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Low dose mercury toxicity and human health

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Abstract

Post Minamata incident there has been awareness about mercury toxicity even among the general public. Previous researches contributed a vast amount of data regarding acute mercury exposure, but gradually information about the low dose [Ninomiya, T., Ohmori, H., Hashimoto, K., Tsuruta, K., Ekino, S., 1995. Expansion of methylmercury poisoning outside minamata: an epidemiological study on chronic methylmercury poisoninig outside of Minamata. Environ. Res. 70 (1) 47–50; Lebel, J., Mergler, D., Lucotte, M., Amorim, M., Dolbec, J., Miranda, D., Arantes, G., Rheault, I., Pichet, P., 1996. Evidence of early nervous system dysfunction in Amazonian populations exposed to low-levels of methylmercury. Neurotoxicology 17 (1) 157–167] of mercury toxicity has been trickling in. With mercury contaminating rain-, ground- and sea-water no one is safe. Polluted water leads to mercury laced fish, meat and vegetable. In aquatic environments, inorganic mercury is microbiologically transformed into lipophilic organic compound 'methylmercury'. This transformation makes mercury more prone to biomagnification in food chains. Consequently, populations with traditionally high dietary intake of food originating from fresh or marine environment have highest dietary exposure to mercury. Extensive research done on locals across the globe have already established this, persons who routinely consume fish or a particular species of fish are at an increased risk of methylmercury poisoning. The easy access of the toxicant to man through multiple pathways air, water, food, cosmetic products and even vaccines increase the exposure. Foetus and children are more susceptible towards mercury toxicity. Mothers consuming diet containing mercury pass the toxicant to foetus and to infants through breast milk. Decreased performance in areas of motor function and memory has been reported among children exposed to presumably safe mercury levels. Similarly, disruption of attention, fine motor function and verbal memory was also found in adults on exposure to low mercury levels. It is an occupational hazard for dental staff, chloralkali factory workers and goldminers, etc. Mercury has been found to be a causative agent of various sorts of disorders, including neurological, nephrological, immunological, cardiac, motor, reproductive and even genetic. Recently heavy metal mediated toxicity has been linked to diseases like Alzeihemer's, Parkinson's, Autism, Lupus, Amyotrophic lateral sclerosis, etc. Besides this, it poses danger to wildlife. Therefore, it becomes imperative to spread the information regarding the threat of mercury exposure amongst the scientists and masses.

Keywords: Mercury pollution; Low dose toxicity; Biomagnification; Neurodegenerative disorders

1. Introduction

In 1950, Minamata bay tragedy caught the world unawares. It has been since recognized that the multiple pathways of mercury contamination through air, water, food, pharmaceuticals, cosmetic products, etc., pose serious concern because it persists in the environment and accumulates in the food web. Amongst three forms of mercury, the organic form is most toxic as it passes the blood brain barrier owing to its lipid solubility. The damage has vast implications with human beings at the top of food chain getting worst of the deal owing to biomagnification. This review was written to focus on recent researches showing adverse health effects of low doses of mercury, to instigate the requirement for a new era of pharmaceutical development and to create further awareness regarding environmental remediation.

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2. Sources of mercury

2.1. Mercury in air

As a natural element mercury is ubiquitous in the environment (Fig. 1), approximately 10,000 tons originates from degassing of earth's crust, to this amount approximately 20,000 tons/year is added by anthropogenic activity (Hansen and Dasher, 1997). Mercury emissions from the coal smoke is the main source of anthropogenic discharge and mercury pollution in atmosphere. It is estimated that the mercury emissions will increase at a rate of 5% a year (Zhang et al., 2002). When medical devices like thermometer/sphygmomanometer or household items like fluorescent night lamps or thermostats are discarded residual mercury is emitted. The US Environmental Protection Agency (EPA) National Emissions Inventory (NEI) had the most complete coverage for all states. It found coal-fired electric utilities accounted for 52.7% of the region's Hg emissions. Other important contributors to regional emissions included municipal waste combustion (5.6%), mercury-cell chlor-alkali plants and hazardous-waste incinerators (4% each), stationary internal combustion engines (ICEs) (3.5%), industrial, commercial and institutional (ICI) boilers (3.3%) and lime manufacturing (3.0%) and medical waste incineration (1%) (Murray and Holmes, 2004). Informal gold mining has used mercury since antiquity. High contamination of Brazilian Amazon (Brazil is world's second largest producer of gold) is indicated by the strong presence of mercury in its biota (Grandjean et al., 1999). It is an occupational hazard for dental staff (Rowland and Baird, 1994), chloralkali factory workers (Barregard and Lindstedt, 1994) goldminers (Grandjean et al., 1999), etc.

2.2. Mercury in water

Mercury in air eventually passes into rivers, lakes and oceans after travelling long distances together with wind. With mercury contaminating rain (Domagalski et al., 2004; Levine, 2004), ground and seawater (Beldowski and Pempkowiak, 2003), no one is safe. Cloud water was collected during nine non-precipitating cloud events on Mt. Mansfield, VT in the northeastern USA between 1 August and 31 October, 1998. Mercury cloud water concentrations ranged from 7.5 to 71.8 ng l (−1), with a mean of 24.8 ng l (−1). Liquid water content explained about 60% of the variability in Hg cloud concentrations (Malcolm et al., 2003). There are also linkages between acidic deposition and fish mercury contamination and eutrophication of estuaries (Driscoll et al., 2003). Numerous factories that directly pump untreated effluents pollute groundwater. The polluted water produces acidic rain which ultimately contaminates all water bodies. Report published in a reputed Indian daily, The Hindustan Times showed result of water samples analysed at IIT, Kanpur. Groundwater samples in India from eight places each from Punjab, Haryana, Andhra Pradesh, Gujarat and Kanpur showed surprisingly high levels of Hg in all samples. Water sample from Panipat (Haryana) had highest level of Hg at concentration 268 times that of safe limit, even the sample with least Hg value had 58 times more mercury than the upper safe limit (Hindustan times, 1999). Algal bloom and leaf fall events can result in elevated methylmercury (MeHg) concentrations in surface waters, potentially leading to increased MeHg accumulation in fish (Balogh et al., 2002).

2.3. Mercury contamination of food

2.3.1. Food of animal origin

The emitted mercury both natural and anthropogenic is in an inorganic form predominantly metallic vapour, which is carried off to great distances by winds and eventually falls in water bodies. In aquatic environments, inorganic mercury is microbiologically transformed into lipophilic organic compound, methylmercury. This transformation makes mercury more prone to biomagnification in food chains. Consequently, populations with traditionally high dietary intake of food originating from fresh or marine environment have highest dietary exposure to Hg. Extensive research done on locals across the globe have already established this for instance polar Eskimos. Persons who routinely consume fish or a particular species of fish are at an increased risk of methylmercury poisoning (Table 1) (Hansen and Dasher, 1997). Since mercury intake is expressed on a per kilogram body weight basis exposure of children under age 14 is two–three times high because of higher food intake per kilogram body weight. After measuring total mercury in the edible portions of 244 selected fish and shellfish purchased in Canada at the retail level, the Canadian advisory to children and women of child-bearing

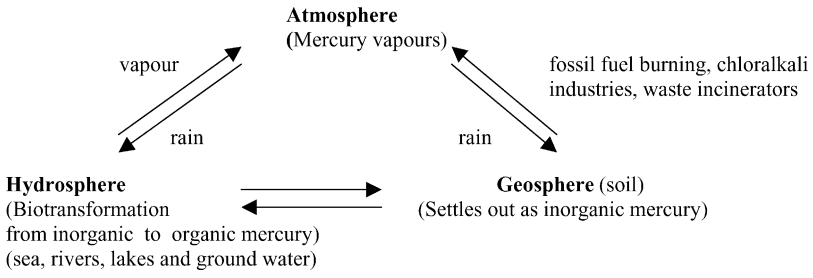

Fig. 1. Mercury and environment.

Table 1
Mercury levels in commercial fish and shellfish

Fish species	Mean mercury concentration (ppm)
Very high risk group	
Mackerel king	0.73
Shark	0.99
Sword fish	0.97
Tile fish	1.45
High risk group	
Tuna (fresh/frozen)	0.38
Tuna (canned albacore)	0.35
Lobster	0.31
Orange roughy	0.54
Spanish Mackerel	0.45
Marlin	0.49
Grouper	0.55
Medium risk group	
White croaker	0.29
Bass	0.27
Carp	0.14
Tile fish	0.15
Tuna (canned light)	0.12
Sablefish	0.22
Scorpion fish	0.29
Weakfish (sea trout)	0.25

age is to limit their consumption of fresh and frozen tuna, swordfish and shark to no more than one meal per month (Dabeka et al., 2004). When 21 fish species, cephalopods and crustaceans were analyzed for mercury accumulation the former two ranked highest (Schumacher et al., 1994). In Yokon delta system, biomagnification factor of 12 was calculated for methylmercury, out of 29% fish species, 62% contained Hg exceeding wildlife critical value for piscivorous animals. Overall 24% fish exceeded critical value for human consumption and 58% wildlife critical value (Duffy et al., 1998). Cattle and pigs kept in area with contaminated river water had twice concentration of blood and hair Hg than control ones (Palheta and Taylor, 1995).

2.3.2. Food of plant origin

Emissions of mercury from the province of Guizhou in Southwestern China to the global atmosphere have been estimated to be approximately 12% of the world total anthropogenic emissions primarily due to mining, chemical discharge and elecricity production. Even though the major source of mercury is inorganic, it was observed that active transformation of inorganic mercury to organic mercury species (MeHg) takes place in water, sediments and soils. It has been reported that the concentration of mercury in rice grains can reach up to 569 μg/kg of total Hg of which 145 μg/kg is in MeHg form (Horvat et al., 2003). While analyzing in situ aquatic and terrestrial plants in vicinity of chloralkali plants growing at Hg conc. 8.9 mg/kg it was found that Cabbage *Bracica oleracea* and amaranthus *Amaranthus oleraceous* accumulated mercury at significant levels (Lanka et al., 1992). Amongst edible mushrooms representing eight species, the highest average content of mercury was found in *Boletus pinicola* at 7.37 ppm DW (Alonso et al., 2000). In southeast Asia, the aquatic macrophyte water spinach (*Ipomoea aquatica* Forsk) is a popular vegetable that is cultivated in freshwater courses, it was found that the vegetable accumulated various heavy metals like mercury, cadmium and lead in a nutrient deficient medium (Gothberg et al., 2004).

2.4. Mercury in pharmaceuticals and utility products

Mercury has always been a popular choice for dental amalgams. Thimerosol is a mercury containing compound used as a preservative in Hepatitis B, Diptheria, Pertussis, Acellular pertussis and Tetanus vaccines. Use of mercury in vaccines have caused furore in concerned circles owing to death of infants and speculations over long-term effects (Westphal and Hallier, 2003). Infants are exposed to phenyl mercury from treated diapers and young children ingesting mercuric chloride in teething powders have been found to develop acrodynia and kawasaki disease (Kazantzis, 2002). Skin whitening creams and soaps from developing countries is a recognized source of chronic mercury poisoning (Harada et al., 1999, 2001). Mercury level of almost 2000 times above the allowable limit was found in blood of an indonesian domestic worker (Soo et al., 2003).

2.5. Mercury and wildlife

It is well known that heavy metals in larger amounts are toxic to animals as well as plants; and mercury is no exception to this, though some of these metals may actually be required in trace amounts to support life. The general signs of mercury toxicity for sheep, cattle, pig, chicken and turkey include lack of appetite, loss of weight, muscular incoordination, unstable gait and lameness. Sea birds from mercury contaminated colony, metal dosed birds and metal dosed mice have demonstrated nephrotoxic lesions of severe type (Nicholson et al., 1983). The possible effects of heavy metal exposure on the condition and health of great tit nestlings (*Parus major*) at four study sites along a pollution gradient near a large non-ferrous smelter in Belgium during three consecutive breeding seasons was taken. When taking into account the number of young in the nest at the time of sampling, nestling body mass and condition were significantly reduced at the most polluted site (Janssens et al., 2003). Methylmercury was attributed for decrease in reproduction of adult fathead minnows at dietary concentrations encountered by predatory fishes in aquatic systems with contaminated food webs, implying that exposed fish populations could be adversely affected by this widespread contaminant (Hammerschmidt et al., 2002). Inorganic mercury disturbs a part of respiration process in shrimp larvae *Pandalus borealis* (St-Amand et al., 1999). Embryotoxicity and teratogenecity of organic mercury compounds have been observed in fish, birds and even mammals (Leonard and Jacquet, 1983).

3. Toxicity of mercury

There have been numerous studies dedicated to the study of mercury toxicity. We have shortlisted a few below for the better understanding towards low dose mercury toxicity (Table 2).

3.1. Low dose mercury affects nervous system of foetus and children

Vulnerable periods during the development of the nervous system are sensitive to environmental insults because they are dependent on the temporal and regional emergence of critical developmental processes (i.e. proliferation, migration, differentiation, synaptogenesis, myelination, and apoptosis). Evidence from numerous sources demonstrates that neural development extends from the embryonic period through adolescence. Different behavioral domains (e.g. sensory, motor and various cognitive functions) are subserved by different brain areas. Of critical concern is the possibility that developmental exposure to neurotoxicants may result in an acceleration of age-related decline in function. This concern is compounded by the fact that developmental neurotoxicity that results in small effects can have a profound societal impact when amortized across the entire population and across the life span of humans (Rice and Barone, 2000).

The difference in sensitivity between foetus and adult organism is between 2 and 5 with foetus being more susceptible to methylmercury toxicity (Snyder, 1971). Maternal consumption during pregnancy of methylmercury contaminated fish in Japan and of methylmercury contaminated bread in Iraq caused psychomotor retardation in the offspring. Studies in Iraq suggested adverse fetal effects when maternal hair mercury concentrations were as low as 20 ppm (Marsh and Turner, 1995). Mothers consuming diet containing mercury pass the toxicant to foetus (Murata et al., 2004) and to infants through breast milk (Grandjean et al., 1995). Decreased performance in areas of motor function and memory has been reported among children exposed to presumably safe mercury levels with maternal hair concentrations at 10–20 μg/g (Grandjean and Weihe, 1998). Detectable subtle effects on brain function in domains of language, memory and motor appeared at prenatal methylmercury exposure particularly during second trimester. Neurobehavioral dysfunction was reported even if maternal hair Hg is 6 μg/g, corresponding value for blood is approximately 24 μg/l (Grandjean et al., 1994).

Autism is a disorder that can lead to life-long disability. Though not proved there is potential link between mercury toxicity and autism in children (Lee et al., 2003). Subtle neurological disorders in children over mercury exposure have been widely reported (Johnson, 2004; Counter and Buchanan, 2004). The neuropathological examination of brains of children prenatally exposed to organic mercury reveals dysplasia of cerebral and cerebellar cortexes, neuronal ectopia and several other developmental disturbances (Geelen and Dormans, 1990).

Table 2
Effect of low dose mercury toxicity on various organ systems

Nervous system	
Adults	Memory loss, including Alzheimer like dementia, deficit in attention, hypoesthesia, ataxia, dysarthrea, subclinical finger tremor impairment of hearing and vision, sensory disturbances, increased fatigue
Children/infants	Deficit in language (late talking) and memory deficit in attention, Autism
Motor system	
Adults	Disruption of fine motor function, decreased muscular strength, increeased tiredness
Children/infants	Late walking
Renal system	Increases plasma creatinine level
Cardiovascular system	Alters normal cardiovascular homoeostasis
Immune system	Decreases overall immunity of the body, exacerbates lupus like autoimmunity, multiple sclerosis, autoimmune thyroiditis or atopic eczema
Reproductive system	Decreases rate of fertility in both males and females, birth of abnormal offsprings

3.2. Low dose mercury affects nervous system of adults

Low concentrations of some metals, including mercury can directly induce α-synuclein fibril formation which are the major constituent of intracellular protein inclusions (Lewy bodies and Lewy neurites) in dopaminergic neurons of the substantia nigra leading to parkinson's (Uversky et al., 2001). Moreover, low concentrations of cobalt and mercury are able to induce oxidative stress, cell cytotoxicity and increase the secretion of β-amyloid 1–40 and 1–42 which may lead to neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases (Olivieri et al., 2002). Mercury binds to sulfhydryl groups of proteins and disulfide groups in amino acids resulting in inactivation of sulfur and blocks related enzymes, cofactors hormones (Mathieson, 1995; Markovich and James, 1999). Besides this, it also alters permeability of cellular membrane by binding to sulfhydryl (–SH) radical (Bapu et al., 1994). Blocked or inhibited sulfur oxidation at cellular levels has been found in many chronic neurodegenerative disorders, including Parkinson's disease, Alzheimer's disease, ALS, Lupus, Rheumatoid arthritis, Autism, etc. (Wilkinson and Waring, 2002). Long-term study of low dose of mercury demonstrated hypoesthesia, ataxia, dysarthrea and impairment of hearing and visual change in the study group, 10 years later, after the end of methylmercury dispersion from Minamata on coast of Shiranui sea (Ninomiya et al., 1995). In another survey of fish eating population with low hair Hg levels <10 ppm it was found that neurological symptoms particularly sensory disturbances such as glove and stocking type occured at a very high rate. (Harada et al., 1994). The adult population of Amazonian ecosystem with hair mercury below 50 μg/g deomonstrated near visual contrast sensitivity,

decreased manual dexterity, tendency for increased muscular fatigue, decreased muscular strength among women significantly in a dose dependent manner (Lebel et al., 1998). Similarly disruption of attention, fine motor function and verbal memory was also found in adults of fish eating populations on exposure to low mercury levels (Yokoo et al., 2003). The effects of mercury exposure at levels around 0.05 mg/m^3 or lower have been of concern, include, increased complaints of tiredness, memory disturbance, subclinical finger tremor, abnormal EEG by computerized analysis and impaired performance in neurobehavioral or neuropsychological tests (Satoh, 2000). Neuropsychological effects in mercury vapor exposed male chloralkali workers with low concentrations of urinary mercury mean U-Hg 5.9 nmol/mmol creatinine (Cr) indicated lowering of visuomotor/psychomotor speed and attention, and immediate visual memory (Ellingsen et al., 2001). Depression and impairment of short-term auditory memory was found in workers exposed to low levels of mercury (Soleo et al., 1990).

3.3. Low dose mercury toxicity affects renal system

Kidneys accumulate highest levels of mercury compared to brain and liver (Hussain et al., 1998). Renal toxicity of mercuric chloride is well documented in literature. Nuclear factor κB (NF-κB) is a thiol-dependent transcriptional factor that promotes cell survival and protects cells from apoptotic stimuli. Mercuric ion Hg (2+) is, one of the strongest thiol-binding agents known, impairs NF-κB activation and DNA binding at low μM concentrations in kidney epithelial cells leading to apoptosis (Dieguez-Acuna et al., 2004). Renal function and immunologic markers among chloralkali workers with long-term low exposure to mercury vapor when examined indicated an effect of exposure on the kidney proximale tubule cells (Ellingsen et al., 2000).

Renal dysfunction increases plasma ceratinine level upon methylmercury intoxication for 5 ppm mercury for 2 years (Yasutake et al., 1997). Decrease in protein (brain and liver) acid and alkaline phosphatase and glutathione S transferase was observed upon 0.5 μmol/ml mercury for five consecutive days, while thiobarbituric acid reactive substances (TBARS) was found to be significantly increased in brain and liver indicating free radical stress (El-Demerdash, 2001).

3.4. Low dose mercury toxicity affects reproduction

Advisories to reduce consumption of contaminated fish have been issued by states since the early 1970s. Most women of child bearing age consume commercial fish and a substantial number also consume sport-caught fish containing mercury, linked to reproductive and developmental effects. Despite this potential exposure to dietary mercury, most are unfamiliar with their state's mercury fish-consumption advisory.Until source control and environmental remediation efforts can reduce the environmental burden of mercury below levels of concern, combined sport and commercial fish consumption advisories will remain the primary means of reducing human exposure to methylmercury (Anderson et al., 2004). If concentration of methylmercury is very high in mothers they do not conceive, if they do there is low rate of pregnancy the foetus is aborted or is stillborn. At even lower doses conception and live birth occurred but the child suffered from serious neurological symptoms (Harada, 1968).

Women exposed to mercury vapour not exceeding the time weighted average air concentration of 0.01 mg/m^3 declared higher prevalence and incidence rates of menstrual disorders, primary subfecundity, and adverse pregnancy outcome (De Rosis et al., 1985). According to WHO report 0.5 mg/kg Hg contaminated food should not be sold for human consumption. Hg accounts for sub-fertility in Hong Kong males (Dickman and Leung, 1998). Organic as well as inorganic mercury decreases the percentage of motile spermatozoa. After 30 min incubation with 20 μmol methylmercuric chloride less than 5% of human spermatozoa were found motile (Ernst and Lauritsen, 1991).

3.5. Low dose mercury toxicity affects immune system

The immune system plays an important regulatory role in the host-defense mechanisms. Patients with certain autoimmune and allergic diseases, such as systemic lupus, multiple sclerosis, autoimmune thyroiditis or atopic eczema, often show increased lymphocyte stimulation by low doses of inorganic mercury in vitro (Prochazkova et al., 2004). It has been repeatedly shown that the heavy metal mercury can induce or exacerbate lupus like autoimmunity in susceptible strains of rats and mice. A hallmark of such autoimmune induction is the accompaniment of an immune shift, in which there is usually an initial skewing toward a Th2-like immune environment (Hudson et al., 2003).

Exposure to methylmercury significantly enhanced lymphocyte responsiveness in most of the exposed groups at the low concentration of 5 μg/l, with the highest proliferative response (four-fold increase) in the methylmercury chlorde group (Ortega et al., 1997). Prolonged exposure to low doses of inorganic mercury, suggested an in vivo functional defect of the monocyte–macrophage system (Soleo et al., 1997). The exposure to very low levels of metallic mercury led to subtle impairment of circulating monocyte and NK cells (as percentages) in a particular group of workers, even though they remained clinically asymptomatic (Vimercati et al., 2001).

3.6. Low dose mercury toxicity affects cardiovascular system

Recent evidence suggests that mercury content in fish may diminish the cardioprotective effect of fish intake (Chan and Egeland, 2004). Prenatal exposure to methylmercury may affect development of cardiovascular homoeostasis, in children with lower birth weight, systolic and diastolic blood pressure, increase 13.9 mm Hg when cord blood mercury concentration

increases from 1 to 10 μg/l cord blood (Sorensen and Murata, 1999).

3.7. Low dose mercury toxicity affects motor activity

There are numerous studies demonstrating locomotory dysfunction in laboratory animals on exposure to mercury (Rocha et al., 2001). Neurobehavioral manifestations of subtle neurotoxic effects on motor functions, associated with low-level methylmercury exposure in humans have also been demonstrated (Dolbec et al., 2000). Women showed comparatively reduced grip strength (Lebel et al., 1996) and increased tendency for muscular fatigue associated with low mercury levels as oberserved in amazonian population (Lebel et al., 1998). Mercury with low content of selenium might be one of the environmental factors which are thought to be involved in production of Ayotropic Lateral Sclerosis (Mano et al., 1990).

3.8. Low dose mercury toxicity affects genome

The reports for mercury genotoxicity have been coming since 1980. First report showing clear cytotoxic effects of 20 years exposure to methylmercury on human population with a wide range of mercury exposure, based on a well-known biological marker, hair mercury a clear relation between methylmercury contamination and cytogenetic damage in lymphocytes at levels well below 50 μg/g was found. Although their results strongly suggest that, under the conditions examined, methylmercury is both a spindle poison and a clastogen, the biological significance of these observations are as yet unknown (Amorim et al., 2000). A long-term follow-up of these subjects should be undertaken. Theoretically, methylmercury-induced chromosome damage in germline cells could give rise to abnormal offspring. Mercuric chloride exposure in short term blood cultures lead to high sister chromosome excahanges/cell and induced C-anaphases (abnormal mitosis) (Rao et al., 2001). The chromosomal genotoxicity of mercury has been attributed to its interation with microtubule assembly mercury inhibits microtubule assembly at concentrations above 1 μM, and inhibition is complete at about 10 μM (Bonacker et al., 2004).

Mercury genotoxicity have been observed in animals as well as in plants. The cytogenetic analysis revealed the effects of mercury on the mitotic and meiotic chromosomes which were significantly correlated with soil-mercury levels. The bioconcentration of mercury in aerial tissues including grain was observed indicating possible contamination of the agricultural food chain (Panda et al., 1992). Low concentrations of inorganic mercury (Hg^{2+}) and methylmercury chloride (CH_3HgCl) added separately or together lead to induction of micronuclei in the binucleated erythrocytes of Prussian carp (Al-Sabti, 1994). The bioaccumulation of methylmercuric chloride and mercuric chloride at low dose exposure was evaluated by determination of mercury levels in the larvae of urodele Pleurodeles waltl. After 12 days of treatment, concentration factors (concentration in the amphibian organism/concentration in the water) of approximately 1200 and approximately 600 were found for methylmercury and mercuric chloride, respectively (Zoll et al., 1988).

3.9. Molecular mechanisms of low dose mercury toxicity

It is difficult to classify the molecular basis of low dose mercury toxicity to tissues and organ systems initially due to lack of data, finally because it is a complex cascade of interrelated events that may directly or indirectly translate into pathological state of a particular organ system. Its neurotoxicity to cerebellum at higher doses has been related to impairment of motor function (Marcelo et al., 2005) and its genotoxicity to neuronal cells in foetal state may result in abnormal offsprings or foetal deaths but its exact mode of activity at low doses, particularly at environmentally relevant concentrations which lead to subtle delays in neurodevelopment remain unexplored. Basically it blocks essential functional groups in biomolecules and also displaces essential metal ions from them. Mercuric ion is known as one of the strongest thiol-binding agents. Intracellular mercury therefore attaches itself to thiol residues of proteins particularly glutathione and cysteine resulting in inactivation of sulfur and blocks related enzymes, cofactors and hormones (Mathieson, 1995). Its molecular interactions with sulfhydryl groups in molecules of albumin, metallothionein, glutathione, and cysteine have been implicated in mechanisms involved in renal (Zalups, 2000) and neuronal toxicity (James et al., 2005 and Fonnum and Lock, 2004). The other functional groups besides –SH for which mercury has high affinity include, $-CONH_2$, $-NH_2$, –COOH and $-PO_4$ (Hayes, 1983). It also blocks immune function of Mn and Zn leading to deficiency of principal antioxidant enzyme, superoxide dismutase, CuZn–SOD and Mn–SOD (Rajanna and Hobson, 1995) which has a role in various diseases, including Alzheimer's disease, Parkinson's disease, Cancer, Downs syndrome, Dengue, etc. (Noor et al., 2002). Moreover, in cerebellar granule cells in culture, low concentration of mercury causes a rise in $[Ca^{2+}]$ which may trigger a cascade of events leading to impairment of mitochondrial energy metabolism and generation of reactive oxygen species (Fonnum and Lock, 2004). Mercury by inhibiting glutamic acid uptake further sensitises neurones to excitotoxic injury (Fonnum and Lock, 2004). The combination of these mercury triggered events enhances free radical stress that has been cited widely in literature (Hussain et al., 1998 and Ali et al., 1992).

Free radical stress has been frequently reported as key player in disease progression of as many as 50 diseases (Halliwell, 1994 and Langseth, 1993), aging and degenerative disorders (Nagy, 2001). Mercury obstructs neurotransmission by acting as a strong competitive inhibitor of muscarinic cholinergic receptors (Coccini et al., 2000), though

this aspect awaits further study. The renal changes in workers with chronic low level exposure to mercury indicated increased tubular antigens and enzymes, altered levels of biochemical enzymes, such as decreased urinary output of eicosanoids and glycosaminoglycans, and a more acidic pH. However since urinary function was normal, the clinical significance of these findings is yet to be determined (Cardenas et al., 1993).

The observed reduced lymphocyte proliferation associated with low levels of mercury (Soleo et al., 1997; Vimercati et al., 2001) may translate into reduced resistance to disease. Low-level, nontoxic inorganic mercury pre-exposure may interact with other risk factors, genetic or acquired, to promote subsequent autoimmune disease development (Via et al., 2003). Though molecular basis of immunotoxicity of mercury is relatively less studied, recent researches show that low dose mercury suppresses immune response by reducing nitric oxide (NO) synthesis by inhibition of the nuclear factor κB (NF-κB) pathway and modulating cytokine expression by p38 mitogen-activated protein kinase (p38 MAPK) activation as observed in J774A.1, murine macrophage cell line (Kim et al., 2002). Mercury salts cause allergy by inducing IgE synthesis and promoting Th2-cytokine profile (Strenzke et al., 2001).

The fetus is especially vulnerable to methylmercury since developing fetal brain processes, such as cellular division, differentiation, and migration are disrupted by binding of mercury to thiol groups of tubulin, the principal protein constituent of neuronal microtubules (Clarkson, 1992). The chromosomal genotoxicity of mercury salts could be due to interaction of Hg^{2+} with the motor protein kinesin mediating cellular transport processes (Bonacker et al., 2004). Genotoxicity of mercurials could have far reaching consequences ranging from birth of abnormal offsprings to neuroegenerative disorders. Recently in a major breakthrough, rise in apolipoprotein-E ε4 genotype has been proposed as a biomarker for low-dose mercury toxicity (Godfrey et al., 2003) and rise in apolipoprotein-E due to mercury has been advocated as a pathogenic factor for Alzheimer disease (Mutter et al., 2004; Godfrey et al., 2003) (Table 3).

Table 3
Brief summary of molecular mechanisms of low doses of mercury toxicity

1	Enhanced free radical stress
2	Altered thiol metabolism
3	Reduced level of glutathione
4	Raised intracellular calcium
5	Induction of mitochondrial damage
6	Interruption of excitatory amino acid pathway
7	Inhibition of muscarinic cholinergic receptors
8	Disruption of microtubule assembly
9	Rise in apolipoprotein-E ε4 genotype
10	Formation of neurofibrillary tangles
11	Inhibits nuclear factor κB (NF-κB) pathway
12	Promotes Th2-cytokine profile
13	Formation of neurofibrillary tangles

4. Conclusion

Multiple pathways of mercury through air, food, water, pharmaceuticals, cosmetics, etc., account for its easy accessibility to man, factors like biomagnification of mercury along the food chain complicate the problem. Fish eating populations are at an increased risk. There are numerous studies establishing mercury toxicity as occupational health hazard for goldminers, chloralkali workers and dental personnel. Since awareness regarding low-dose mercury toxicity is less; safety precautions are generally not taken even sometimes at personal level, e.g. children play with liquid metal of a broken thermometer.

In view of numerous recent reports regarding low-dose mercury toxicity, its environmental contamination should be checked. A few countries have awareness campaigns, in some cases they are successful for instance. The Netherlands has reduced thimerosol (merthiolate) exposure through pharmaceuticals (Van't Veen, 2001). Recent literature reports that thimerosol has been removed from most of the children's vaccines, but it is still present in flu vaccines given to pregnant women, the elderly, and to children in developing countries (James et al., 2005). The governments of respective countries should ensure mercury free air, water and food by making strict laws regarding contaminating industrial units, ensuring proper disposal of mercury garbage and encouraging procedures without use of mercury. Media and NGOs should raise a voice against any negligence on part of government besides educating the masses about mercury hygiene. There should be awareness among general public from abstaining mercury laced cosmetic products. Scientists should work towards making vaccines in which mercury is not a preservative.

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