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Mercury exposure and early effects: an overview

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KEY WORDS
Mercury exposure; low doses; early effects

SUMMARY
Objectives: *This paper was given as a keynote address at the conference on The Assessment of the Effects Due to Low Doses of Inorganic Mercury following Environmental and Occupational Exposures: Human and* in vitro *Studies on the Specific Mechanisms of Toxicity in Gargnano, Italy, in September 2001.* Methods: *The most relevant literature over the past 40 years has been reviewed, and in particular, the proceedings of the World Health Organisation conferences on the health effects of inorganic and organic mercury exposure have been considered.* Results: *In an uncontaminated environment the general population is exposed to mercury vapour from the atmosphere and from dental amalgam, while the diet, mainly from fish, is the principal source for methyl mercury absorption. Mercury vapour release from amalgam fillings increases with chewing, with absorption and uptake by the brain and kidneys. Infants exposed to phenyl mercury from treated diapers and young children ingesting mercurous chloride in teething powders have developed acrodynia (pink disease), and Kawasaki disease and the use of mercurial skin lightening creams has been followed by the development of the nephrotic syndrome. Both mercury compounds and mercury vapour have given rise to contact dermatitis in the general population. Epidemics of mercury poisoning have followed release of mercury into the environment from industrial activity, with uptake of methyl mercury from fish eating in Minamata Bay and uptake of both inorganic and methyl mercury following release of mercury vapour and deposition into waterways from gold recovery procedures in the Amazon basin. The ingestion of wheat and barley seed treated with an alkyl mercury fungicide for sowing, by a largely illiterate population in Iraq, led to a major outbreak of poisoning with a high fatality rate. Following exposure to mercury vapour, the earliest clinically observed adverse effects at urine mercury levels of the order of 30-100 mg/g creatinine, are objectively detectable tremor, psychological disorder and impaired nerve conduction velocity in sensitive subjects, with subjective symptoms of irritability, fatigue and anorexia. At these and at lower levels, proteinuria has also been observed. Both glomerular and tubular damage may occur at exposure levels lower than those giving rise to central nervous system effects. An immunological effect has also been observed in studies on clinically asymptomatic workers with low level exposure.* Conclusions: *As mercury can give rise to allergic and immunotoxic reactions which may be genetically regulated, in the absence of adequate dose-response studies for immunologically sensitive individuals, it has not been possible to set a level for mercury in blood or urine below which mercury related symptoms will not occur.*

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RIASSUNTO

«Esposizione al mercurio ed effetti precoci: rassegna critica». *Il mercurio, presente nell'ambiente di vita, in basse concentrazioni, deriva da sorgenti naturali ed antropogeniche. L'intossicazione da mercurio può essere conseguente sia ad esposizioni occupazionali che ambientali. Epidemie di intossicazioni da mercurio organico sono causate da un rilasciamento del metallo nell'ambiente da sorgenti industriali con successiva ingestione di metilmercurio attraverso il consumo di pesce pescato nella Baia di Minamata. Intossicazioni conseguenti ad assorbimento di mercurio inorganico e di metilmercurio sono state documentate in lavoratori addetti al recupero dell'oro con conseguente rilasciamento di vapori del metallo e deposizione di esso nel letto dei fiumi. In un ambiente non contaminato la popolazione generale è esposta a vapori di mercurio presenti nell'atmosfera e negli amalgami dentali, invece la dieta, ed in particolare il pesce, costituisce la principale sorgente per l'assorbimento del metilmercurio. Il rilascio di vapori di mercurio dagli amalgami dentali aumenta con la masticazione, con conseguente assorbimento e deposizione nel cervello e nei reni. Neonati esposti a fenilmercurio presente in pannolini trattati e bambini che avevano ingerito cloruro di mercurio presente in particolari dentifrici hanno sviluppato acrodinia e malattia di Kawasaki; l'uso di creme cutanee schiarenti a base di mercurio ha causato sindromi nefrosiche. A seguito di un'esposizione a vapori di mercurio i più precoci effetti clinici si possono osservare allorquando i livelli di mercurio urinario sono compresi fra 30 e 100 μg/g creatinina. Sono obiettivabili tremori, alterazioni psicologiche e alterazione della velocità di conduzione in soggetti particolarmente sensibili, associati a sintomi di irritabilità, affaticamento e anoressia. Per questi livelli e anche per i livelli più bassi è stata osservata la presenza di proteinuria. Sia il danno glomerulare che il danno tubulare possono instaurarsi per livelli di esposizione più bassi rispetto a quelli che possono causare alterazioni a carico del sistema nervoso centrale. Un effetto immunologico è stato osservato in uno studio su lavoratori clinicamente asintomatici esposti a bassi livelli di mercurio. Dal momento che il mercurio può causare reazioni allergiche e immunotossiche che possono essere regolate geneticamente, potrebbe non essere possibile identificare un livello di mercurio nel sangue e nelle urine al di sotto del quale, in soggetti particolarmente sensibili, non si sviluppino gli specifici sintomi causati dal metallo.*

Mercury is ubiquitious in the global environment, present in the earth's crust mainly in sulphide ores, as cinnabar. Release of mercury vapour occurs from degassing of the earth's crust evaporation from oceans, and from volcanic emissions. The mercury concentration in the general atmosphere varies from 2-4 ng/m^3 in remote uncontaminated areas to around 20 ng/m^3 in urban areas, with high levels up to 18 μg/m^3 close to active volcanoes (15). The release of mercury from natural sources has been estimated to be of the order of 2,700 to 6,000 tons per annum (26).

ANTHROPOGENIC SOURCES

Mercury mining is the principal anthropogenic source for mercury release into the environment. Another major source is in the extraction of gold from ore concentrates, as widely carried out in China, Indonesia and the Amazon Basin in Brazil. Other sources are the combustion of fossil fuels, the smelting of metal sulphide ores, waste incineration, cement production and industrial applications. The global release of mercury from anthropogenic sources has been estimated to be of the order of 2,000 to 3,000 tons per annum (26).

Of the major industrial applications of mercury, the electrolysis of sodium chloride in the chloralkali industry uses about one quarter of the more than 10,000 tons of mercury produced yearly. In the electrical industry, mercury is used in lamps, measurement, control and medical instruments. Medicaments include mercurous chloride or calomel, teething powders, skin bleaching ointments and soaps, a major use being dental amalgam fillings. The cytotoxic properties of organomercury compounds has resulted in their use in mildew proofing paints and fungicides in seed treatment. Many of these uses have now been banned in most, but not in all countries (20).

SPECIATION

Mercury is present in the environment as metallic mercury vapour, mercuric and mercurous salts and organomercury compounds. Occupational exposure most commonly follows the inhalation of metallic mercury vapour, mixed exposures to inorganic mercuric aerosols also occur, as for example mercuric chloride aerosol in the chloralkali industry. Population exposure to mercury vapour occurs, at a lower level, following release from dental amalgam fillings on chewing. Following deposition into water, methylation occurs as a result of microbial action. Methylation in the aquatic environment is followed by uptake in fish with food chain biomagnification. The ratio of methyl mercury concentration in fish tissue to the concentration of inorganic mercury in sea water is as high as 10,000 or even 100,000 to one. Following the ingestion of fish, biotransformation is followed by the accumulation of inorganic mercury in the human body.

HEALTH EFFECTS: OCCUPATIONAL EXPOSURE

Cinnabar, mined in Almaden, Spain, since Phoenician times, was used by the Romans as a durable, red pigment. Pliny in the 1st century AD described mercury poisoning as a disease of slaves, for the Almaden mines, contaminated with mercury vapour were too unhealthy for Romans to work in. In the 16th century, Paracelsus, a Swiss physician, gave a detailed description of mercurialism. Ramazzini, the father of occupational medicine, included in his treatise a description of the ill effects of rubbing into the skin mercurial ointments used in the treatment of syphilis and mercury poisoning in the mirror makers of Venice. In Britain, the terms 'mad as a hatter' and 'hatter's shakes' referred to the erethism and tremor respectively of workers inhaling mercury vapour making felt out of rabbit fur in heated mercuric nitrate solution.

Exposure to high concentrations of mercury vapour, in terms of mg/m^3 has given rise to chest pain, cough, dyspnoea and haemoptysis due to erosive bronchitis and bronchiolitis with interstitial pneumonitis, terminating in respiratory insufficiency. In survivors, psychotic reaction develops, with delirium, hallucination and a suicidal tendency. Exposure levels of 44 mg/m^3 have been recorded following accidental exposure. The central nervous system is the critical organ for mercury vapour exposure.

With continuing occupational exposure to mercury vapour at concentrations above 100 $\mu g/m^3$, mercurial tremor develops, initially as a fine tremor of the fingers, eyelids and lips, interrupted by coarse shaking movements. With progression, a generalised tremor with violent chronic spasms of the extremities is seen. Together with this, mercurial erethism develops, characterised by behavioural and personality effects, excitability, insomnia and loss of memory. At long term, lower exposure levels, of the order of 25-80 $\mu g/m^3$, micromercurialism, an asthenic, vegetative syndrome characterised by weakness, fatigue, anorexia and gastrointestinal disturbance is seen.

Occupational exposure to metallic mercury has frequently been associated with proteinuria, both in workers with evidence of mercurialism and those without, with a significant correlation between urinary mercury and protein excretion (11). Less commonly, occupational exposure has been followed by the nephrotic syndrome. The nephrotic syndrome has occurred in chloralkali workers exposed to mercury vapour and mercuric compounds. Three cases were observed in a group of workers exposed to mercury vapour, mercuric and mercurous compounds, including the production of calomel (13). The nephrotic syndrome has also been reported following accidental exposure to mercury vapour (2).

While the central nervous system is the target organ following exposure to mercury vapour, the kidney is the target organ following absorption of inorganic bivalent mercury salts. Both glomerular and tubular damage may occur, at exposure levels lower than those giving rise to central nervous system effects. Glomerular damage is caused by an autoimmune reaction resulting in antibody formation on the basal membrane of the glomeruli indicative of a type III immune complex hypersensitivity. In addition, tubular damage may also occur,

with necrosis and damage of the distal and middle portion of the proximal tubules resulting in a loss of renal tubular enzymes, α-glutamyl transferase and lysosomial enzymes including N-acetyl-β-glucosaminidase. In some cases aminoaciduria and tubular glycosuria have also been observed. A significant association has been observed in a group of chloralkali workers with a median urine mercury concentration of 25.4 μg/g creatinine between urinary mercury concentration and urinary excretion of N-acetyl-β-glucosaminidase indicative of slight dose related tubular cell damage (16).

HEALTH EFFECTS: POPULATION EXPOSURE

The general population in an uncontaminated environment is exposed to mercury vapour from the atmosphere and from dental amalgam while the diet is the principal source for methyl mercury absorption. In most foodstuffs the mercury level is below the limit of detection of 20 ng/g, the principal source being fish, with an average daily intake estimated at 2.4 μg methyl mercury (25). However, air and water can contribute significantly to the daily intake of total mercury in contaminated environments. The mishandling of mercury in the home has resulted in severe intoxication, and children of mercury workers have been exposed to mercury vapour from contaminated work clothes.

The release of mercury vapour from dental amalgam fillings is the principal source of mercury vapour absorption in an unexposed population. Urinary and faecal mercury levels have been shown to increase for a period of several days after insertion and removal of dental amalgam. Mercury vapour release increases with chewing, followed by absorption and uptake by body tissues, in particular the brain and kidneys (26). While the daily amount of mercury absorbed from the atmosphere from respiratory exposure is of the order of 32-64 ng in remote areas and about 160 ng in urban areas, the estimated daily absorption of mercury vapour from dental fillings has been estimated to vary between 3,000 and 17,000 ng (28). Occupational exposure also occurs in dental personnel, exposure levels for mercury vapour being on average up to 30 μg/m^3 in dental clinics, with values of 150 to 170 μg/m^3 having been reported (12).

Mercury has been widely used in the past in pharmaceuticals and cosmetic agents. Calomel, mercurous chloride was used in the treatment of syphilis, as a purgative, a diuretic and in teething powders, having given rise to cases of acute mercury poisoning, following oxidation to mercuric mercury in the gastro-intestinal tract. Banned in most countries, Calomel may still be used as a purgative in some parts of the world. Mercurous chloride in teething powders given to children below the age of five years resulted in acrodynia, known as Pink disease. Infants exposed to phenyl mercury from diapers also developed Pink disease, with an increased urinary excretion of α-glutamyl transpeptidase from the brush borders of renal tubular cells (8). Affected children became irritable and miserable, with profuse sweating, swelling and irritation of the extremities, cheeks and nose followed by desquamation. While urinary mercury excretion was elevated above 50 μg/l there was no evidence of a dose response relationship. Acrodynia has also been reported following exposure to mercury vapour from broken fluorescent electric light bulbs (23) and to mercury vapour from interior latex paint in the home. A similar condition seen in children, known as 'Kawasaki disease', the mucocutaneous lymph node syndrome, showed increased serum lgE levels and eosinophilia, an immunologically mediated hypersensitivity reaction to environmental pollution with mercury (19).

Skin lightening creams and soap have been extensively used in the past by many African women, now banned in the EEC and North America but not in all countries. The creams contained up to 10% of ammoniated mercury and the soaps up to 3% mercuric iodide. In one study of 60 adult African women using skin lightening cream with a mean urinary mercury excretion of 109 μg/litre, 26 with a mean urinary excretion of 150 μg Hg/litre developed the nephrotic syndrome (5).

Both mercury vapour and mercuric compounds give rise to contact dermatitis, thiomersal, sodium ethylmercurithiosalicylate being the commonest sensitiser after nickel and chromium in the general population, ammoniated mercury also being a

common sensitiser (17). Metallic mercury has given rise to sensitisation from amalgam fillings, also in dental personnel. Following insertion of the amalgam, facial dermatitis with erythematous and urticarial rashes have developed within hours. Contact allergy has been shown in patients with amalgam fillings and oral lichen planus on patch testing. Patch testing has also shown evidence of contact hypersensitivity in dental personnel and students. A type IV cell-mediated delayed hypersensitivity reaction is involved (7).

At the end of 1953, an unusual neurological disorder affected villagers of both sexes and all ages living in Minamata Bay, Japan. The outbreak was associated with the consumption of fish and shellfish caught in the bay, alkyl mercury poisoning having been diagnosed after an interval, following comparison with a fatal case in a worker manufacturing alkyl mercury fungicides. The source of mercury was effluent released into the bay from a factory producing vinyl chloride, using mercuric chloride as a catalyst. Inorganic mercury discharged into the bay was subsequently methylated by methyl group donating microorganisms in the sediments of the bay. Over 700 people were affected with a 40% mortality and a high rate of permanent disability. A further outbreak of methyl mercury poisoning in Japan in 1965 in Niigata affected another 500 or so inhabitants again following the consumption of methyl mercury bioconcentrated in fish. Presenting features were numbness of the extremities and around the mouth, slurred speech, unsteady gait and increasing disability. Emotional lability with euphoria and depression followed progressing to mental confusion, drowsiness and stupor.

In 1971 Iraq imported a large consignment of wheat and barley seed treated with an alkyl mercury fungicide for sowing, distributed to a largely illiterate population. The grain was used to make bread and by March 1972 there had been 6530 hospital admissions with 459 deaths from alkyl mercury poisoning (4). The incidence of the disease may have been as high as 73 per 10,000 although the true extent of the outbreak remains unknown (14).

The principal clinical features in the above epidemics were paraesthesia of the extremities, abnormalities of gait, concentric constriction of the visual fields, dysarthria, astereognosis and gross arm ataxia. Prenatal effects were also seen, as infantile cerebral palsy. Estimation of hair mercury level was found to be of particular value in epidemiological studies.

Gold mining in the Amazon basin has been followed by the production of a mercury gold amalgam which on heating to obtain pure gold, releases mercury vapour into the working and local environment with deposition into waterways, with bioaccumulation of methyl mercury in freshwater fish. More than half a million people have been exposed with an annual discharge of 90 to 120 tons of mercury into local ecosystems (18). Inorganic mercury poisoning has followed inhalation of mercury vapour by workers and their families living in the immediate vicinity of the work site, and neurotoxic effects in villagers consuming freshwater fish with raised methyl mercury levels downstream from the worksite. In children living near the worksite, there has been intake of mercury vapour and mercuric salts from contaminated dusts, together with methyl mercury intake from local fish eating. Mercury in urine as an indicator of mercury vapour inhalation and mercury in blood as an indicator of recent exposure to organic mercury in fish have shown raised levels, above 100 μg/l for urine mercury, above 200 μg/l for blood mercury, in one small scale study (6).

In a study on Amazonian children average mercury exposures were shown to increase upstream towards the goldmining fields. Most riverine children eat fish daily or twice daily. In 246 eligible children, more than 80% had hair mercury concentrations above 10 μg/g, a limit above which adverse effects in brain development are likely to occur. Neuropsychological tests of motor function, attention and visuospatial performance showed decrements associated with hair mercury concentrations (10). In this study, the current hair mercury concentrations in both child and mother correlated highly and with no major dietary changes within the household, current hair mercury concentrations in both mother and child were likely to reflect past exposures, including the child's prenatal exposure level. It was queried in this study as to whether the

neurotoxic effects could have resulted from prenatal exposure when the sensitivity to methyl mercury is about three times greater than in adults. The results were compared to a further study on almost 1000 7-year old Faroese children where performance on neuropsychological tests revealed deficits in several functional domains at increased prenatal exposures to methyl mercury (9).

Health effects: carcinogenicity

An excess risk of glioblastoma has been observed in a study on dentists and dental nurses in Sweden (3). However, this has not been confirmed in studies elsewhere. An excess lung cancer risk has been observed in several studies on mercury exposed workers, but confounding factors were present in all. The evaluation by the International Agency for Research on Cancer (27) concluded that metallic mercury and inorganic mercury compounds are not classifiable as to their carcinogenicity to humans (Group 3) but methyl mercury compounds are possibly carcinogenic to humans (Group 2B) based on the finding of an increased incidence of renal adenoma and adenocarcinoma in mice.

Exposure levels

Mercury levels in blood and urine are indicators of exposure where the exposure is recent, relatively constant and long term. Evaluated on a group basis these indicators are used for biological monitoring following occupational exposure to mercury vapour and inorganic mercury compounds. Mercury level in blood is also an indicator of occupational and environmental exposure to methyl mercury, which is excreted in urine only to a limited extent, while mercury in hair is useful as an indicator of environmental exposure to methyl mercury.

Reference/normal values have been given as 5-10 µg/l for total mercury in whole blood, 4 µg/l for mercury in urine, 1-2 µg/kg for mercury in hair (26). The main source for variation in an unexposed population being dental amalgam for urine levels and fish consumption for blood and hair levels.

In general, when exposure to mercury vapour is greater than 80 µg/m^3, with a urine mercury level of the order of 100 µg/g creatinine, the probability of developing tremor, erethism and proteinuria is high (table 1). Exposure in the range of 25 to 80 µg/m^3, with a urine mercury level of the order of 30 to 100 µg/g creatinine, objectively detectable tremor, psychomotor disorder and impaired nerve conduction velocity may be observed in sensitive subjects, together with subjective symptoms of irritability, fatigue and loss of appetite. At lower urinary mercury concentrations of the order of 25-35 µg/g creatinine, in a few studies tremor has been recorded electrophysiologically. Proteinuria has also been observed at these levels. Epidemiological data on exposure levels corresponding to less than 30-50 µg mercury/g creatinine are inadequate, but with larger populations exposed to low concentrations of mercury, since a specific no observed effect level cannot be established, it cannot be excluded that adverse effects may occur in sensitive individuals (26).

Table 1 - *Mercury vapour exposure: Dose-response relationships (26)*

Exposure	Urine mercury	Effect
Above 80 µg/m^3	100 µg/g creat.	tremor, erethism, proteinuria – high probability
25-80 µg/m^3	30-100 µg/g creat.	objectively detectable tremor, psychomotor performance disorder, impaired nerve conduction velocity, fatigue, anorexia, irritability
	25-35 µg/g creat.	tremor recorded electro-physiologically, proteinuria (uncommon)
	<30 µg/g creat.	mild adverse effects in sensitive individuals cannot be excluded

Concentrations of total mercury in air and urine at which effects are observed at a low frequency in workers subjected to longterm exposure to mercury vapour as estimated by WHO (2000) are shown in table 2. The air concentrations measured by static air samplers were taken as a time-weighted average, assuming 40 hours per week for long term exposure. The air concentration of 15 μg/m³ for renal tubular effects was 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. These mercury vapour concentrations were considered to be approximately equivalent to ambient air concentrations, allowing for a conversion factor between static and personal sampling and the volume of air inhaled per week in relation to the volume inhaled over 40 hours per week in the workplace. The lowest observed adverse effect level (LOAEL) for mercury vapour was considered by WHO (2000) to be of the order of 15-30 μg/m³. Applying an uncertainty factor of 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 NOAEL, a guideline for mercury vapour of 1 μg/m³ as an annual average has been proposed. As inorganic mercury is retained only half as much as vapour, the guideline is also considered to protect 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 (28).

An immunological effect has been observed in studies on clinically asymptomatic mercury exposed workers with low level mercury exposure. Workers in a fluorescent light bulb factory with prolonged exposure to inorganic mercury with a mean urinary mercury excretion of 6.0 μg/l showed evidence of a reduction in tumour necrosis factor alpha suggesting an *in vivo* functional defect of the monocyte-macrophage system (21). A further study in workers with a very low exposure to metallic mercury, with a mean urinary mercury level of 9.7 μg/l showed a significant impairment in polymorphonuclear leukocyte chemotaxis and a subtle impairment of circulating monocyte and natural killer cells. It was suggested this provided a sensitive indicator of metallic mercury exposure (24).

Animal studies have shown that inorganic Hg may induce auto immune glomerulonephritis in all species tested but not in all strains indicating a genetic predisposition. As mercury can give rise to allergic and immunotoxic reactions which are partly genetically regulated there may be a small fraction of the population which is particularly sensitive. A consequence of an immunological aetiology is that it is not possible to set a level for mercury in blood or urine, below which mercury related symptoms will not occur in individual cases (26).

The complexity of the health effects of mercury is in part due to the fact that mercury vapour, divalent mercury salts and methyl mercury are not distinct entities following absorption, for several forms of metabolic transformation occur (table 3). Following absorption, mercury vapour is rapidly oxidised to divalent ionic mercury, although due to the short transit time after absorption and high lipid solubility, mercury vapour is also deposited in the brain unoxidised. Oxidation follows converting

Table 2 - *Concentrations of mercury in air and urine at which effects are observed at a low frequency in workers subjected to long-term exposure to mercury vapour (28)*

Observed effect	Mercury level	
	Air (μg/m³)	Urine (μg/l)
Objective tremor	30	100
Renal tubular effects Changes in plasma enzymes	15	50
Non-specific symptoms	10-30	25-50

Table 3 - *Mercury: Metabolic Transformation (26)*

Oxidation of metallic mercury vapour to divalent mercury
Reduction of divalent mercury to metallic mercury
Methylation of inorganic mercury
Conversion of methyl mercury to divalent inorganic mercury

mercury to the ionic form, serving as a trap which leads to accumulation in brain and foetal tissues. Reduction of divalent mercury to metallic mercury also occurs to a small degree, resulting in the exhalation of a small amount of mercury vapour (22). There is limited evidence for the synthesis of organo mercury compounds following absorption of inoganic mercury. Thus a slight increase in the concentration of methyl mercury in blood and urine has been observed in dentists and workers in the chloralalkali industry (1). However, the conversion of methyl mercury to inorganic mercury is a key step in the process of excretion after exposure to methyl mercury (25). If the organomercurial in an organ is more rapidly excreted than inorganic mercury, biotransformation will decrease the overall excretion rate and the ratio of inorganic to organic mercury will increase with time. The fraction of total mercury present as inorganic mercury depends on the duration of exposure to methyl mercury and on the time elapsed since cessation of exposure. This process may give rise to considerable accumulation of inorganic mercury, even if the demethylation rate is slow (26).

Recommendations for further research made by the Task Group on Environmental Health Criteria for Inorganic Mercury (26) have been summarised in table 4. A number of these recommendations have been followed up in the research project "Valutazione degli effetti conseguenti a basse dosi di mercurio inorganico da esposizioni ambientali ed occupazionali: studio dei meccanismi di tossicità specifica *in vitro* e nell'uomo" (Assessment of the effects due to low doses of inorganic mercury following environmental and occupational exposures: human and *in vitro* studies on the specific mechanisms of toxicity), supported by the Italian Ministry of University and Scientific Research (MURST). In particular, the prevalence of immunological effects and hypersensitivity following low dose exposure with or without subjective symptoms, renal, neurobehavioural and neuroendocrinal effects, the characterisation of exposure and the pharmaco-kinetics of mercury release from amalgam fillings, which were investigated, were discussed at this conference, held in the Palazzo Feltrinelli, Gargnano, Brescia, Italy on 27-28 September 2001. In this research project, in order to study mechanisms underlying mercury release from dental amalgams, an experimental standardized model based on a cell system required for standard corrosion tests was developed. Different conditions of salivary flow, bimetallism and wear were considered. The percutaneous absorption of mercury and mechanisms of tissue specific toxicity were investigated in *in vitro* studies.

To summarise, mercury, a toxic metal with no evidence of essentiality, is present in the global environment, absorbed in minute concentration by the population as a whole, with increasing levels related to anthropogenic activity. The complexity of mercury speciation in relation to effects, and the presence of immunotoxic reactions in part genetically related, has made it not possible, at the present time, to set a level at which effects are unlikely to occur in a sensitive fraction of the population.

Table 4 - *Recommendations for Further Research (26)*

1. Determination of exposure to different chemical forms of mercury at low exposure levels. Development of micro techniques for speciation of small quantities in biological samples
2. Pharmacokinetics of mercury release from amalgam fillings in relation to time, diet, technical and physiological conditions. Development of tests for identifying especially sensitive individuals, e.g. local mucosal reactions, intra-oral electrochemical measurements, immunotoxicity
3. Use of mercury compounds in pharmaceuticals and cosmetics
4. Binding, biotransformation and transport of different forms of mercury in animals and humans, including interactions with selenium
5. Transplacental transport of mercury and distribution in foetal organs, foetotoxic and developmental effects, emphasis on neurobehavioral effects
6. Research in neurobehavioral effects of mercury in the occupationally exposed population – dentists, etc
7. Epidemiology of the role of mercury in inducing glomerulonephritis in the general population
8. Prevalence of immunological effects and hypersensitivity in low dose exposure to mercury with or without subjective symptoms
9. A case-control study of brain tumours, in particular glioblastoma and exposure to mercury

References

1. Aitio A, Valkonen S, Kivisto H, et al: Effects of occupational mercury exposure on plasma lysosomial hydrolases. Int Arch Occup Environ Health 1983; *53*: 139-147
2. Agner E, Jans H: Mercury poisoning and nephrotic syndrome in two young siblings. Lancet 1978; *2*: 951
3. Ahlbom A, Norell S, Nylander M, et al: Dentists, dental nurses and brain tumours. Br Med J 1986; *292*: 662
4. Bakir F, Damluji SF, Amin-Zaki L, et al: Methyl mercury poisoning in Iraq. Science 1973; *181*: 230-241
5. Barr RD, Rees PH, Cordy PE, et al: Nephrotic syndrome in adult Africans in Nairobi. Br Med J 1972; *2*: 131-134
6. Cleary D, Thornton I, Brown N, et al: Mercury in Brazil. Nature 1994; *369*: 613-614
7. Coombs RRA, Gell PGH: Classification of allergic reactions responsible for clinical hypersensitivity and disease. In Gell PGH, Coombs RRA, Lachmann PJ (ed): *Clinical Aspects of Immunology*. 3rd ed. Oxford: Blackwell Scientific Publications, 1975: 761-781
8. Gotelli C, Astolfi E, Cox C, et al: Early biochemical effects of an organic mercury fungicide on infants: dose makes the poison. Science 1985; *227*: 638-640
9. Grandjean P, Weihe P, White RF, et al: Cognitive deficit in 7-year old children with prenatal exposure to methyl mercury. Neurotoxicol Teratol 1997; *19*: 417-428
10. Grandjean P, White RF, Nielsen A, et al: Methyl mercury neurotoxicity in Amazonian children downstream from gold mining. Environ Health Perspect 1999; *7*: 587-591
11. Joselow MM, Goldwater LJ: Absorption and excretion of mercury in man XII. Relationship between urinary mercury and proteinuria. Arch Environ Health 1967; *15*: 155
12. Joselow MM, Goldwater LJ, Alvarez A, et al: Absorption and excretion of mercury in man. Arch Environ Health 1968; *17*: 39-43
13. Kazantzis G, Schiller KFR, Asscher A W, et al: Albuminuria and the nephrotic syndrome following exposure to mercury and its compounds. Quart J Med 1962; *31*: 403-418
14. Kazantzis G, Al-Mufti AW, Al-Jawad Y, et al: Epidemiology of organomercury poisoning in Iraq: II Relationship of mercury levels in blood and hair to exposure and to clinical findings. Bull World Health Organ 1976; *53*: s37-s48
15. Lindqvist O, Jernelov A, Johannson K, et al: *Mercury in the Swedish environment: global and local sources*. Solna: National Environmental Protection Board, 1984: 105
16. Langworth S, Elinder CG, Sundquist KG, et al: Renal and immunological effects of occupational exposure to inorganic mercury. Br J Ind Med 1992; *49*: 394-401
17. North American Contact Dermatitis Group: Epidemiology of contact dermatitis in North America 1972. Arch Dermatol 1973; *108*: 537-540
18. Nriagu JO, Pfeiffer WC, Malm O, et al: Mercury pollution in Brazil. Nature 1992; *356*: 389
19. Orlowski JP, Mercer RD: Urine mercury levels in Kawasaki disease. Pediatrics 1980; *66*: 633-636
20. Renzoni A, Zino F, Franchi E: Mercury levels along the foodchain and risk for exposed populations. Environ Res 1998; 77: 68-72
21. Soleo L, Vacca A, Vimercati L, et al: Minimal immunological effects on workers with prolonged low exposure to inorganic mercury. Occup Environ Med 1997; *54*: 437-442
22. Sugata Y, Clarkson TW: Exhalation of mercury – further evidence for an oxidation-reduction cycle in mammalian tissues. Biochem Pharmacol 1979; *28*: 3474-3476
23. Tunnessen WW, Mcmahon KJ, Baser M: Acrodynia exposure to mercury from fluorescent light bulbs. Pediatrics 1987; *79*: 786-789
24. Vimercati L, Santarelli L, Pesola G, et al: Monocyte-macrophage system and polymorphonuclear leukocytes in workers exposed to low levels of metallic mercury. Sci Total Environ 2001; *270*: 157-163
25. WHO: *Environmental Health Criteria 101: Methylmercury*. Geneva: World Health Organization 1990: 144
26. WHO: *Environmental Health Criteria 118: Inorganic mercury*. Geneva: World Health Organization, 1991: 168
27. WHO: Mercury and mercury compounds. In *IARC Monographs on the evaluation of carcinogenic risks to humans*. 1993; *58*: 239-345
28. WHO: *Air Quality Guidelines for Europe: Mercury*. Copenhagen: World Health Organization, 2000: 157-161