

## Metallic mercury: the health effects of long-term, low to moderate exposures

Mercury is found widely in the environment, occurring both naturally and as a result of human activities. It exists in several forms, namely metallic (or elemental) mercury, inorganic mercury and organic mercury. Inorganic mercury compounds are formed when mercury combines with elements such as chlorine, sulphur or oxygen to form oxides or salts of mercury. With the exception of red cinnabar, these are mostly white powders or crystals. Organic mercury compounds contain mercury covalently bound to hydrocarbons (aliphatic or aromatic). Methylmercury is the most common organic mercury compound found in the environment.

This article focuses on metallic mercury, a shiny silver-white liquid metal at room temperature that evaporates to form mercury vapour in the atmosphere.

One of the major uses of elemental mercury is as a cathode in the electrolysis of sodium chloride to make caustic soda and chlorine. It is also used in the manufacture of lamps, batteries, and in old-fashioned switches, thermometers and barometers. Dental amalgam contains elemental mercury mixed with a silver-tin alloy. Globally, most of the mercury released into the environment by human activities is due to the

### How are we exposed to elemental mercury?

Everyone is exposed to mercury to a small extent, as it occurs naturally at very low levels in air, water and food. Brief accidental exposure to higher levels of metallic mercury can occur on contact with broken thermometers, fluorescent light bulbs and similar equipment. Some may have prolonged exposure to metallic mercury vapour as a result of their employment in certain occupations, such as dentistry, chemical manufacturing and the chemical processing industries. For metallic mercury the predominant route of exposure is through inhalation of its vapour.

### How does it enter and leave the body? (Kinetics and Metabolism)

When the vapour is breathed in, mercury is readily absorbed from the lungs, with around 80% being retained in the body. Only a small amount of elemental mercury can be absorbed into the body through the skin (about 2% of the amount that is taken up by the lungs). Ingested liquid mercury metal is poorly absorbed through the intestine, with only around 0.01% of the total amount entering the body by this route.

Once absorbed, elemental mercury is widely distributed throughout the body, accumulating particularly in the kidneys where it has a half-life

of around 60 days and in the brain with an even longer half-life. The body eliminates metallic mercury predominantly through the urine and faeces, with only a small amount being exhaled.

Elemental mercury readily passes through the blood-brain barrier and into the placenta due to its high lipophilicity (fat solubility).

In the blood, elemental mercury undergoes oxidation in the red blood cells and other organs to form divalent mercury (the mercuric ion). This ionic mercury mainly exists in a non-diffusible form, binding to albumin and globulins, and may become retained in various organs.

### Estimating exposure

The extent of occupational exposure to mercury can be assessed by measuring levels in the atmosphere. However, the most appropriate estimate of personal exposure is given by measuring the urinary levels of mercury (U-Hg), as these reflect the total longer term exposures from all routes.

Ideally, concentrations are expressed as micrograms of mercury per gram of creatinine ( $\mu\text{g Hg/g creatinine}$ ). The correction to the level of creatinine eliminates any variation caused by differing levels of hydration in the subjects. For short-term (acute) exposure, the measurement of the blood levels of mercury is more appropriate (B-Hg).

### What is known about the health effects of metallic mercury?

The extent of the effects produced from exposure to metallic mercury will largely depend on the dose (how much), the duration (how long) and the route of exposure (how you came into contact with it).

Exposure to high levels by inhalation can cause respiratory effects (cough, difficulty breathing), central nervous system effects (tremor, irritability), kidney damage (protein and blood in the urine, acute renal failure), gastrointestinal disturbances (inflammation of the mucous membrane linings of the mouth, nausea and diarrhoea) and cardiovascular effects (increased blood pressure and heart rate).

Inhalation of high concentrations of elemental mercury over the longer-term may cause neurotoxicity (fatigue, tremor, headache, depression, hallucination), nephrotoxicity (proteins and enzymes in the urine), and effects on the oral cavity (inflammation of the mucous membrane linings of

the mouth, sore gums and mouth ulcers). The consensus of the scientific literature is that effects on the central nervous system are the most sensitive outcome of mercury toxicity (with the exception of the excretion of urinary NAG1, a sensitive marker of potential kidney toxicity).

Subtle alterations of colour vision, as assessed e.g. by the Lanthony D 15 test, have been identified as being particularly sensitive, showing a dose-dependent relationship with a threshold at a group level of somewhere below  $50 \mu\text{g Hg/g creatinine}$ . A study of 21 exposed industrial workers and suitably matched controls found that colour perception can gradually return to normal after exposure is reduced to below the equivalent of  $10 \mu\text{g Hg/g creatinine}$  (as a group mean).

A review of the relevant literature shows that most markers of kidney toxicity are within the normal range in workers occupationally exposed to metallic mercury vapour at levels of  $<35 \mu\text{g Hg/g creatinine}$ , and are not different from control subjects who have no occupational exposure. The evidence suggests that mercury in urine levels below  $30 \mu\text{g Hg/g creatinine}$  are not associated with any toxicity.

Children are often considered to be potentially more vulnerable to the toxic effects of chemicals than adults. A recent study followed, for 5 years, more than 500 children randomly assigned to receive either amalgam or composite fillings for dental treatment of caries. The difference in mean urinary mercury levels was statistically significant, at  $0.9 \mu\text{g Hg/g creatinine}$  in the amalgam group and  $0.6 \mu\text{g Hg/g creatinine}$  in the composite fillings group. No statistically significant differences were found between the two groups on neuropsychological testing.

There is little reliable data on the effects of metallic mercury on the immune system. However, low to moderate exposures to inorganic mercury do not seem to produce adverse clinical effects on the immune system.

Epidemiological studies (looking at incidences of health effects within a population) have failed to show any clear evidence of a link between mercury exposure and increased mortality from infections or malignancies. <sup>1</sup> N-acetyl-beta-D-glucosaminidase

There appears to be a possible relationship between exposure to organic mercury (methylmercury) and increased risks of acute coronary events, coronary heart disease, heart disease and cardiovascular mortality. The results of epidemiological studies on populations exposed to metallic mercury and cardiovascular effects are equivocal. Discrepancies between the studies

might possibly be explained by interactions of mercury with other trace metals such as selenium. Selenium is known to protect the blood lipids, such as low-density lipoprotein (LDL), from oxidative damage. There is substantial variation in body selenium levels between different populations due to variations in dietary selenium concentrations.

At present, the evidence that mercury can alter the genetic material (i.e. is mutagenic) or is involved in causing or exacerbating cancer (i.e. is carcinogenic) is ambiguous. There is no indication that mercury increases mutagenic or carcinogenic risks to humans at exposure levels of  $<50 \mu\text{g Hg/g}$  creatinine. The WHO International Agency for Research on Cancer (IARC) has categorised elemental mercury and inorganic mercury in Category 3 as “not classifiable as to carcinogenicity to humans”.

Elemental mercury has been shown to cause developmental effects in laboratory animals, in which behavioural effects and learning difficulties have been observed in offspring when exposed to high concentrations of mercury vapour.

There is no conclusive evidence in humans, from a limited number of epidemiological studies and public register data, that occupational exposure to mercury vapour is harmful to reproductive organs, fertility or offspring development. Studies of industrial workers exposed to mercury, including male and female workers and the wives of exposed men, found no adverse effects attributable to exposure giving a U-Hg concentration of less than  $50 \mu\text{g/l}$  (equating to about  $40 \mu\text{g Hg/g}$  creatinine).

As well as the kidney, mercury is known to accumulate in endocrine glands including the thyroid and the pituitary. Small but statically significant mercury-induced changes in active thyroid hormones have been detected. These changes were reversible once mercury exposure at the workplace ceased. Studies in exposed workers have not identified any clear effect on the pituitary or male sex-hormone functions that could be attributed to a moderately low mercury exposure.

### The views of the regulatory and international bodies

In 2009, the EU published an Indicative Occupational Exposure Limit Value (IOELV) of  $0.02 \text{ mg/m}^3$  averaged over an 8 hour day (TWA). This value is in the process of being transposed into national legislation in almost all EU member states. In the United States, the American Conference of Industrial Hygienists has set an eight hour time weighted average of  $0.025 \text{ mg/m}^3$ .

Additionally, the EU has banned the export of metallic mercury and some other mercury compounds from March 2011 and the USA will have an export ban on metallic mercury from January 2013. There continues to be strong pressure from the regulatory bodies to remove mercury wherever possible from industrial uses and products. The Chlor-Alkali industry has committed to ending its use of mercury by 2020.

### What research is needed on this topic?

Examination of the available data, taking into account the reversibility of certain effects after cessation or reduction of exposure, supports a no-observed adverse effect level (NOAEL) for long-term exposure to metallic mercury equivalent to a mercury in urine level of  $30 \mu\text{g Hg/g}$  creatinine.

Good-quality epidemiological data on the reversibility of long-term exposure ( $>10$  years) equating to concentrations in the range  $20$ – $55 \mu\text{g Hg/g}$  creatinine are currently lacking. Further studies would help to fill this gap in the toxicological knowledge.

Additional work on the kinetic relationship between U-NAG and the effect of mercury exposure on the proximal tubular cells of the kidneys would also be beneficial. At present, it is not known whether the increased excretion of NAG should be considered a toxic effect or is simply concomitant with the excretion of mercury from these cells.

A better understanding of this relationship is particularly important since some regulators have placed considerable importance on changes in this kidney parameter. Supplementary studies are also required to confirm the reversibility of the increased excretion of NAG that was observed in one study when exposure was reduced so that U-Hg fell from  $50$  to  $10 \mu\text{g Hg/g}$  creatinine.

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#### Euro Chlor

Euro Chlor provides a focal point for the chlor-alkali industry's drive to achieve a sustainable future through economically and environmentally-sound manufacture and use of its products. Based in Brussels, at the heart of the European Union, this business association works with national, European and international authorities to ensure that legislation affecting the industry is workable, efficient and effective. Chlorine and its co-product caustic soda (sodium hydroxide) are two key chemical building blocks that underpin 55% of European chemical industry turnover.

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