

Chapter 6.9

Mercury

General description

Mercury exists in three oxidation states: Hg° (metallic), Hg^{+} (mercurous) and Hg^{++} (mercuric) mercury. The latter forms a variety of inorganic as well as organometallic compounds. In the case of organometallic derivatives, the mercury atom is covalently bound to one or two carbon atoms. In its elemental form, mercury is a dense, silvery-white, shiny metal, which is liquid at room temperature and boils at 357 °C. At 20 °C, the vapour pressure of the metal is 0.17 Pa (0.0013 mm Hg), and a saturated atmosphere at this temperature contains 14 mg/m³. Mercury compounds differ greatly in solubility; at 25 °C, the solubilities of metallic mercury, mercurous chloride and mercuric chloride in water are 60, 2 and 69 g/litre, respectively (1).

Sources

Mercury is emitted to the atmosphere by natural degassing of the earth's surface and by re-evaporation of mercury vapour previously deposited on the earth's surface. Mercury is emitted in the form of elemental vapour (Hg°). Annual natural emissions are estimated to be between 2700 and 6000 tonnes (2), some of which originate from previous anthropogenic activity. Anthropogenic sources of mercury are numerous and worldwide. Mercury is produced by the mining and smelting of cinnabar ore. It is used in chloralkali plants (producing chlorine and sodium hydroxide), in paints as preservatives or pigments, in electrical switching equipment and batteries, in measuring and control equipment (thermometers, medical equipment), in mercury vacuum apparatus, as a catalyst in chemical processes, in mercury quartz and luminescent lamps, in the production and use of high explosives using mercury fulminate, in copper and silver amalgams in tooth-filling materials, and as fungicides in agriculture (especially as seed dressings). The Almaden mercury mine in Spain, which accounts for 90% of the total output of the European Union, produces more than 1000 tonnes per year (3), but the amount of mercury released to the environment is unknown. In total, human activities have been estimated to add 2000–3000 tonnes to the total annual release of mercury to the global environment (2,4). However, it should be stressed that there are considerable uncertainties in the estimated fluxes of mercury in the environment and in its speciation.

The global cycle of mercury involves the emission of Hg° from land and water surfaces to the atmosphere, transport of Hg° in the atmosphere on a global scale, possible conversion to unidentified soluble species, and return to land and water by various depositional processes. The ultimate deposition of mercury, probably as cinnabar ore, is believed to be in ocean sediments. Part of the inorganic mercury emitted becomes oxidized to Hg^{++} and then methylated or in other ways transformed into organomercurials. The methylation is believed to involve a non-enzymatic reaction between Hg^{++} and a methylcobalamine compound (an analogue of vitamin B₁₂) that is produced by bacteria (5). This reaction takes place primarily in aquatic systems. The intestinal bacteria flora of various animal species, including fish, are also able to convert ionic mercury into methylmercuric compounds (CH_3Hg^{+}), although to a much lower degree (6). Methylmercury is avidly accumulated by fish and marine mammals and attains its highest concentrations in large predatory species at the top of the aquatic food-chain. By this means, it enters the human diet. Certain microorganisms can demethylate CH_3Hg^{+} ; others can reduce

Hg^{++} to Hg° . Thus, microorganisms are believed to play an important role in the fate of mercury in the environment and hence human exposure.

Occurrence in air

This topic has been reviewed by Lindqvist et al. (7). Background mercury levels in the troposphere of the northern hemisphere are now estimated at 2 ng/m^3 . Levels in the upper troposphere are only slightly lower, but few measurements have been reported. In areas of Europe remote from industrial activity, such as rural parts of southern Sweden and Italy, mean concentrations of total mercury in the atmosphere are reported to be usually in the range $2\text{--}3 \text{ ng/m}^3$ in summer and $3\text{--}4 \text{ ng/m}^3$ in winter. Mean mercury concentrations in urban air are usually higher; for example, a value of 10 ng/m^3 has been reported in Mainz, Germany, and in an urban area of Italy. Individual determinations may cover a wide range of values. In the same urban area of Italy, the range was $2\text{--}3 \text{ ng/m}^3$. Within the European Union, the following ranges for atmospheric mercury have been documented: remote areas $0.001\text{--}6 \text{ ng/m}^3$, urban areas $0.1\text{--}5 \text{ ng/m}^3$ and industrial areas $0.5\text{--}20 \text{ ng/m}^3$ (8).

“Hot spots” of mercury concentration have been reported in the atmosphere close to industrial emissions or above areas where mercury fungicides have been used extensively. Fujimura (9) reported air levels of up to $10\,000 \text{ ng/m}^3$ near rice fields where mercury fungicides had been used and values of up to $18\,000 \text{ ng/m}^3$ near a busy motorway in Japan. Air values may rise to 600 and 1500 ng/m^3 near mercury mines and refineries (10).

Few data are available on the speciation of mercury in the atmosphere. However, it is generally assumed that metallic mercury vapour is the predominant form (7,10,11). Johnson & Braman (12) reported the presence of organomercury compounds in the atmosphere above a highly polluted ocean bay in Florida, United States of America) and in a metropolitan area (Tampa, FL). In the latter, mercury vapour accounted for 50%, mercuric halide vapour and monomethylmercury for 25% and 21% respectively, and dimethylmercury for only 1% of total gaseous mercury. The water-soluble fraction is, on average, 5–10% of the total gaseous mercury (7). All published studies to date indicate that particulate mercury accounts for less than 5% of total mercury in the atmosphere.

Total mercury, assumed to be mainly metallic mercury vapour, has a residence time of 0.4–3 years and is therefore globally distributed (7). The “water-soluble” form may have a residence time of only a few weeks. This water-soluble form and particulate mercury, which also has a short residence time, although accounting for only a small fraction of total mercury, may nevertheless be important in transport and depositional processes. Furthermore, the possibility that some conversion of water-insoluble to water-soluble forms of mercury takes place in the atmosphere has been raised.

No data are available on indoor air pollution due to mercury vapour. Fatalities and severe poisonings have resulted from heating metallic mercury and mercury-containing objects in the home. Incubators used to house premature infants have been found to contain mercury vapour at levels approaching occupational threshold limit values; the source was mercury droplets from broken mercury thermostats. The exposure to mercury vapour released from latex paint containing mercury compounds to prolong shelf-life, can reach levels of $300\text{--}1500 \text{ ng/m}^3$ (13). Indoor air pollution caused by central-heating thermostats and by the use of vacuum cleaners following thermometer breakage, etc., should also be considered.

Release of mercury from amalgam fillings has been reviewed by Clarkson et al. (14). They concluded that amalgam surfaces release mercury vapour into the mouth, and that this is the predominant source of human exposure to inorganic mercury in the general population.

Routes of exposure

Air

The only two sources of human exposure to metallic mercury vapour are the general atmosphere and dental fillings. In adults, the daily amount absorbed into the bloodstream from the atmosphere as a result of respiratory exposure is about 32 ng in rural areas and about 160 ng in urban areas, assuming rural concentrations of 2 ng/m³ and urban concentrations of 10 ng/m³ (absorption rate 80%). Depending upon the number of amalgam fillings, the estimated average daily absorption of mercury vapour from dental fillings varies between 3000 and 17 000 ng (4,14,15). Tracheal measurements of mercury have found concentrations in the range 1000–6000 ng/m³ during inhalation and less than 1000 ng/m³ when subjects breathed through their noses (16). However, these figures have been questioned by some authors, and their recalculations reduce the estimated daily mercury intake from dental fillings to about 2000 ng (17).

Drinking-water

Mercury in drinking-water is usually in the range 5–100 ng/litre, the average value being about 25 ng/litre. The forms of mercury occurring in drinking-water are not well studied, but Hg⁺⁺ is probably the predominant species, present as complexes and chelates with ligands.

Food

Concentrations of mercury in most foodstuffs (11) are often below the detection limit (usually 20 ng/g fresh weight). Fish and marine mammals are the dominant sources, mainly in the form of methylmercury compounds (70–90% of the total). The normal concentrations in edible tissues of various species of fish cover a wide range, from 50 to 1400 ng/g fresh weight depending on factors such as pH, the redox potential of the water and the species, age and size of the fish. Large predatory fish, such as pike, trout and tuna, as well as seals and toothed whales contain the highest average concentrations. Furthermore, exposure to organomercurials might occur through the use of skin-lightening cream and other pharmaceuticals containing mercury. Thiomersal is used for the preservation of vaccines and immunoglobulins (at a level of 100 µg thiomersal per injection).

Relative significance of different routes of exposure

Human exposure to the three major forms of mercury present in the environment is summarized in Table 1. Although the choice of values given is somewhat arbitrary, the table nevertheless provides a perspective on the relative magnitude of the contributions from various media. Humans may be exposed to additional quantities of mercury occupationally and in heavily polluted areas, and to other forms of mercury, for example, to aryl and alkoxyaryl compounds widely used as fungicides.

Mercury intake from drinking-water is about 50 ng/day, mainly as Hg⁺⁺; only a small fraction is absorbed. Intake of fish and fish products, averaged over months or weeks, results in an average daily absorption of methylmercury variously estimated to be between 2000 and 4700 ng (10). The absorption of inorganic mercury from foodstuffs is difficult to estimate because levels of

total mercury are close to the limit of detection in many food items, and the chemical species and ligand binding of mercury have not usually been identified.

The intake of total dietary mercury has been measured over a number of years for various age groups. Daily intake measured according to age group during a US Food and Drug Administration (FDA) market basket survey (1984–1986) was: 310 ng for infants of 6–11 months; 900 ng for children of 2 years and 2000–3000 ng in adults (18). In Belgium, two surveys estimated the total mercury intake from all foodstuffs to vary between 6500 and 13 000 ng (19,20).

Table 1. Estimated average daily intake (retention) of mercury compounds (ng)

Media	Estimated average daily intake (retention) ^a		
	Mercury vapour	Inorganic mercury compounds	Methylmercury
Atmosphere	40–200 ^b (30–160)	0 ^c	0 ^c
Food: fish	0	600 ^d (60)	2400 ^d (2300)
non-fish	0	3600 (360)	?
Drinking-water	0	50 (5)	0
Dental amalgam	3800–21 000 (3000–17 000)	0	0
Total	3900–21 000 (3100–17 000)	4200 (420)	2400 (2300)

^a Figures in parentheses are the amounts retained estimated from pharmacokinetic parameters, i.e. 80% of inhaled vapour, 95% of ingested methylmercury and 10% of inorganic mercury.

^b Assumes an air concentration of 2–10 ng/m³ and a daily respiratory volume of 20 m³.

^c For the purposes of comparison, it is assumed that in atmospheric concentrations, species of mercury other than mercury vapour are negligible.

^d It is assumed that 80% of the total mercury in edible fish tissues is in the form of methylmercury and 20% in the form of inorganic mercury compounds. It should be noted that fish intake may vary considerably between individuals and across populations. In certain communities, whose major source of protein is fish, intake may exceed this estimate by an order of magnitude or more.

Toxicokinetics

The kinetics and biotransformation of mercury depend on its chemical and physical form.

Absorption

Elemental mercury (Hg⁰)

Approximately 80% of inhaled mercury vapour is absorbed via the lungs and retained in the body. The amount retained is the same whether inhalation takes place through the nose or the mouth (10). Elemental mercury is poorly absorbed in the gastrointestinal tract (less than 0.01% in rats), although increased blood levels of mercury have been measured in humans following accidental ingestion of several grams of metallic mercury (10). Skin absorption is insignificant in relation to human exposure to mercury vapour (21).

Inorganic mercurous (Hg⁺) and mercuric (Hg⁺⁺) mercury

The deposition and absorption of inhaled aerosols of inorganic mercury depend on particle size, solubility, etc. (22). No data have been reported for humans. In dogs, Morrow et al. (23) have reported that 45% of deposited mercury(II) oxide aerosols (mean diameter 0.16 µm) were

cleared in less than 24 hours and the remainder cleared with a half-time of 33 days. Some 10–15% of an oral, nontoxic dose of mercuric mercury is absorbed from the gastrointestinal tract in adults and retained in body tissues. In children, the gastrointestinal absorption is probably greater.

Organic mercury

Information on the pulmonary retention of gaseous dimethylmercury and aerosols of the monomethylmercury compounds is lacking. From cases of human poisoning via inhalation and from the ability of these mercurials to cross cell membranes rapidly, it seems likely that a large fraction of the inhaled alkylmercurial is absorbed into the bloodstream. The alkylmercurials are absorbed almost completely in the gastrointestinal tract and retained in the body. Certain methylmercury compounds are probably absorbed across the skin.

Distribution

Elemental mercury (Hg°)

Following exposure to mercury vapour the element is found in blood as physically dissolved elemental mercury. Within a few minutes, the mercury is oxidized to mercuric mercury in the erythrocytes, a reaction catalysed by the enzyme catalase. Thus, following short-term exposure to mercury vapour, the maximum concentration of mercury in erythrocytes is seen after less than one hour, whereas plasma levels peak after about 10 hours (24). Before oxidation, Hg° readily crosses cell membranes, including the blood–brain and placental barriers. Following oxidation, Hg^{++} ions (or complexes) are distributed in the body via the blood. The kidneys and the brain are the main targets for deposition of mercury following exposure to mercury vapour; absorbed inorganic mercury salts are mainly deposited in the kidneys.

The uptake and/or elimination of mercury following exposure to mercury vapour can be altered by a moderate intake of alcohol, possibly owing to inhibition of catalase. Thus, the amount of mercury in the red blood cells of humans exposed to mercury vapour was significantly reduced in humans given alcohol before mercury exposure (25).

Inorganic mercurous (Hg^{+}) and mercuric (Hg^{++}) mercury

The kidneys are the predominant site of inorganic mercury accumulation. However, accumulation also occurs in the cells of the mucous membranes of the gastrointestinal tract, although a significant part of this accumulation is later eliminated owing to cell shedding and therefore never reaches the general circulation. Mercuric mercury in the blood is divided about equally between erythrocytes and plasma. In erythrocytes, mercury is probably mainly bound to sulfhydryl groups on the haemoglobin molecule and possibly also to glutathione. The distribution between different plasma-protein fractions varies with dose and time following exposure.

Mercuric mercury penetrates the blood–brain and placental barriers only to a limited extent. However, mercuric mercury does accumulate in the placenta, fetal membranes and amniotic fluid. The rate of uptake from blood and different organs varies widely; so does the rate of elimination from different organs. Thus, the distribution of mercury within the body and within organs varies widely with dose and time following absorption. However, under all conditions the dominating mercury pool in the body after exposure to mercuric mercury is the kidney. Inorganic divalent mercury can induce metallothioneine; a large proportion of the mercury in the kidneys is soluble and bound to metallothioneine. Further, the inorganic mercury ion probably

forms complexes with selenium, which could be more lipophilic than the mercury ions themselves and may, according to experimental studies, to cross biological membranes to a certain extent.

Organic mercury

Distribution of methylmercury takes place via the bloodstream to all tissues in the body, the initial phase being complete in about 3 days. The pattern of tissue distribution is much more uniform than following inorganic mercury exposure, except in red cells, where the concentration is 10–20 times greater than the plasma concentration. Methylmercury readily crosses the blood–brain and placental barriers. Methylmercury is accumulated and concentrated in the fetus, especially in the brain. As with other forms of mercury, the kidneys retain the highest tissue concentration, although the total amount of mercury deposited in muscles might be higher. Experimental studies have demonstrated that the kinetics and elimination of methylmercury show sex differences. At the end of the initial phase of distribution, approximately 1% of the body's methylmercury is found in one litre of blood in the human adult weighing 70 kg (10). The brain:blood concentration ratio is about 5:1. Methylmercury accumulates in hair in the process of formation of hair strands. The hair:blood concentration ratio is approximately 250:1 in humans at the time of incorporation into hair. Methylmercury undergoes biotransformation to inorganic mercury by demethylation, particularly in the gut.

Elimination

Elemental mercury (Hg⁰)

Following short-term exposure to mercury vapour, about one-third of the absorbed mercury will be eliminated in unchanged form through exhalation, while the remainder will be predominantly eliminated through the faeces (26). Following long-term exposure (several years), about equal amounts will be excreted through the urine and faeces (27). Tracer studies with human volunteers indicate that the decline of mercury levels in the blood following a single-dose exposure is best described by two exponential terms with equivalent half-times of about 3 and 30 days each. The lower half-time accounts for 90% of the mercury in the blood compartment. However, the elimination of inorganic mercury follows a complicated pattern, with biological half-times that differ according to the tissue and the time following exposure. Thus, the half-time in the kidneys for inorganic mercury was found to be 64 days, about the same as that for the body as a whole (25,26). A more recent study on 10 occupationally exposed dentists and dental nurses demonstrated a median half-time of 41 days, assuming first-order kinetics for the clearance of urinary mercury obtained from mercury vapour (28).

Blood levels can serve as indicators of recent mercury vapour exposure, although speciation must be carried out in order to eliminate the possible influence of dietary intake of mercury from fish. However, there are at present no general and suitable indicator media that will reflect concentrations of inorganic mercury in the critical organs, brain and kidney, under different exposure conditions (4). This is to be expected in view of the complicated pattern of metabolism for different mercury compounds. One important consequence is that concentrations of mercury in urine or blood may be low quite soon after exposure has ceased, despite the fact that concentrations in the critical organs may still be high. Conversely, urine levels correlate with long-term exposure, although only on a group basis. Individual (including diurnal) variability of urine levels can be considerable. Faecal excretion has never been used for biological monitoring for mercury vapour, and hair concentrations would probably reflect adsorption of Hg⁰ from the atmosphere and not the blood levels (14).

Inorganic mercurous (Hg^+) and mercuric (Hg^{++}) mercury

Excretion of absorbed inorganic mercury is mainly via urine and faeces, the rates by each pathway being roughly equal. The whole-body half-time in adults is about 40 days. With respect to biological monitoring, mercury vapour is principally eliminated in the form of mercuric mercury, so that the information provided above on monitoring of Hg^0 is applicable.

Organic mercury

Excretion of methylmercury is predominantly via the faeces. Methylmercury is slowly broken down in the gut to inorganic mercury, and most, if not all, of the mercury excreted is in the inorganic form. Enterohepatic recirculation probably explains the absence of methylmercury in the faeces. The whole-body half-time of methylmercury is usually between 70 and 80 days, but substantial differences occur. The half-time in the brain is roughly the same as that in the whole body, whereas the half-time in the blood compartment is somewhat less. Further, laboratory animal studies involving tracer techniques have shown that, following acute administration of methylmercury, blood mercury concentrations will initially reflect organ concentrations reasonably well but, with time, an increasing fraction of the body burden will be in the brain, muscles and kidney (29). Sex differences in whole-body clearance and tissue distribution of intestinally absorbed methylmercury have been demonstrated in rodents (30,31). In particular, a sex-related difference has been observed in the ratio between concentrations of mercury in blood and in potential target organs.

The blood concentration might be a useful indicator of the body burden of mercury, although the erythrocyte mercury concentration is more specific for methylmercury exposure. Thus, if exposure to mercury vapour or other inorganic mercury compounds is suspected, mercury should be speciated or a serum sample analysed. Mercury in hair, when measured along the length of a hair strand, has also been used as an indicator of past blood levels. However, hair mercury concentrations may be augmented by the binding of exogenous mercury to the surface. Further, concomitant oral exposure to inorganic mercury adds more to the concentration in the blood than in the hair.

Health effects

Owing to differences in toxicokinetics, the health effects of mercury and its compounds will depend upon the chemical form of mercury concerned.

Mercury vapour

The health effects of mercury vapour have been reviewed recently (32). Damage is mainly to the nervous system, but effects are also seen, depending on dose, in the oral mucosa and the kidneys. Effects on the nervous system are manifested as tremor and a syndrome of psychological abnormalities labelled erethism, which include deficits in short-term memory, irritability and social withdrawal. The peripheral nervous system may also be involved, as evidenced by decreased nerve conduction velocity. The effects on the nervous system, especially those on motor functions, are usually reversible. Cognitive decrements and emotional alterations, which develop more insidiously, may be the most harmful effects of current exposures in the workplace.

Mercury vapour can elicit the nephrotic syndrome, characterized by excessive loss of protein (mainly albumin) in the urine, and oedema (33,34). Differences in individual susceptibility

appear to be considerable. Low levels of exposure to mercury vapour are associated with mild proteinuria and enzymuria only (33). In general, the early renal effects of mercury appear to be reversible following cessation of exposure.

Host-related factors may be particularly important in the development of the nephrotic syndrome in workers exposed to mercury vapour or compounds of inorganic mercury (35). Increased circulating antiglomerular basement membrane antibodies were demonstrated in 8 out of 131 occupationally exposed males (36) and another study showed correlations between increased levels of immunoglobulins IgA and IgM and exposure to inorganic mercury (37). However, no dose–effect relationship was established, and in both studies an unknown fraction of the study population had relatively high exposures. A study on 36 chloralkali workers with a mean urinary mercury concentration of 13 µg/g did not show any effects on white blood cells, immunoglobulins or autoantibodies (38). However, since animal studies have demonstrated that immunological effects exist and are genetically determined (39,40), an immunotoxic effect of low doses of inorganic mercury in susceptible individuals cannot be excluded given the limited number of exposed workers investigated.

Most recently, a study on monkeys demonstrated that mercury exposure from amalgam might enrich the intestinal flora with mercury-resistant bacterial species, which in turn also become resistant to antibiotics (41). The human implication of this observation in monkeys is presently unclear, but antibiotic resistance is generally an increasing problem in human medicine.

The pituitary appears to accumulate mercury following exposure to mercury vapour. However, at a mercury exposure giving rise to a mean urinary mercury level of 37 µg/g of creatinine there was no association between mercury exposure and serum levels of prolactin, thyroid-stimulating hormone, luteinizing-hormone or follicle-stimulating hormone (42).

Limited information is available on the effects of mercury vapour on the early stages of the human life cycle. Effects on pregnancy and birth in women occupationally exposed to mercury vapour have been reported, but insufficient details were available to evaluate dose–response relationships.

Urine is the most frequently used indicator medium for assessing body-burden following chronic exposure to mercury vapour. The mercury concentration in approximately 98% of all urine samples from people without known exposure to mercury is less than 5 µg/litre (43). Mild proteinuria may occur in the most sensitive adults at urine values of 50–100 µg/litre following chronic occupational exposures. Objective tremor and psychomotor disturbances usually appear at urine values of more than 300 µg/litre, but no clear threshold has been established (Table 2). In sensitive individuals, effects might already be seen already at urine values of around 100 µg/litre (32). Most effects of mercury vapour usually disappear within a few months after cessation of exposure.

Table 2. Concentrations of total mercury in air and urine at which effects are observed at a low frequency in workers subjected to long-term exposure to mercury vapour

Observed effect ^a	Mercury level		Reference
	Air ^b (µg/m ³)	Urine (µg/litre)	
Objective tremor	30	100	(4)

Renal tubular effects; changes in plasma enzymes	15 ^c	50	(44)
Nonspecific symptoms	10–30	25–100	(4)

^a These effects occur with low frequency in occupationally exposed groups. Other effects have been reported, but air and urine levels are not available.

^b The air concentrations measured by static air samplers are taken as a time-weighted average, assuming 40 hours per week for long-term exposure (at least five biological half-times, equivalent to 250 days).

^c Calculated from the urine concentration, assuming that a mercury concentration in air of 100 µg/m³ measured by static samplers is equivalent to a mercury concentration of 300 µg/litre in the urine.

Inorganic divalent mercury compounds

These are corrosive poisons; acute single oral doses can induce severe gastrointestinal toxicity and systemic shock. Subsequent death due to kidney failure may occur. Information on the chronic effects of inorganic mercury compounds in humans or animals indicates that the kidney is the target organ. However, reports of health effects due to chronic exposure to compounds of inorganic mercury are rare.

Occupational exposure to mercuric oxide has been shown to damage the peripheral nervous system; the effects appear to be reversible. Exposure to inorganic divalent mercury compounds as well as Hg⁰ have been known to produce acrodynia (“pink disease”) in susceptible children. Dose–effect relationships have not been reported, but absorption levels associated with these effects are probably higher than those associated with the earliest effects of mercury vapour. In general, effects from chronic exposure appear to be reversible.

Methylmercury compounds

Damage is almost exclusively limited to the nervous system. In human adults, the damage is selective to certain areas of the brain associated with sensory and coordination functions, particularly neurons in the visual cortex and granule cells of the cerebellum. Effects such as constricted visual fields and ataxia appear to have a latent period of weeks to months. Such effects are usually irreversible. The first effect usually noted is a subjective complaint of paraesthesia in the extremities and around the mouth. Paraesthesia may or may not be irreversible. The peripheral nervous system may also be affected, especially at high doses, but usually after effects have already appeared in the Central Nervous System.

The prenatal period is the stage of human life most susceptible to methylmercury exposure. This was demonstrated during the intoxications that occurred decades ago in Japan and Iraq. Following these episodes, severe effects, such as cerebral palsy, were seen in the offspring of exposed mothers in whom effects had been minimal or absent. One report by Eyssen et al. (45) suggested that the mildest effects of prenatal exposure, such as psychomotor retardation, may be associated with maternal hair levels of mercury during pregnancy of 10–30 µg/g. These effects were seen only in prenatally exposed males but not in females. Data from the outbreak of acute mercury poisoning in Iraq are consistent with the report of Eyssen et al. A more recent study by Kjellström et al (46) presents data from New Zealand in which slight changes in test performance (Denver test) were observed in groups of children whose mothers had hair concentrations of mercury of 6–15 µg/g. The estimates of dose–response relationships at these low exposure levels are subject to considerable uncertainty (47). All prenatal effects to date have been found to be irreversible.

Blood and scalp hair levels are the most commonly used parameters for indicating the body burden of mercury following exposure to methylmercury compounds; levels of methylmercury are related to fish consumption. Mercury blood levels of more than 200 µg/litre may be associated with health effects in adults, but a concentration of 40-50 µg/litre in a pregnant woman could be associated with a toxic risk for the fetus. Since the major route of exposure to methylmercury is oral (Table 1), this aspect will not be discussed further.

Evaluation of human health risks

Exposure evaluation

In areas remote from industry, atmospheric levels of mercury are about 2–4 ng/m³, and in urban areas about 10 ng/m³. This means that the daily amount absorbed into the bloodstream from the atmosphere as a result of respiratory exposure is about 32–64 ng in remote areas and about 160 ng in urban areas. This exposure to mercury from outdoor air is marginal, however, compared to exposure from dental amalgams, given that the estimated average daily absorption of mercury vapour from dental fillings varies between 3000 and 17 000 ng.

Health risk evaluation

Sensitive population groups

With regard to exposure to mercury vapour, sensitive population groups have not been conclusively identified from epidemiological, clinical or experimental studies. However, the genetic expression of the enzyme catalase, which catalyses the oxidation of mercury vapour to divalent mercuric ion varies throughout populations, Swiss and Swedish studies revealed a gene frequency of the order of 0.006 for this trait (48,49). Thus, 30–40 per million of the population are almost completely lacking catalase activity (homozygotes) and 1.2% are heterozygotes with a 60% reduction in catalase activity. Information as to the degree that other enzymes in the blood are able to take over the oxidation is lacking.

Effects on the kidney of inorganic mercury and phenylmercury are believed to occur first in a subgroup of individuals whose susceptibility may be genetically determined. However, the proportion of this subgroup in the general population is unknown. Virtually nothing is known on the relative sensitivity at different stages of the life cycle to mercury vapour or inorganic cationic compounds, except that the developing rat kidney is less sensitive than the mature tissue to inorganic mercury (50).

The prenatal stage appears to be the period of life when sensitivity to methylmercury is at its greatest; neuromotor effects in exposed Iraqi populations indicated that sensitivity at this time is at least three times greater than that in adults.

Mercury vapour

Time-weighted air concentrations are the usual means of assessing human exposure. Reported air values depend on the type of sampling. Static sampling generally gives lower values than personal sampling. In order to convert the air concentrations quoted in Table 2 to equivalent concentrations in ambient air, two factors have to be taken into account. First, the air concentrations listed in Table 2 were measured in the working environment using static samplers. The conversion factor may vary, depending on exposure conditions. The values shown should be increased by a factor of 3 to correspond to the true air concentrations inhaled by the workers as determined by personal samplers. Second, the total amount of air inhaled at

the workplace per week is assumed to be 50 m³ (10 m³/day × 5 days) whereas the amount of ambient air inhaled per week would be 140 m³ (20 m³/day × 7 days). Thus the volume of ambient air inhaled per week is approximately three times the volume inhaled at the workplace. Thus, to convert the workplace air concentrations quoted in Table 2 to equivalent ambient air concentrations, they should first be multiplied by 3 to convert to actual concentrations in the workplace, and divided by 3 to correct for the greater amount of ambient air inhaled per week by the average adult. It follows that the mercury vapour concentrations quoted in Table 2 are approximately equivalent to ambient air concentrations.

Since these figures are based on observations in humans, an uncertainty factor of 10 would seem appropriate. However, the lowest-observed-adverse-effect levels (LOAELs) in Table 2 are rough estimates of air concentrations at which effects occur at a "low frequency." Because it seems unlikely that such effects would occur in occupationally exposed workers at air concentrations as low as one half of those given in Table 2, it seems appropriate to use an uncertainty factor of 20. Thus, the estimated guideline for mercury concentration in air would be 1 µg/m³.

Inorganic compounds

Cationic forms of inorganic mercury are retained in the lungs about half as efficiently as inhaled mercury vapour (40% versus 80% retained); thus, the estimated guideline providing adequate protection against renal tubular effects would be twice as high as for mercury vapour.

Methylmercury compounds

It does not seem appropriate to set air quality guidelines for methylmercury compounds. Inhalation of this form of mercury, if it is present in the atmosphere, would make a negligible contribution to total human intake. However, mercury in the atmosphere may ultimately be converted to methylmercury following deposition on soils or sediments in natural bodies of water, leading to an accumulation of that form of mercury in aquatic food-chains. In this situation, guidelines for food intake would be appropriate, such as those recommended by the Joint FAO/WHO Expert Committee on Food Additives.

Guidelines

It is necessary to take into account the different forms of mercury in the atmosphere and the intake of these forms of mercury from other media. The atmosphere and dental amalgams are the sole sources of exposure to mercury vapour, whereas the diet is the dominant source of methylmercury compounds.

Current levels of mercury in outdoor air, except for regional "hot spots", are typically in the order of 0.005–0.010 µg/m³ and thus are marginal compared to exposure from dental amalgams. The exposure to mercury from outdoor air at these air levels is not expected to have direct effects on human health.

The predominant species of mercury present in air, Hg⁰, is neither mutagenic nor carcinogenic. Exposure to airborne methylmercury is 2–3 orders of magnitude below the food-related daily intake and will, in this context, be regarded as insignificant. Therefore, it is only possible to derive a numerical guideline for inhalation of inorganic mercury, by including mercury vapour and divalent mercury.

The LOAELs for mercury vapour are around 15–30 $\mu\text{g}/\text{m}^3$. Applying an uncertainty factor of 20 (10 for uncertainty due to variable sensitivities in higher risk populations and, on the basis of dose–response information, a factor of 2 to extrapolate from a LOAEL to a likely no-observed-adverse-effect level (NOAEL)), a guideline for inorganic mercury vapour of 1 $\mu\text{g}/\text{m}^3$ as an annual average has been established. Since cationic inorganic mercury is retained only half as much as the vapour, the guideline also protects against mild renal effects caused by cationic inorganic mercury. However, present knowledge suggests that effects on the immune system at lower exposures cannot be excluded.

An increase in ambient air levels of mercury will result in an increase in deposition in natural bodies of water, possibly leading to elevated concentrations of methylmercury in freshwater fish. Such a contingency might have an important bearing on acceptable levels of mercury in the atmosphere. Unfortunately, the limited knowledge of the global cycle and of the methylation and bioaccumulation pathways in the aquatic food-chain does not allow any quantitative estimates of risks from these post-depositional processes. Therefore, an ambient air quality guideline value that would fully prevent the potential for adverse health impacts of post-depositional methyl mercury formation cannot be proposed. However, in order to prevent possible health effects in the near future, ambient air levels of mercury should be kept as low as possible.

References

1. *Mercury and mercury compounds*. Lyon, International Agency for Research on Cancer, 1994 (IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, Vol. 58).
2. LINDBERG, S. ET AL. Group report: mercury. In: Hutchinson, T.W. & Meena, K.M., ed. *Lead, mercury, cadmium and arsenic in the environment*. New York, Wiley, 1987, pp. 17–34.
3. SECO, J.M. Big mercury deposit found in Spain. *Financial Times*, 30 October 1987.
4. *Inorganic mercury*. Geneva, World Health Organization, 1991 (Environmental Health Criteria, No. 118).
5. WOOD, J.M. & WANG, H.K. Microbial resistance to heavy metals. *Environmental science and technology*, **17**: 82a–90a (1983).
6. NIELSEN, J.B. Toxicokinetics of mercuric chloride and methylmercuric chloride in mice. *Journal of toxicology and environmental health*, **37**: 85–122 (1992).
7. LINDQVIST, O. ET AL. *Mercury in the Swedish environment: global and local sources*. Solna, National Swedish Environmental Protection Board, 1984, pp. 1–105 (Report No. 1816).
8. LAHMANN, E. ET AL. *Heavy metals: identification of air quality and environmental problems in the European Community*, Vol. 1 & 2. Luxembourg, Commission of the European Communities, 1986 (Reports No. EUR 10678 EN/I and EUR 10678 EN/II).
9. FUJIMURA, Y. Studies on the toxicity of mercury (Hg Series No. 7). II. The present status of mercury contamination in the environment and foodstuffs. *Japanese journal of hygiene*, **18**: 402–411 (1964).
10. *Mercury*. Geneva, World Health Organization, 1976 (Environmental Health Criteria, No. 1).
11. MATHESON, D.H. Mercury in the atmosphere and in precipitation. In: Nriagu, J.O., ed. *The biogeochemistry of mercury in the environment*. Amsterdam, Elsevier, 1979, pp. 113–129.
12. JOHNSON, D.C. & BRAMAN, R.S. Distribution of atmospheric mercury species near ground. *Environmental science and technology*, **8**: 1003–1009 (1974).

13. BEUSTERIEN, K.M. ET AL. Indoor air mercury concentrations following application of interior latex paint. *Archives of environmental contamination and toxicology*, **21**: 62–64 (1991).
14. CLARKSON, T.W. ET AL. Mercury. In: Clarkson, T.W. et al., ed. *Biological monitoring of toxic metals*. New York, Plenum, 1988, pp. 199–246.
15. SKARE, I. & ENGQVIST, A. Human exposure to mercury and silver released from dental amalgam restorations. *Archives of environmental health*, **49**: 384–394 (1994).
16. LANGWORTH, S. ET AL. Mercury exposure from dental fillings. II. Release and absorption. *Swedish dental journal*, **12**: 71–72 (1988).
17. OLSSON, S. & BERGMAN, M. Daily dose calculations from measurements of intra-oral mercury vapor. *Journal of dental research*, **71**: 414–423 (1992).
18. *Methylmercury*. Geneva, World Health Organization, 1990 (Environmental Health Criteria, No. 101).
19. FOUASSIN, A. & FONDU, M. Evaluation de la teneur moyenne en mercure de la ration alimentaire en Belgique. *Archives belges de médecine sociale, hygiène, médecine du travail et médecine légale*, **36**: 481–490 (1978).
20. BUCHET, J.P. ET AL. Oral daily intake of cadmium, lead, manganese, chromium, mercury, calcium, zinc, and arsenic in Belgium. A duplicate meal study. *Food and chemical toxicology*, **21**: 19–24 (1983).
21. HURSH, J.B. ET AL. Percutaneous absorption of mercury vapor by man. *Archives of environmental health*, **44**: 120–127 (1989).
22. TASK GROUP ON LUNG DYNAMICS. Deposition and retention models for internal dosimetry of the human respiratory tract. *Health physics*, **12**: 173–208 (1966).
23. MORROW, P.E. ET AL. Clearance of insoluble dust from the lower respiratory tract. *Health physics*, **10**: 543–555 (1964).
24. CHERIAN, M.G. ET AL. Radioactive mercury distribution in biological fluids and excretion in human subjects following inhalation of mercury vapour. *Archives of environmental health*, **33**: 109–114 (1978).
25. HURSH, J.B. ET AL. The effect of ethanol on the fate of mercury vapor inhaled by man. *Journal of pharmacology and experimental therapeutics*, **214**: 520–527 (1980).
26. HURSH, J.B. ET AL. Clearance of mercury (Hg-197, Hg-203) vapor inhaled by human subjects. *Archives of environmental health*, **31**: 301–309 (1976).
27. TEJNING, S. & OHMAN, H. Uptake, excretion and retention of metallic mercury in chlor-alkali workers. In: *Proceedings of the 15th International Congress on Occupational Health*. London, Permanent Commission and International Association on Occupational Health, 1966, p. 239.
28. SKARE, I. & ENGQVIST, A. Urinary mercury clearance of dental personnel after a longterm intermission in occupational exposure. *Swedish dental journal*, **14**: 255–259 (1990).
29. NIELSEN, J.B. & ANDERSEN, O. Time dependent deposition of mercury after oral dosage. *Metals compounds in environment and life: interrelationship between chemistry and biology*, **4**: 341–348 (1992).
30. THOMAS, D.J. ET AL. Sexual differences in the distribution and retention of organic and inorganic mercury in methyl mercury-treated rats. *Environmental research*, **41**: 219–234 (1986).
31. NIELSEN, J.B. & ANDERSEN, O. Evaluation of mercury in hair, blood and muscle as biomarkers for methylmercury exposure in male and female mice. *Archives of toxicology*, **68**: 317–321 (1994).

32. ALESSIO, L. ET AL. Inorganic mercury. *In: Roi, R. & Sabbioni, E., ed. CEC criteria document for occupational exposure limit values – inorganic mercury.* Ispra, Italy, Joint Research Centre, 1993.
33. FOA, V. ET AL. Patterns of some lysosomal enzymes in the plasma and of proteins in urine of workers exposed to inorganic mercury. *International archives of occupational and environmental health*, **37**: 115–124 (1976).
34. BUCHET, J.P. ET AL. Assessment of renal function of workers exposed to inorganic lead, cadmium or mercury vapor. *Journal of occupational medicine*, **22**: 741–750 (1980).
35. KAZANTZIS, G. ET AL. Albuminuria and the nephrotic syndrome following exposure to mercury and its compounds. *Quarterly journal of medicine*, **31**: 403–418 (1962).
36. ROELS, H. ET AL. Surveillance of workers exposed to mercury vapour: Validation of a previously proposed biological threshold limit value for mercury concentration in urine. *American journal of industrial medicine*, **7**: 45–71 (1985).
37. BENCKO, V. ET AL. Immunological profiles in workers occupationally exposed to inorganic mercury. *Journal of hygiene, epidemiology, microbiology and immunology*, **34**: 9–15 (1990).
38. LANGWORTH, S. ET AL. Minor effects of low exposure to inorganic mercury on the human immune system. *Scandinavian journal of work, environment & health*, **19**: 405–413 (1993).
39. DRUET, P. ET AL. Nephrotoxin-induced changes in kidney immunobiology with special reference to mercury-induced glomerulonephritis. *In: Bach, P.H. et al., ed. Nephrotoxicity assessment and pathogenesis.* New York, Wiley, 1982, pp. 206–221.
40. HULTMAN, P. & ENESTRÖM, S. The induction of immune complex deposits in mice by peroral and parenteral administration of mercuric chloride; strain dependent susceptibility. *Clinical and experimental immunology*, **67**: 283–292 (1987).
41. LORSCHIEDER, F.L. ET AL. The dental amalgam mercury controversy – inorganic mercury and the CNS; genetic linkage of mercury and antibiotic resistances in intestinal bacteria. *Toxicology*, **97**: 19–22 (1995).
42. ERFURTH, E.M. ET AL. Normal pituitary hormone response to thyrotropin and gonadotropin releasing hormones in subjects exposed to elemental mercury vapour. *British journal of industrial medicine*, **47**: 639–644 (1990).
43. INSTITUT FÜR WASSER-, BODE- UND LUFTHYGIENE DES BUNDESGESUNDHEITSAMTES. *Messung und Analyse von Umweltbelastungsfaktoren in der Bundesrepublik Deutschland: Umwelt und Gesundheit.* Berlin, Umweltbundesamt, 1989.
44. CÁRDENAS, A. ET AL. Markers of early renal changes induced by industrial pollutants. I: Application to workers exposed to mercury vapour. *British journal of industrial medicine*, **50**: 17–27 (1993).
45. EYSSEN, G.E.M. ET AL. Methylmercury exposure in northern Quebec II. *Neurologic findings in children*, **118**: 470–478 (1983).
46. KJELLSTRÖM, T. ET AL. *Physical and mental development of children with prenatal exposure to mercury from fish. Stage 1. Preliminary tests at age 4.* Stockholm, National Swedish Environmental Protection Board, 1986 (Report 3080).
47. MARSH, D.O. ET AL. Fetal methylmercury poisoning; clinical and toxicological data on 29 cases. *Annals of neurology*, **7**: 348–355 (1980).
48. AEBI, H. Investigation of inherited enzyme deficiencies with special reference to acatalasia. *In: Crow, J.F. & Neel, J.V., ed. Proceedings from 3rd International Congress of Human Genetics, Chicago 1966.* Baltimore, Johns Hopkins, 1967, p. 189.
49. PAUL, K.G. & ENGSTEDT, L.M. Normal and abnormal catalase activity in adults. *Scandinavian journal of clinical laboratory investigation*, **10**: 26 (1958).

50. DASTON, G.P. ET AL. Toxicity of mercuric chloride to the developing rat kidney. I. Post-natal ontogeny of renal sensitivity. *Toxicology and applied pharmacology*, **71**: 24–41(1983).