds), sialorrhoea and perioral paraesthaesia. Central nervous effects after slight exposure include numbness in the limbs; as the level of exposure increases, there are tremors, ataxia, dysarthria, and visual field constrictions.

Organic mercury poisoning became notorious after the Minimata tragedy, where an epidemic of a condition resembling cerebral palsy was ascribed to its teratogenic effect.[21] Milder forms are present with lower levels of exposure,[22] with features including mental retardation, spasticity, seizures, chorea, tremors, cataracts, small size, anorexia, and renal dysfunction.[23] Other effects seen from poisoning include cardiac arrhythmias, hepatic enzyme disturbances, respiratory tract irritation, and blistering of the skin.[19]

Mercury in the environment

Mercury is naturally present in the earth's crust. It is also present in the atmosphere either derived naturally from the degassing of the earth's crust, emissions from volcanoes, evaporation from the world's seas, or from industrial pollution, which has greatly increased our exposure.

Elemental mercury and its inorganic salts have a wide range of uses within industry. In the gold-mining areas of the Amazon, where mercury is used in the extraction of gold, there is extensive human and environmental contamination owing to the methods used.[24–26] In the Western world, mercury plays a role in the production of chlorine as an electrolytic catalyst, as well as its use in calibration instruments and fluorescent lights. Even with modern techniques of industrial hygiene, workers exposed to mercury and their families[27] have increased mercury concentrations in the urine, though no symptoms of overt poisoning, with normal industrial exposure.[28] More bizarre sources include crematoria.[29] As nearly 70% of people who now die are cremated in the UK, it is estimated that a single crematorium emits approximately 5.5 kg of mercury a year. However the largest source of mercury pollution is emissions from coal fired power plants.

Organic mercury and human exposure from it has mirrored environmental pollution. The first case of organic mercury poisoning arose amongst research workers at St Bartholomew's Hospital in 1865 as they tried to manufacture organic mercurial compounds. Three technicians had significant methylmercury exposure and two subsequently died as a result.[30] A chemistry professor in the United States was similarly poisoned in 1997.[31] However, micro-organisms are the prime producers as they biotransform the metallic mercury in their environment to organic mercury compounds.[32] The extent of the problem was only realised following the Japanese disaster at Minamata where a factory's effluent was discharged into the local fishing grounds. By a process of biomagnification, the methylmercury accumulated to sufficient amounts in predatory fish[33] to poison over 800 people who relied on the fish for their nutrition. A number were infants *in utero*.[34] This problem is worldwide, leading to restrictions on fishing in the Great Lakes in the United States and some commentators to conclude that all fish are polluted with methylmercury.[32] Other studies have linked fish consumption and increased methylmercury levels in man, though without overt symptoms of poisoning.[35,36] (Further studies are presently underway.) Other more direct poisonings from methlymercury have arisen owing to its use as a fungicide particularly in Second and Third World countries. Inadvertent ingestion of treated corn has caused mass outbreaks of poisoning. The largest occurred in Iran in the autumn of 1971, resulting in 6530 cases of poisoning with 459 deaths.[37] Smaller outbreaks have also occurred in Ghana[38] and Pakistan.[39] In other countries methylmercury has been used as a fungicide in paints, and poisoning has resulted.[40]

Medicine and mercury

The mercury sphygmomanometer invented by Scipione Riva-Rocci has been the mainstay for blood pressure monitoring for the last century.[41] Only within the last decade have automated mechanical devices of sufficient accuracy become available.[42] Suggestions that the mercury sphygmomanometer may be responsible for mercury poisoning have rarely been discussed with no records in the literature of it directly being responsible for the deaths of patient or operator. However concerns arise from the fact the each mercury sphygmomanometer contains approximately 64–85 g of elemental mercury. The

actual amount has been found to vary considerably, as mercury is slowly lost either by direct spillage, vaporisation or secondary to oxidation. Studies have indicated that between 62–87% of mercury manometers are affected in this way.[43] Where the mercury has been lost to remains debatable. Environmental lobbyists and journalists[44] have been keen to speculate, claiming the subsequent vaporisation of mercury was endangering health staff's well being with chronic mercury exposure. Fortunately though there is little evidence for this, though reports do exist on both sides of the Atlantic recounting toxicity to medical technicians charged with repairing and servicing the mercury manometers.[45] Such problems usually arise owing to mercury spills in small, enclosed areas with poor ventilation, often in a well-heated room where the spillage has been inadequately disposed of. (For information on dealing with mercury spillages see appendix 1.) Although these problems exist, it was concluded in an American study[46] that 'the prevention of mercury exposure in the occupational settings . . . should be readily achievable'. The importance of mercury in sphygmomanometers is also diminished by the relatively small amounts of mercury involved compared with industry. (In 1992 the United States, according to the USEPA's Toxic Release Inventory, released nearly 16000 pounds (approximately 7000 kg) of elemental mercury to soils, surface waters, and the atmosphere.)

The sphygmomanometer is not alone in medicine as an instrument relying on mercury for its properties. The mercury thermometer will also be affected by the Community's legislation. No reports exist of intact thermometers causing mercury poisonings, although once broken thermometers may cause problems. The most significant poisoning was due to inhalation of mercury vapour occurring in a neonate in an isolette (incubator), where a mercury-operated switch had broken, spilling mercury into a confined area that was maintained at 25°C.[47] However the majority of incidents involving mercury thermometers are directly related to trauma, as the thermometer is broken. The sites of injury include the floor of the mouth,[48] rectal injury,[49] eye injury,[50] and injuries to hands and fingers,[51] and the lower limb.[52] In almost all of these cases the extent of injury is related to local tissue damage rather than systemic effects. Despite this, since January 1992, mercury thermometers have been banned from import, manufacture, or sale in Sweden.[53]

The other main medicinal use of mercury has been as a dental amalgam. Its use within dental surgeries has in the past been somewhat chequered with at least one death attributed to the poor environmental controls present within the surgery.[54] However, the amount of mercury adsorbed into the body from a dental amalgam remains largely disputed. All parties agree that some mercury from the amalgam is vaporised and absorbed by the body, particularly after chewing and brushing teeth.[55–57] However the amount of mercury released and the quantity required to have an effects within the body is yet to be ascertained. A review of seven studies reported the daily dose ranging from 1.7 μg/day to 17.5 μg/day.[58] (The General Public Threshold (NOAEL)—no observed adverse effect level ie, the level at which adverse effect have never been observed—is 5 μg/m^3.) Owing to the prevalence of dental fillings the US government commissioned a review of the literature published in 1993 which concluded: '. . . Current scientific evidence does not show that exposure to mercury from amalgam restorations poses a serious health risk in humans except for an exceedingly small number of allergic reactions.'[59]

Despite this and other follow-up reports,[60] the issue remains in dispute with '*The Times*' reporting a case of a woman requiring admission to a psychiatric unit claiming that mercury fillings 'drove woman to attack mother'.[61] In Lorscheider's review of dental amalgams, he concluded that there was insufficient evidence to prove that amalgams were safe.[62] A US study showed that despite low levels of mercury some evidence of subtle preclinical behavioural effects are present,[63] further substantiating this view. The debate will no doubt continue though present evidence shows there is little room for concern (see Eley's series of articles on the dental amalgam in the *British Dental Journal*).[64]

Conclusion

Overt mercury poisoning is rare in the modern world, although it is widely spread in the environment both naturally and as a result of pollution. Its toxicity is well known, though the presentation of its symptoms depends largely on the route of administration and its form. Modern clinical use of mercury appears to be safe, owing to the very limited exposure in our daily lives, thought caution is necessary if handling large amounts of mercury or repairing mercury-containing instruments. The symptoms purportedly caused by chronic low-dose mercury poisonings as with dental amalgam remains unproven, though research continues in this area.

Appendix 1: Dealing with spilt mercury[65]

Spilled mercury can shatter into tiny droplets. This increases the surface area and also the rate of evaporation and represents a hazard. Therefore a mercury spillage should be treated seriously. The recommended action is to ensure that the area is segregated to prevent the contamination from spreading, and to maximise ventilation by opening windows. Wearing protective gloves and mask join up the globules of mercury to form a large pool using a wooden spatula or equivalent before aspirating into a syringe. The aspirate is then placed in a specially designated container, or if that is unavailable, in a jar of water prior to sealing it. Spreading a paste containing equal parts of sulphur and calcium hydroxide over the surface further decontaminates it, by forming black insoluble mercury (II) sulphide therefore rendering it non-volatile, preventing the further evaporation of mercury.[66] The paste is mixed with the remains of the spilt mercury for a minimum of 2 to 3 min, and then disposed of via the spatula into an appropriate waste container. The area is

wiped with a damp cloth, which is then placed in a sealed polythene bag for appropriate disposal. Mercury that may remain in cracks in the floor or other inaccessible places can be treated using a dry mix of calcium hydroxide and sulphur. The waste canister containing the mercury requires to be disposed of appropriately, either via a suitable metal reclaiming company or as toxic waste.

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