Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 3 [6] May 2014: 272-285

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD
Global Impact Factor 0.533
Universal Impact Factor 0.9804

ORIGINAL ARTICLE

Methylmercury Cycle and Its Implications on Human Health

Shabnum Nabi
Interdisciplinary Brain Research Centre, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, U.P.
Email: shabnum_nabi@yahoo.com

ABSTRACT
Methylmercury poisoning was first recognized in Minamata, Japan around 1960. Hundreds of fishermen and their families were severely poisoned during the 1950s by methyl mercury that bioaccumulated in fish as a result of the release of mercury to the bay from a local chemical plant. Many severe effects were observed including parasthesia (abnormal physical sensations such as numbness), gait disturbances, sensory disturbances, tremors, hearing impairment and many mortalities. By 1960 the serious and mysterious affliction, affecting both adults and infants, was recognized as methyl mercury poisoning, a hitherto unrecognized disease. Through mercury's contamination of rain-, ground and sea-water nobody is safe. Tainted water leads to mercury laced fish, meat and vegetable. In aquatic milieu, inorganic mercury is microbiologically transformed into lipophilic organic compound 'methylmercury'. This conversion makes mercury more horizontal to biomagnification in food chains. As a result, populace with customarily high dietary intake of food originating from fresh or marine milieu has highest dietary exposure to mercury. Far-reaching research done on locals across the sphere have already established this, persons who habitually devour fish or a particular species of fish are at an amplified risk of methylmercury poisoning. The trouble-free admittance of the toxicant to man in the course of multiple alleyways air, water, food, cosmetic products and even vaccines increase the exposure. Fetus and children are more vulnerable towards mercury toxicity. Mothers consuming diet containing mercury pass the toxicant to fetus and to infants through breast milk. Dwindled recital in areas of motor function and memory has been accounted among children exposed to seemingly safe mercury levels. Likewise, distraction of attention, fine motor function and verbal memory was also found in adults on contact to low mercury levels. It is a work-related danger for dental staff, chloralkali factory workers and goldminers, etc. Mercury has been found to be a contributory means of various sorts of ailments, including neurological, nephrological, immunological, cardiac, motor, reproductive and even genetic. Recently heavy metal arbitrated toxicity has been coupled to diseases like Alzeihemer's, Parkinson's, Autism, Lupus, Amyotrophic lateral sclerosis, etc. Moreover this, it poses danger to wildlife. Therefore, it becomes vital to stretch the information concerning the threat of mercury exposure amid the scientists and masses.
Keywords: Mercury; Toxicity; Biomagnification; Neurodegenerative deficits

Received 11.01.2014 Revised 13.04.2014 Accepted 22.04. 2014

INTRODUCTION

The Spanish have known for 2,000 years that slaves in the mercury mines gradually got sick and died. In the 1960s and '70s, acute and widespread poisonings such as those in Minamata, Japan, made mercury notorious as a nervous system toxicant and as a cause of birth defects. 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.

Mercury and its sources

Mercury has no positive role in the human body (Goyer, 1996); in fact a safe level of mercury exposure is very difficult to determine. It can be present in the environment in several different forms, and while all forms of mercury are toxic to humans, the pattern of toxicity varies with its chemical form, the route of

exposure, the amount, the duration and timing of exposure(Agency for Toxic Substances and Disease Registration), and the vulnerability of the person exposed (European Commission, 2005). For example, pure elemental mercury (also known as quicksilver or Hg) is liquid at room temperature. If ingested, quicksilver has very low toxicity because it is not absorbed by the gastrointestinal tract and is eliminated completely in the stool. If quicksilver is agitated or heated, however, the liquid mercury becomes a vapor which is readily absorbed by inhalation and is highly toxic to the lungs and central nervous system. The nervous system is the primary target of mercury toxicity, but, depending upon the specific exposure, the kidneys, liver and lungs are also important targets. Table 1 gives an overview of the different forms of mercury, their uses, routes of exposure and their toxicity. The two biggest sources of exposure to mercury for the general population are through our consumption of fish, and associated with medical and dental practices. People in developed countries have significant exposure from the mercury in their dental fillings (European Commission, 2005). However, our environmental exposure to methyl mercury, a highly toxic form of organic mercury found in ocean and freshwater fish and marine mammals, is a cause of great concern.

Mercury in ambient air

Mercury in Ambient Air is now routinely measured in both urban and rural sites due to the toxicity and mobility of this element. In addition workplace air monitoring for mercury and cell room monitoring are essential to protect the health of the workers in the relevant industries. As 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 are 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).

Levels corresponding to the intake dose

	INTAKE DOSE	**HAIR**	**BLOOD**
FAO/WHO Joint Expert Committee on Food Additives (JECFA)	1.6 µg/kg body weight Provisional Tolerable Weekly Intake (PTWI)[i]	14 mg/kg[ii] 2 µg/ gram corresponds approximately to the PTWI	
US EPA reference dose US National Research Council (NRC)	0.1 µg/kg body weight per day[iii] OR 0.7 µg/kg body weight per week	1 µg/ gram of hair[iv]	5.8 µg/L[v]

Table1. Comparison of methyl mercury limits

i FAO/WHO Joint Expert Committee on Food Additives (JECFA), Summary & Conclusions. 61st Meeting, Rome, 10-19 June 2003. See www.chem.unep.
ch/mercury/Report/JECFA-PTWI.htm
ii Taking the average from the two studies in the Seychelles and Faroe Islands, the committee established this level in maternal hair refl ecting exposures that would be without appreciable adverse effects in the offspring in these two study populations.
iii United States Environmental Protection Agency (1997) Mercury Study Report to Congress, Volume VII: Characterization of Human Health and Wildlife Risks from Mercury Exposure in the United States. p. 19
http://www.epa.gov/ttn/oarpg/t3/reports/volume7.pdf accessed 8 November 2006
iv United States Environmental Protection Agency (1997a), Mercury Study Report to Congress Volume IV: An Assessment of Exposure to Mercury in the United States.
http://www.epa.gov/ttn/oarpg/t3/reports/volume4.pdf
v United States Environmental Protection Agency (1997a), op.cit.

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). In Europe the highest background concentration of TGM is measured in central Europe (e.g. Germany and Poland), where the concentrations may reach up to 2.5 ng/m3 (EMEP; 1999). The concentrations in rural areas are normally very low, close to the mean global values (EMEP, 1999). The values in urban areas are usually higher and vary between 5-15 ng/m3 (IPCS, 1991) and in some contaminated places even higher (Dizdarevic, 2001). The reference concentrations (RfC) recommended by the US EPA amounts to 0.3 mg/m3 (IRIS, 1995), which means that in general mercury concentrations in air do not represent a considerable intake of Hg for humans. The WHO has estimated the daily intake of each form of Hg on the assumption that 75% of Hg is in elemental Hg from, 5% as inorganic Hg and 20% of MeHg. By assuming a daily ventilation of 20 m3, and the amount absorbed across the pulmonary membranes (80% of elemental Hg, 50'% of inorganic Hg, and 80% of MeHg) daily intakes were calculated and given in Table 2. Informal gold mining has used mercury since antiquity. An increase in ambient air levels of mercury will result in an increase of direct human exposure and in an increase of mercury flux entering terrestrial and aquatic ecosystems leading to elevated concentrations of methylmercury in freshwater fish and marine biota. Such a contingency might have an important bearing on acceptable levels of mercury in the atmosphere. Although the different processes affecting the global atmospheric cycle of mercury and the mechanisms driving the methylation and bioaccumulation pathways in the aquatic food-chain are not completely understood, a preliminary quantitative estimate of risks from these post-depositional processes is possible. In order to prevent possible health effects of exposed populations in the near future, a strategy for emission reductions of mercury is strongly needed.

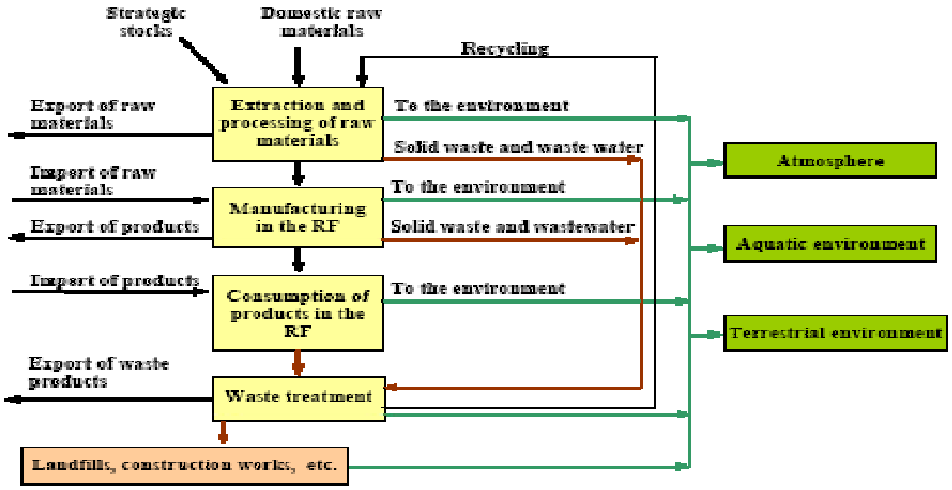

Figure1: Schematic illustration of the overall flow of mercury through the Technosphere

Exposure	Elemental Hg Vapor	Inorganic Hg Compounds	Methylmercury
Air	0.03(0.024)*	0.002(0.001)	0.008(0.0069
Dental Amalgams	3.8-21 (3-17)	0	0
Food -fish -non-fish	0 0	0.60 (0.042) 3.6 (0.25)	2.4 (2.3)** 0
Drinking Water	0	0.050 (0.0035)	0
Total	3.9-21 (3-1-17)	4.3 (0.3)	2.41 (2.31)

The data in parenthesis represent retained Hg in the body of an adult.
* If the concentration is assumed to be 15 ng/m3 in an urban area the figure would be 0.3(0.24) mg/day
** 100 g of fish per week with the Hg concentration of 0.2 mg/kg.

Table 2: Estimated average daily intakes and retention in (mg/day) of different mercury forms in the general population not occupationally exposed **(IPCS, 1991)**.

Mercury in water

Levels of mercury in rainwater are in the range 5–100 ng/litre, but mean levels as low as 1 ng/litre has been reported (IPCS, 1990). Naturally occurring levels of mercury in groundwater and surface water are less than 0.5 μg/litre, although local mineral deposits may produce higher levels in groundwater. A small number of ground waters and shallow wells surveyed in the USA were shown to have mercury levels that exceeded the maximum contaminant level of 2 μg/litre set by the US Environmental Protection Agency for drinking-water (Ware, 1989). An increase in the mercury concentration up to 5.5 μg/litre was reported for wells in Izu Oshima Island (Japan), where volcanic activity is frequent (Magara et al., 1989). The concentration range for mercury in drinking-water is the same as in rain, with an average of about 25 ng/litre (IPCS, 1990). In a contaminated lake system in Canada, methylmercury was found to constitute a varying proportion of total mercury, depending on the lake (IPCS, 1990). There have been no reports of methylmercury being found in drinking-water. Mercury in air ultimately surpasses into rivers, lakes and oceans after roving lengthy distances jointly along with wind. By means of mercury polluting rain (Domagalski et al., 2004; Levine, 2004), ground and seawater (Beldowski and Pempkowiak, 2003), nobody is secure. Cloud water was composed throughout nine non-impulsing cloud events on Mt. Mansfield, VT in the northeastern USA between 1 August and 31 October, 1998. Mercury cloud water concentrations ranged from7.5 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 connections among acidic eevidence and fish mercury contagion and eutrophication of estuaries (Driscoll et al., 2003). Several industrial units that directly pump untreated sewages contaminate groundwater. The acidic rain produced by polluted water eventually contaminates all water bodies. In India, groundwater samples collected from eight places each from Andra Pradesh, Gujarat, Punjab, Haryana, and Kanpur illustrated astonishingly high levels of Hg in all samples. Water sample collected from Panipat (Haryana) showed elevated levels of Hg at dilution of 268 times that of safe limit, yet the illustration with slightest Hg value had 58 times more mercury than the upper safe limit (Hindustan times, 1999). Potentially increased MeHg accumulation in fish happens due to Algal bloom and leaf fall events, that result in elevated methylmercury (MeHg) concentrations in surface waters (Balogh et al., 2002).

Mercury infectivity of provisions

Food is the main source of mercury in non-occupationally exposed populations. Fish and fish products account for most of the organic mercury in food. The average daily intake of mercury from food is in the range 2–20 μg, but may be much higher in regions where ambient waters have become contaminated with mercury and where fish constitute a high proportion of the diet (Galal-Gorchev, 1991).

Foodstuff of animal derivation

The emanated mercury in-cooperation with natural and anthropogenic is in an inorganic form principally metallic vapor, which is passed off to immense remoteness by winds and finally descends in water bodies. In water milieu, inorganic mercury is microbiologically converted into lipophilic organic complex, methylmercury. This conversion makes mercury more flat to biomagnifications in food chains. Accordingly, inhabitants with customarily lofty dietary intake of food deriving from fresh or marine milieu have elevated dietary exposure to Hg. Widespread investigation done on locals transversely the sphere have already recognized this for instance polar Eskimos. People who devour fish or a particular species of fish on regular basis are at an elevated threat of methylmercury poisoning (Table 3) (Hansen and Dasher, 1997). In view of the fact that mercury intake is articulated on a per kilogram body weight basis, revelation of children under age 14 is two–three times high because of elevated food intake per kilogram body weight. After computing total mercury in the edible fractions of 244 chosen fish and shellfish obtained in Canada at the retail level, the Canadian advisory to children and women of child-bearing 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 scrutinized for mercury accretion the former two ranked highest (Schumacher et al., 1994). In Yokon delta system, biomagnification factor of 12 was analyzed for methylmercury, out of 29% fish species, 62% contained Hg beyond the wildlife grave value for piscivorous animals. By and large 24% fish go beyond grave value for human ingestion and 58% wildlife grave value (Duffy et al., 1998). Farm animals and pigs kept in area with infected river water had twofold concentration of blood and hair Hg than control ones (Palheta and Taylor, 1995).

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

Table 3: Mercury levels in commercial fish and shellfish

Foodstuff of plant basis

Emanations of mercury from the region of Guizhou in Southwestern China to the global milieu have been calculated to be around 12% of the planet total anthropogenic emanations principally due to mining, chemical discharge and electricity production. Even though the main cause of mercury is inorganic, it was find out that active conversion of inorganic mercury to organic mercury species (MeHg) occur in water, sediments and soils. It has been accounted that the intensity of mercury in rice grains can raise up to 569 µg/kg of total Hg of which 145 µg/kg is in MeHg form (Horvat et al., 2003). While scrutinizing in situ aquatic and terrestrial plants in environs of chloralkali plants growing at Hg conc. 8.9 mg/kg it was established that Cabbage *Bracica oleracea* and amaranthus. *Amaranthus oleraceous* gathered mercury at significant levels (Lanka et al., 1992). In the midst of edible mushrooms representing eight species, the utmost average content of mercury was found in *Boletus pinicola* at 7.37 ppm DW (Alonso et al., 2000). It was found that the aquatic macrophyte water spinach (*Ipomoea aquatica* Forsk) of southeast asia which is a popular vegetable and is cultivated in freshwater courses, accumulated various heavy metals like lead, cadmium and mercury in a nutrient scarce medium (Gothberg et al., 2004).

Mercury in pharmaceuticals and utility goods

Mercury utilization in vaccines have caused fracas in related circles owing to death of infants and assumptions over long-term effects (Westphal and Hallier, 2003). Infants are exposed to phenyl mercury from treated diapers and young children consuming mercuric chloride in teething powders have been found to build up 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). In an Indonesian domestic worker mercury level was found to almost 2000 times above the tolerable limit (Soo et al., 2003).

Mercury and wildlife

Loss of weight, lack of appetite, unstable gait, muscular in coordination, and lameness are the general signs of mercury toxicity for cattle, pig, chicken and turkey. Sea birds from mercury infected colony, metal dosed birds and metal dosed mice have confirmed nephrotoxic lesions of acute type (Nicholson et al., 1983). Near a large nonferrous smelter in Belgium the possible effects of heavy metal exposure on the condition and health of great tit nestlings (*Parus major*) during three consecutive breeding seasons was taken in to account. While analyzing, the number of young in the nest at the time of sampling, nestling body mass and condition was found considerably declined at the most infected site (Janssens et al., 2003).

Methylmercury was ascribed for decline in reproduction of adult fathead minnows at nutritional applications encountered by predatory fishes in aquatic systems with infected food webs, entailing that bared fish populace could be harmfully affected by this widespread noxious waste (Hammerschmidt et al., 2002). In shrimp larvae *Pandalus borealis* a part of respiration process is disturbed by inorganic mercury (St-Amand et al., 1999). In fish, birds and even mammal's embryotoxicity and teratogenecity of organic mercury compounds have been observed (Leonard and Jacquet, 1983).

Health effects of mercury at a glance

High doses of mercury can be fatal to humans, but even relatively low doses of mercury containing compounds can have serious adverse impacts on the developing nervous system, and have recently been linked with possible harmful effects on the cardiovascular, immune and reproductive systems (European Commission, 2005). Mercury and its compounds affect the central nervous system, kidneys, and liver and can disturb immune processes; cause tremors, impaired vision and hearing, paralysis, insomnia and emotional instability. During pregnancy, mercury compounds cross the placental barrier and can interfere with the development of the fetus, and cause attention deficit and developmental delays during childhood (World Health Organisation, 2005). There have been numerous studies dedicated to the study of mercury toxicity. I have short listed a few below for the better understanding towards low dose mercury toxicity (Table 4).

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 atopic eczema
Reproductive system	Decreases rate of fertility in both males and females, birth of abnormal offsprings

Table 4: Effect of low dose mercury toxicity on various organ systems

How toxic is mercury to nervous system of fetus and children

Susceptible phases during the growth and development of the nervous system are vulnerable to ecological abuse as they are reliant on the temporal and regional emergence of critical developmental processes (i.e. proliferation, migration, differentiation, synaptogenesis, myelination, and apoptosis). Confirmation from many sources displays that neural development extends from the embryonic period through adolescence. Dissimilar behavioral areas (e.g. sensory, motor and various cognitive functions) are subserved by dissimilar brain domains. Of grave apprehension is the option that developmental contact to neurotoxicants may result in an increase of age-related decrease in function. This apprehension is complexed by the actuality that developmental neurotoxicity that consequences in small effects can have a thoughtful societal influence when amortized across the entire populace and across the life span of humans (Rice and Barone, 2000). The differentiation in sensitivity between fetus and adult organism is between 2 and 5 with fetus being more vulnerable to methylmercury infectivity (Snyder, 1971). In Iraq

methylmercury contaminated bread and fish consumption by mothers during pregnancy caused psychomotor retardation in the offspring. Adverse fetal effects were suggested by a study in Iraq, when maternal hair mercury intensities were as low as 20 ppm (Marsh and Turner, 1995).

Mothers consuming foodstuff containing mercury surpass the toxicant to fetus (Murata et al., 2004) and to toddlers through breast milk (Grandjean et al., 1995). Declined performance in domains of motor function and memory has been accounted among children exposed to seemingly secure mercury levels with maternal hair concentrations at 10–20μg/g (Grandjean and Weihe, 1998). Noticeable slight effects on brain function in domains of language, memory and motor appeared at prenatal methylmercury exposure chiefly during second trimester. Neurobehavioral dysfunction was accounted even if maternal hair Hg is 6μg/g; equivalent value for blood is approximately 24μg/l (Grandjean et al., 1994). Autism is a disorder that can direct to lifetime disability. Though not proved there is potential link between mercury toxicity and autism in children (Lee et al., 2003). Slight neurological disarrays in children over mercury exposure have been widely accounted (Johnson, 2004; Counter and Buchanan, 2004). The neuropathological assessment of brains of children prenatally uncovered to organic mercury discloses dysplasia of cerebral and cerebellar cortexes, neuronal ectopia and several other developmental commotions (Geelen and Dormans, 1990).

How toxic is mercury to nervous system of adults

Synuclein fibrils 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 can directly be induced by low concentrations of some metals, including mercury (Uversky et al., 2001). Likewise, low dilutions of cobalt and mercury are adept to stimulate oxidative stress, cell cytotoxicity and augment the discharge of β-amyloid 1–40 and 1–42 which may direct to neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases (Olivieri et al., 2002). Mercury unites to sulfhydryl groups of proteins and disulfide groups in amino acids ensuing in inactivation of sulfur and obstructs associated enzymes, cofactors and hormones (Mathieson, 1995; Markovich and James, 1999). Moreover this, it also modifies permeability of cellular membrane by fastening to sulfhydryl (SH) radical (Bapu et al., 1994). Obstructed or repressed sulfur oxidation at cellular levels has been found in numerous unremitting neurodegenerative disorders, including Alzheimer's disease, ALS, Parkinson's disease, Lupus, Autism, Rheumatoid arthritis etc. (Wilkinson and Waring, 2002). Long-term low dose study of mercury verified hypoesthesia, dysarthrea, ataxia, and impairment of visual and hearing change in the study group, 10 years later on, afterwards the termination of methylmercury spreading from Minamata on Coast of Shiranui Sea (Ninomiya et al., 1995). It was found in another survey of fish eating population with low hair Hg levels <10 ppm that neurological signs predominantly sensory turbulences such as glove and stocking type occurred at a very high rate (Harada et al., 1994). The adult populace of Amazonian bionetwork with hair mercury below 50 μg/g verified near visual contrast sensitivity declined manual dexterity, tendency for elevated muscular fatigue, declined muscular potency among women notably in a dose dependent manner (Lebel et al., 1998). Likewise commotion of attention, fine motor task and verbal memory was also found in adults of fish eating populace on exposure to low mercury levels (Yokoo et al., 2003). The effects of mercury exposure at levels around 0.05 mg/m3 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).

How toxic is mercury to renal system

Kidneys mount up maximum levels of mercury in contrast to brain and liver (Hussain et al., 1998). Literature shows a well documented mercuric chloride induced renal toxicity. Nuclear factor kB (NF-kB) is a thiol-reliant transcriptional factor that supports cell endurance and defends cells from apoptotic stimuli. The robust thiol-binding agents known, Mercuric ion Hg (2+) at low μM concentrations impairs NF-kB activation and DNA binding in kidney epithelial cells leading to apoptosis (Dieguez-Acuna et al., 2004). Renal function and immunologic markers when examined among chloralkali workers exposed to long-term low mercury vapor indicated an effect of exposure on the kidney proximale tubule cells (Ellingsen et al., 2000). Upon methylmercury intoxication (5 ppm mercury) for 2 years, renal dysfunction elevates plasma ceratinine level (Yasutake et al., 1997). 0.5 μmol/ml mercury for five consecutive days showed decrease in protein (brain and liver), glutathione S transferase and acid and alkaline phosphatase, while brain and liver thiobarbituric acid reactive substances (TBARS) were significantly increased indicating free radical stress (El-Demerdash, 2001).

How mercury affects reproduction

Advisories to lessen the ingestion of infected fish have been delivered by states since the early 1970s. Majority of women of child bearing age devour marketable fish and ample number also eat sport-caught fish confining mercury, allied to reproductive and developmental effects. Regardless of this probable revelation to dietary mercury, most are unknown with their state's mercury fish-consumption advisory. Until source jurisdiction and milieu cure efforts can decline the milieu 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 methylmercury concentration in mothers is extremely high they do not conceive, if they will do so there is low rate of pregnancy, the fetus is aborted or is stillborn. At even subordinate dosages conception and live birth occurred but the child underwent from severe neurological symptoms (Harada, 1968). Women uncovered to mercury vapor not beyond the time weighted average air concentration of 0.01 mg/m3 affirmed elevated occurrence and prevalence rates of menstrual disorders, primary sub fecundity, and unpleasant pregnancy outcome (De Rosis et al., 1985). According to WHO report 0.5 mg/kg Hg polluted food should not be sold for human ingestion. Hg reports for sub-fertility in Hong Kong males (Dickman and Leung, 1998). Organic as well as inorganic mercury declines the proportion 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).

How mercury affects immune system

In the host-defense mechanisms the immune system plays an imperative dogmatic function. Patients with definite autoimmune and allergic disorders, such as multiple sclerosis, systemic lupus, atopic eczema or autoimmune thyroiditis, often show elevated lymphocyte stimulation by low doses of inorganic mercury in vitro (Prochazkova et al., 2004). It has been frequently revealed that the heavy metal mercury can stimulate or aggravate lupus like autoimmunity in vulnerable strains of rats and mice. A characteristic of such autoimmune stimulation is the supplement of an immune shift, in which there is generally a preliminary skewing toward a Th2-like immune milieu (Hudson et al., 2003). Revelation to methylmercury considerably increased lymphocyte responsiveness in majority of the bare groups at the low concentration of 5 μg/l, with the utmost proliferate response (four-fold augment) in the methylmercury chloride group (Ortega et al., 1997). Protracted contact to low doses of inorganic mercury, recommended an in vivo functional fault of the monocyte–macrophage system (Soleo et al., 1997). The contact to depleted levels of metallic mercury direct to slight 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).

How mercury affects cardiovascular system

Indication recommends that mercury content in fish may moderate 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 13.9mmHgwhen cord blood mercury concentration increases from 1 to 10 μg/l cord blood (Sorensen and Murata, 1999).

How mercury affects motor activity

There are copious investigations representing locomotory dysfunction in laboratory animals on contact to mercury (Rocha et al., 2001). Neurobehavioral signs of slight neurotoxic effects on motor functions, linked with low-level methylmercury exposure in humans have also been confirmed (Dolbec et al., 2000). Women illustrated relatively declined grip potency (Lebel et al., 1996) and elevated affinity for muscular weariness limked with low mercury levels as pragmatic in amazonian populace (Lebel et al., 1998). Mercury with low content of selenium possibly will be one of the milieu aspects which are thought to be concerned in creation of Ayotropic Lateral Sclerosis (Mano et al., 1990).

How mercury affects genome

Mercury genotoxicity has been usually attributed to its ability to react with the sulfhydryl groups of tubulin, impairing spindle function and leading to chromosomal aberrations and polyploidy (De Flora *et al.*, 1994). Another important mechanism of mercury genotoxicity is its ability to produce free radicals that can cause DNA damage (Schurz *et al.*, 2000 and Ehrenstein *et al.*, 2002). *In vivo* studies have demonstrated a clastogenic effect of mercury on people exposed to this element in their working environment or through the consumption of contaminated food, or sometimes accidentally. Increased numbers of chromosome alterations and micronuclei have been reported in people who consume contaminated fish Amorim *et al.*, 2000 and Franchi *et al.*, 1994 and in miners and workers of explosive factories Al-Sabti *et al.*, 1992 and Anwar and Gabal, 1991. Negative results were also obtained in some cases (Hansteen *et al.*, 1993 and Mabille *et al.*, 1984), demonstrating that cytogenetic monitoring of peripheral blood lymphocytes in individuals exposed to mercury from different sources may not be

completely specific (De Flora *et al.*, 1994). The effects of CH_3HgCl contamination have been studied in an increasing way since the outbreaks in Japan and Iraq. Many of these studies had their focus on the neurological effects of CH_3HgCl exposure in adult animals and used high doses of this compound (1900 to 30,000 ppb = µg/L) to obtain its most severe effects (National Research Council, 2000). Most of the *in vitro* studies with lymphocytes also used high doses (250-6250 µg/L) of mercury compounds in order to evaluate its clastogenic effects (Ogura *et al.*, 1996, Betti *et al.*, 1993 and Betti *et al.*, 1992).

Molecular mechanisms of low dose mercury toxicity

It is hard to categorize the molecular basis of low dose mercury toxicity to tissues and organ systems originally due to lack of data, lastly because it is a composite flow of interconnected events that may directly or indirectly interpret into pathological state of a specific organ system. Its neurotoxicity to cerebellum at elevated doses has been connected to destruction of motor function (Marcelo et al., 2005) and its genotoxicity to neuronal cells in fetal state may conclude in malformed offsprings or fetal demise but its accurate mode of activity at low doses, remarkably at environmentally related concentrations which lead to slight hindrances in neurodevelopment stay uncharted. Essentially it obstructs necessary functional groups in biomolecules and also displaces crucial metal ions from them. Mercuric ion is identified as one of the powerful thiol-binding agents. Intracellular mercury hence attaches itself to thiol residues of proteins predominantly glutathione and cysteine ensuing in inactivation of sulfur and chunks associated enzymes, cofactors and hormones (Mathieson, 1995). Its molecular interfaces with sulfhydryl groups in molecules of albumin, metallothionein, glutathione, and cysteine have been concerned in mechanisms involved in renal (Zalpus, 2000) and neuronal toxicity (James et al., 2005 and Fonnum and Lock, 2004). The other useful groups alongside SH for which mercury has lofty affinity include, CONH2, NH2, COOH and PO4 (Hayes, 1983). It also obstructs immune function of Mn and Zn leading to lack of principal antioxidant enzyme, superoxide dismutase, CuZn–SOD and Mn–SOD (Rajanna and Hobson, 1995) which has a function in variety of disorders, including Alzheimer's disease, Parkinson's disease, Cancer, Downs syndrome, Dengue, etc. (Noor et al., 2002). Besides, in cerebellar granule cells in culture, low concentration of mercury brings about a rise in [Ca2+] which may activate a flow of events leading to mutilation of mitochondrial energy metabolism and production of reactive oxygen species (Fonnum and Lock, 2004). Mercury by restraining glutamic acid uptake further sensitises neurones to excitotoxic injury (Fonnum and Lock, 2004). The amalgamation of these mercury activated events boosts free radical stress that has been quoted broadly in literature (Hussain et al., 1998 and Ali et al., 1992). Free radical stress has been repeatedly 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 blocks neurotransmission by performing 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 kB (NF-kB) 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 Hg2+ 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 5).

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 _4 genotype
10	Formation of neurofibrillary tangles
11	Inhibits nuclear factor _B (NF-_B) pathway
12	Promotes Th2-cytokine profile
13	Formation of neurofibrillary tangles

Table 5: Brief summary of molecular mechanisms of low doses of mercury toxicity

CONCLUDING REMARKS

Numerous pathways of mercury by means of air, food, water, pharmaceuticals, cosmetics, etc., report for its effortless openness to man, aspects like biomagnification of mercury along the food chain obscure the problem. Fish devouring populace are at an elevated risk. There are several studies ascertaining mercury toxicity as industrial health danger for goldminers, chloralkali workers and dental personnel. Since consciousness regarding low-dose mercury toxicity is fewer; safety measures are generally not taken even occasionally at personal level, e.g. children play with liquid metal of a busted thermometer. In view of plentiful current reports concerning low-dose mercury toxicity, its environmental infectivity should be taken into account. A few countries have consciousness operations; in some cases they are flourishing for instance. The Netherlands has declined thimerosol (merthiolate) revelation through pharmaceuticals (Van't Veen, 2001). Literature accounts that thimerosol has been evacuated from most of the children's vaccines, but it still exists in flu vaccines given to pregnant women, the aged, and to children in mounting countries (James et al., 2005). The administrations of relevant countries should guarantee mercury free air, water and food by making firm laws concerning polluting occupational units, ensuring proper clearance of mercury waste and cheering measures without utilization of mercury. Media and NGOs should hoist a voice against any carelessness on part of administration in addition to educating the ample about mercury cleanliness. There should be alertness among common public from abstention mercury fortified cosmetic products. Scientists should effort towards creating vaccines in which mercury is not a preservative.

REFERENCES

1. Agency for Toxic Substances and Disease Registration , US CDC. Toxicologic Profi les, Mercury. Health Effects Chapter. Available at http://www.atsdr. cdc.gov/toxprofi les/tp46-c2.pdf Accessed 17 Jul. 2006.
2. Ali, S.F., LeBel, C.P., Bondy, S.C., 1992. Reactive oxygen species formation as a biomarker of methylmercury and trimethyltin neurotoxicity. Neurotoxicology 13 (3), 637–648.
3. Alonso, J., Salgado, M.J., Garcia, M.A., Melgar, M.J., 2000. Accumulation of mercury in edible macrofungi: influence of some factors. Arch. Environ. Contam. Toxicol. 38 (2), 158–162.
4. Al-Sabti, K., Lloyd, D.C., Edwards, A.A. and Stegnar, P. 1992. A Survey of lymphocyte chromosomal damage in Slovenian workers exposed to occupational clastogens. *Mutat. Res.* **280**: 215-223.
5. Amorim, A.I.M., Mergler, D., Bahia, M.O., Dubeau, H., Miranda, D., Lebel, J., Burbano, R.R. and Lucotte, M. 2000. Cytogenetic damage related to low levels of methylmercury contamination in the Brazilian Amazon. *An Acad. Bras. Cienc.* **72**: 497-507.
6. Anderson, H.A., Hanrahan, L.P., Smith, A., Draheim, L., Kanarek, M., Olsen, J., 2004. The role of sport-fish consumption advisories in mercury risk communication: a 1998–1999 12-state survey of women age 18–45. Environ. Res. 95 (3), 315.
7. Anwar, W.A. and Gabal, M.S. 1991. Cytogenetic study in workers occupationally exposed to mercury fulminate. *Mutagenesis* **6**: 189-192.
8. Balogh, S.J., Huang, Y., Offerman, H.J., Meyer, M.L., Johnson, D.K., 2002. Episodes of elevated methylmercury concentrations in prairie streams. Environ. Sci. Technol. 36 (8), 1665–1670.
9. Bapu, T.C., Purohit, R.C., Sood, P.P., 1994. Fluctuation of trace elements during methylmercury toxication, and chelation therapy. Hum. Exp. Toxicol. 13 (12), 815–823.
10. Beldowski, J., Pempkowiak, J., 2003. Horizontal and vertical variabilities of mercury concentration and speciation in sediments of the Gdansk Basin, Southern Baltic Sea. Chemosphere 52 (3), 645–654.

11. Betti, C., Barale, R. and Pool-Zobel, B.L. 1993. Comparative studies on cytotoxic and genotoxic effects of two organic mercury compounds in lymphocytes and gastric mucosa cells of Sprague-Dawley rats. *Environ. Mol. Mutagen.* **22**: 172-180.
12. Betti, C., Davini, T. and Barale, R. 1992. Genotoxic activity of methyl mercury chloride and dimethyl mercury in human lymphocytes. *Mutation Research* **281**: 255-260.
13. Bonacker, D., Stoiber, T., Wang, M., Bohm, K.J., Prots, I., Unger, E., Thier, R., Bolt, H.M., Degen, G.H., 2004. Genotoxicity of inorganic mercury salts based on disturbed microtubule function. Arch. Toxicol. 78 (10), 575–583.
14. Cardenas, A., Roels, H., Bernard, A.M., Barbon, R., Buchet, J.P., Lauwerys, R.R., 1993. Markers of early renal changes induced by industrial pollutants. I. Application to workers eposed to mercury vapour. J. Ind. Med. 50, 17–27.
15. Chan, H.M., Egeland, G.M., 2004. Fish consumption, mercury exposure, and heart diseases. Nutr. Rev. 62 (2), 68–72.
16. Clarkson, T., 1992. Mercury: major issues in environmental health. Environ. Health Perspect. 100, 31–38.
17. Coccini, T., Randine, G., Candura, S.M., Nappi, R.E., Prockop, L.D., Manzo, L., 2000. Low level exposure to methylmercury modifies muscarinic cholinergic receptor binding characterstics in rat brain and lymphocytes: physiologic implications and new opportunities in biologic monitoring. Environ. Health Perspect. 108, 29–33.
18. Counter, S.A., Buchanan, L.H., 2004. Mercury exposure in children: a review. Toxicol. Appl. Pharmacol. 15 198 (2), 209–230.
19. Dabeka, R., McKenzie, A.D., Forsyth, D.S., Conacher, H.B., 2004. Survey of total mercury in some edible fish and shellfish species collected in Canada in 2002. Food Addit. Contam. 21 (5), 434–440.
20. De Flora, S., Benniceli, C. and Bagnasco, M. 1994. Genotoxicity of mercury compounds. A review. *Mut. Res.* **31**: 57-79.
21. De Rosis, F., Anastasio, S.P., Selvaggi, L., Beltrame, A., Moriani, G., 1985. Female reproductive health in two lamp factories: effects of exposure to inorganic mercury vapour and stress factors. Br. J. Ind. Med. 42 (7), 488–494.
22. Dickman, M.D., Leung, K.M., 1998. Mercury and organochlorine exposure from fish consumption in Hong Kong. Chemosphere 37 (5), 991–1015.
23. Dieguez-Acuna, F.J., Polk, W.W., Ellis, M.E., Simmonds, P.L., Kushleika, J.V., Woods, J.S., 2004. Nuclear factor _B activity determines the sensitivity of kidney epithelial cells to apoptosis: implications for mercury-induced renal failure. Toxicol. Sci. 82 (1), 114–122.
24. Dizdarevic, 2001. The influence of mercury production in idrija mine on the environment in the Idrija region and over a broad area, Mat. and Geoenviron., 48:, 56-64.
25. Dolbec, J., Mergler, D., Sousa, P.C.J., Sousa, M.S., Lebel, J., 2000. Methylmercury exposure affects motor performance of a riverine population of the Tapajos river, Brazilian Amazon. Int. Arch. Occup. Environ. Health 73 (3), 195–203.
26. Domagalski, J.L., Alpers, C.N., Slotton, D.G., Suchanek, T.H., Ayers, S.M., 2004. Mercury and methylmercury concentrations and loads in the Cache Creek watershed, California. Sci. Total Environ. 327 (1–3), 215–237.
27. Driscoll, C.T., Driscoll, K.M., Mitchell, M.J., Raynal, D.J., 2003. Effects of acidic deposition on forest and aquatic ecosystems in New York state. Environ. Pollut. 123 (3), 327–336.
28. Duffy, L.K., Rodgers, T., Patton, M., 1998. Regional health assessment relating to mercury content of fish caught in the Yukon kuskowim delta rivers system. Alaska Med. 40 (4), 75–77.
29. Ehrenstein, C., Shu, P., Wickenheiser, E.B., Hirner, A.V., Dolfen, M., Emons, H. and Obe, G. 2002. Methyl mercury uptake and associations with the induction of chromosomal aberrations in Chinese hamster ovary (CHO) cells. *Chem. Biol. Interact.* **141**: 259-74.
30. El-Demerdash, F.M., 2001. Effects of selenium and mercury on the enzymatic activities and lipid peroxidation in brain, liver, and blood of rats. J. Environ. Sci. Health B 36 (4), 489–499.
31. Ellingsen, D.G., Efskind, J., Berg, K.J., Gaarder, P.I., Thomassen, Y., 2000. Renal and immunologic markers for chloralkali workers with low exposure to mercuryvapor. Scand. J. Work Environ. Health 26 (5), 427–435.
32. Ellingsen,D.G., Bast-Pettersen, R., Efskind, J., Thomassen, Y., 2001. Neuropsychological effects of low mercury vapor exposure in chloralkali workers. Neurotoxicology 22 (2), 249–258.
33. EMEP (1999) Monitoring and modelling of lead, cadmium and mercury transboudary transport in the atmopshere of Europe. Joint report of EMEP Centers: MSC-E and CCC. EMEP report 3/99, July 1999.
34. Ernst, E., Lauritsen, J.G., 1991. Effect of organic and inorganic mercury on human sperm motility. Pharmacol. Toxicol. 68 (6), 440–444.
35. European Commission, SEC (2005)101 Communication from the Commission to the Council and the European Parliament on Community Strategy Concerning Mercury EXTENDED IMPACT ASSESSMENT (COM(2005) fi nal) 28.1.2005. p78.
36. Fonnum, F., Lock, E.A., 2004. The contributions of excitotoxicity, glutathione depletion and DNA repair in chemically induced unjury to neurones: exemplefied with toxic effects on cerebellar granule cells. J. Neurochem. 88 (3), 513–531.
37. Franchi, E., Loprieno, G., Ballardin, M., Petrozzi, L. and Migliore, L. 1994. Cytogenetic monitoring of fishermen with environmental mercury exposure. *Mut. Res.* **320**: 23-29.
38. Galal-Gorchev H., (1991). Dietary intake of pesticide residues, cadmium, mercury, and lead. *Food Additives and Contaminants*, 8:793–806.
39. Geelen, J.A., Dormans, J., 1990. The early effects of methylmercury on developing rat brain. Acta Neuropathol. (Berl.) 80 (4), 432–438.

40. Godfrey, M., Wojeik, D., Cheryl, K., 2003. Apolipoprotein-E as a potential biomarker for mercury neurotoxicity. J. Alzheimer's Dis. (5), 189–195.
41. Gothberg, A., Greger, M., Holm, K., Bengtsson, B.E., 2004. Influence of nutrient levels on uptake and effects of mercury, cadmium, and lead in water spinach. Environ. Qual. 33 (4), 1247–1255.
42. Goyer RA. "Toxic Effects of Metals," in Klaasen CD, Editor. Casarett and Doull's Toxicology; the Basic Science of Poisons. 5th Edition. McGraw-Hill: New York; 1996, pgs 691-736.
43. Grandjean, P., Weihe, P., 1998. Cognitive performance of children prenatally exposed to safe levels of methylmercury. Environ. Res. 77, 165–172.
44. Grandjean, P., Weihe, P., Nielson, J.B., 1994. Significance of intrauterine and postnatal exposures. Clin. Chem. 40 (7 pt 2), 1935–2000.
45. Grandjean, P., Weihe, P., White, R.F., 1995. Milestone development in infants exposed to methylmercury from human milk. Neurotoxicology 16 (1), 27–34.
46. Halliwell, B., 1994. Free radicals, antioxidants and human disease: curiosity, casuse or consequence? Lancet 344, 721–724.
47. Hammerschmidt, C.R., Sandheinrich, M.B., Wiener, J.G., Rada, R.G., 2002. Effects of dietary methylmercury on reproduction of fathead minnows. Environ. Sci. Technol. 1 36 (5), 877–883.
48. Hansen, J.C., Dasher, G., 1997. Organic mercury: an environmental threat to the health of dietary exposed societies? Rev. Environ. Health 12 (2), 107–116.
49. Hansteen, H., Ellingsen, D.G., Clausen, K.O. and Kjuus, H. 1993. Chromosome aberrations in chloralkali workers previously exposed to mercury vapour. *Scandinavian J. Work Environ. Health* **19**: 375-381.
50. Harada, M., 1968. Minimata Disease, Study Group of Minimata Disease. Kumamoto University, Japan, pp. 93–124.
51. Harada, M., Nakachi, S., Chen, T., Hamada, H., Ono, Y., Tsuda, T., Yanagida, K., Kizaki, T., Ohno, H., 1994. Monitoring of mercury pollution in Tanzinaia: relation between head hair mercury and health. Sci. Total Environ. 156 (3), 269–277.
52. Harada, M., Nakachi, S., Cheu, T., Hamada, H., Ono, Y., Tsuda, T., Yanagida, K., Kizaki, T., Ohno, H., 1999. Monitoring of mercury pollution in Tanzania: relation between head hair mercury and health. Sci. Total Environ. 227 (2–3), 249–256.
53. Harada, M., Nakachi, S., Tasaka, K., Sakashita, S., Muta, K., Yanagida, K., Doi, R., Kizaki, T., Ohno, H., 2001. Wide use of skin-lightening soap may cause mercury poisoning in Kenya. Sci. Total Environ. 269 (1–3), 183–187.
54. Hayes, J.A., 1983. Metal toxicity. In: Homburger, F., Hayes, J.A., Pelikan, E.W. (Eds.), A Guide to General Toxicology, vol. 5. Education Series, Cambridge, pp. 227–237.
55. Horvat, M., Nolde, N., Fajon, V., Jereb, V., Logar, M., Lojen, S., Jacimovic, R., Falnoga, I., Liya, Q., Faganeli, J., Drobne, D., 2003. Total mercury, methylmercury and selenium in mercury polluted areas in the province Guizhou, China. Sci. Total Environ. 304 (1–3), 231–256.
56. Hudson, C.A., Cao, L., Kasten-Jolly, J., Kirkwood, J.N., Lawrence, D.A., 2003. Susceptibility of lupus-prone NZM mouse strains to lead exacerbation of systemic lupus erythematosus symptoms. J. Toxicol. Environ. Health A 23 66 (10), 895–918.
57. Hussain, S., Rodgers, D.A., Duhart, H.M., Ali, S.F., 1998. Mercuric chloride-induced reactive oxygen species and its effect on antioxidant enzymes in different regions of rat brain. J. Environ. Sci. Health B 32 (3), 395–409.
58. Hussain, S., Rodgers, D.A., Duhart, H.M., Ali, S.F., 1998. Mercuric chloride-induced reactive oxygen species and its effect on antioxidant enzymes in different regions of rat brain. J. Environ. Sci. Health B 32 (3), 395–409.
59. IPCS/WHO (1990) Environmental health Criteria 101. Methylmercury. World Health Organisation, Geneva, 1990.
60. IPCS/WHO (1991) Environmental Health Criteria 118. Inorganic mercury, World Health Organisation, Geneva, 1991.
61. IRIS (1995) Mercury, elemental.
62. James, S.J., Slikker III, W., Melnyk, S., New, E., Pogribna, M., Jernigan, S., 2005. Thimerosal neurotoxicity is associated with glutathione depletion: protection with glutathione precursors. Neurotoxicology 26 (1), 1–8.
63. James, S.J., Slikker III, W., Melnyk, S., New, E., Pogribna, M., Jernigan, S., 2005. Thimerosal neurotoxicity is associated with glutathione depletion: protection with glutathione precursors. Neurotoxicology 26 (1), 1–8.
64. Janssens, E., Dauwe, T., Pinxten, R., Bervoets, L., Blust, R., Eens, M., 2003. Effects of heavy metal exposure on the condition and health of nestlings of the great tit (*Parus major*), a small songbird species. Environ. Pollut. 126 (2), 267–274.
65. Johnson, C.L., 2004. In the environment: sources, toxicities, and prevention of exposure. Pediatr. Ann. 33 (7), 437–442.
66. Kazantzis, G., 2002. Mercury exposure and early effects: an overview. Med. Lav. 93 (3), 139–147.
67. Kim, S.H., Johnson, V.J., Sharma, R.P., 2002. Mercury inhibits nitric oxide production but activates proinflammatory cytokine expression in murine macrophage: differential modulation of NF-_B and p38 MAPK signaling pathways. Nitric Oxide 7 (1), 67–74.
68. Langseth, L., 1993. From the editor: antioxidants and diseases of brain. Antioxidant Vitamin News Lett. 4, 3.
69. Lanka, M., Panda, K.K., Panda, B.B., 1992. Monitoring and assessment of mercury pollution in the vicinity of chloralkali plant. Bioconcentration of mercury in situ aquatic and terrestrial plants at Ganjam, India. Arch. Environ. Contam. Toxicol. 22, 195–202.
70. Lebel, J., Mergler, D., Lucotte, M., Amorim, M., Dolbec, J., 1998. Neurotoxic effects of low-level methylmercury contamination in the Amazonian Basin. Environ. Res. 79 (1), 20–32.

71. 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.
72. Lee, D.A., Lopez-Alberola, R., Bhattacharjee, M., 2003. Childhood autism: a circuit syndrome? Neurologist 9 (2), 99–109.
73. Leonard, A., Jacquet, P., 1983. Mutagenicity and teratogenicity of mercury compounds. Mutat. Res. 114 (1), 1–18.
74. Levine, S., 2004. Who will stop the mercury rain? US News World Rep. 136 (11), 70–71.
75. Mabille, V., Roels, H., Jacquet, P., Léonard, A. and Lauweris, R. 1984. Cytogenetic examination of leucocytes of workers exposed to mercury vapour. *International Archiv. Occup. Environ. Health* **53**: 257-260.
76. Magara Y et al., (1989). Effects of volcanic activity on heavy metal concentration in deep well water. In: *Technical Papers, Water Nagoya '89; 7th Regional Conference and Exhibition of Asia-Pacific, Nagoya, Japan*. International Water Supply Association, pp. 411–419.
77. Malcolm, E.G., Keeler, G.J., Lawson, S.T., Sherbatskoy, T.D., 2003. Mercury and trace elements in cloud water and precipitation collected on Mt. Mansfield, Vermont. J. Environ. Monit. 5 (4), 584–590.
78. Malcolm, E.G., Keeler, G.J., Lawson, S.T., Sherbatskoy, T.D., 2003. Mercury and trace elements in cloud water and precipitation collected on Mt. Mansfield, Vermont. J. Environ. Monit. 5 (4), 584–590.
79. Mano, Y., Takayanagi, T., Abe, T., Takizawa, Y., 1990. Amyotrophic lateral sclerosis and mercury-preliminary report. Rinsho Shinkeigaku 30 (11), 1275–1277.
80. Marcelo, O., Dietricha, C.E., Mantesea, G.A., Diogo, O.S., Marcelo, F., 2005. Motor impairment induced by oral exposure to methylmercury in adult mice. Environ. Toxicol. Pharmacol. 19 (1), 169–175.
81. Markovich, D., James, K.M., 1999. Heavy metals mercury, cadmium, and chromium inhibit the activity of the mammalian liver and kidney sulfate transporter sat-1. Toxicol. Appl. Pharmacol. 154 (2), 181–187.
82. Marsh, D.O., Turner, M.D., 1995. Foetal methylmercury studying Peruvian fish eating population. Neurotoxicology 16 (4), 717–726.
83. Mathieson, P.W., 1995. Mercury: god of TH2 cells. Clin. Exp. Immunol.102 (2), 229–230.
84. Mathieson, P.W., 1995. Mercury: god of TH2 cells. Clin. Exp. Immunol.102 (2), 229–230.
85. Murata, K., Weihe, P., Budtz-Jorgensen, E., Jorgensen, P.J., Grandjean, P., 2004. Delayed brainstem auditory evoked potential latencies in 14-year-old children exposed to methylmercury. J. Pediatr. 144 (2), 177–183.
86. Murray, M., Holmes, S.A., 2004. Assessment of mercury emissions inventories for the Great Lakes states. Environ. Res. 95 (3), 282–297.
87. Mutter, J., Naumann, J., Sadaghiani, C., Schneider, R., Walach, H., 2004. Alzheimer disease: mercury as apathogrnetic factor and apolipoprotein-E as a moderator. Neuroendocrinol. Lett. 25 (5), 275–283.
88. Nagy, I.Z., 2001. On the true role of oxygen free radicals in the living state, aging, and degenerative disorders. Ann. NY 928, 187–199.
89. National Research Council (NRC) 2000. Committee on the Toxicological Effects of Methylmercury, Board on Environmental Studies and Toxicology. Toxicological Effects of Methylmercury. The National Academy Press, Washington, DC, USA. pp. 33-35.
90. Nicholson, J.K., Kendall, M.D., Osborn, D., 1983. Cadmium and mercury nephrotoxicity. Nature 304 (5927), 633–635.
91. 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.
92. Noor, R., Mittal, S., Iqbal, J., 2002. Superoxide dismutase applications and relevance to human diseases. Med. Sci. Monit. 8 (9), 210–215.
93. Ogura, H., Takeuchi, T. and Morimoto, K. 1996. A comparison of the 8- hydroxydeoxyguanosine, chromosome aberrations and micronucleus techniques for the assessment of the genotoxicity of mercury compounds in human blood lymphocytes. *Mutat. Res.* **340**: 175-182.
94. Olivieri, G., Novakovic, M., Savaskan, E., Meier, F., Baysang, G., Brockhaus, M., Muller-Spahn, F., 2002. The effects of _-estradiol on SHSY5Y neuroblastoma cells during heavy metal induced oxidative stress, neurotoxicity and beta-amyloid secretion. Neuroscience 113 (4), 849–855.
95. Ortega, H.G., Lopez, M., Takaki, A., Huang, Q.H., Arimura, A. and Salvaggio, J.E. 1997. Neuroimmunological effects of exposure to methylmercury forms in the Sprague-Dawley rat. Activation of the hypothalamic-pituitaryadrenal axis and lymphocyte responsiveness. *Toxicol. Indust. Health* **13**: 57-66.
96. Palheta, D., Taylor, A., 1995. Mercury in environmental and biological samples from a goldmining area in the Amazon region of brazil. Sci. Total Environ. 168 (1), 63–69.
97. Prochazkova, J., Sterzl, I., Kucerova, H., Bartova, J., Stejskal, V.D., 2004. The beneficial effect of amalgam replacement on health in patients with autoimmunity. Neuro. Endocrinol. Lett. 25 (3), 211–218.
98. Rajanna, B., Hobson, M., 1995. Influence of mercury on uptake of [3H] dopamine and [3H] norepinephrine by rat brain synaptosomes. Toxicol. Lett. 27 (1–3), 7–14.
99. Rice, D., Barone Jr., S., 2000. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ. Health Perspect. 108 (Suppl. 3), 511–513.
100. Rocha, J.B., Rocha, L.K., Emanuelli, T., Pereira, M.E., 2001. Effect of mercuric chloride and lead acetate treatment during the second stage of rapid post-natal brain growth on the behavioral response to chlorpromazine and on _-ALA-D activity in weaning rats. Toxicol. Lett. 125 (1–3), 143–150.
101. Satoh, H., 2000. Occupational and environmental toxicology of mercury and its compounds. Ind. Health 38 (2), 153–164.

102. Schumacher, M., Batiste, J., Bosque, M.A., Domingo, J.L., Corbella, J., 1994. Mercury concentrations in marine species from the coastal area of Tarragona Province, Spain. Dietary intake of mercury through fish and seafood consumption. Sic. Total Environ. 156 (3), 269–273.
103. Schurz, F., Sabater-Vilar, M. and Fink-Gremmels, J. 2000. Mutagenicity of mercury chloride and mechanisms of cellular defence: the role of metal-binding proteins. *Mutagenesis* **15**: 525-530.
104. Snyder, R.D., 1971. Congenital mercury poisoning. New Engl. J. Med. 284, 1014–1016.
105. Soleo, L., Urbano, M.L., Petrera, V., Ambrosi, L., 1990. Effects of low exposure to inorganic mercury on psychological performance. Br. J. Ind. Med. 47 (2), 105–109.
106. Soleo, L., Vacca, A., Vimercati, L., Bruno, S., Di, L.M., Zocchetti, C., Stefano, R., Candilio, G., Lasorsa, G., Franco, G., Foa, V., 1997. Minimal immunological effects on workers with prolonged low exposure to inorganic mercury. Occup. Environ. Med. 54 (6), 437–442.
107. Soleo, L., Vacca, A., Vimercati, L., Bruno, S., Di, L.M., Zocchetti, C., Stefano, R., Candilio, G., Lasorsa, G., Franco, G., Foa, V., 1997. Minimal immunological effects on workers with prolonged low exposure to inorganic mercury. Occup. Environ. Med. 54 (6), 437–442.
108. Soo, Y.O., Chow, K.M., Lam, C.W., Lai, F.M., Szeto, C.C., Chan, M.H., Li, P.K., 2003. A whitened face woman with nephrotic syndrome. Am. J. Kidney Dis. 41 (1), 250–253.
109. Sorensen, N., Murata, K., 1999. Prenatal methylmercury exposure as a cardiovascular risk factor at 7 years of age. Epidemiology 10 (4), 370–375.
110. St-Amand, L., Gagnon, R., Packard, T.T., Savenkoff, C., 1999. Effect of inorganic mercury on the respiration and swimming activity of the shrimp larvae, *Pandalus borealis*. Comp. Biochem. Physiol. C: Pharmacol. Toxicol. Endocrinol. 122 (1), 33–43.
111. Strenzke, N., Grabbe, J., Plath, K.E., Rohwer, J., Wolff, H.H., Gibbs, B.F., 2001. Mercuric chloride enhances immunoglobulin E-dependent mediator release from human basophils. Toxicol. Appl. Pharmacol. 174 (3), 257–263.
112. The Hindustan Times. Polluting India's groundwater. September 2 1999. www.hindustantimes.com.
113. Uversky, V.N., Li, J., Fink, A.L., 2001. Metal-triggered structural transformations, aggregation, and fibrillation of human _-synuclein. A possible molecular NK between Parkinson's disease and heavy metal exposure. J. Biol. Chem. 276 (47), 44284–44296.
114. Van't Veen, A.J., 2001. Vaccines without thiomersal: why so necessary, why so long coming? Drugs 61 (5), 565–572.
115. Via, C.S., Nguyen, P., Niculescu, F., Papadimitriou, J., Hoover, D., Silbergeld, E.K., 2003. Low-dose exposure to inorganic mercury accelerates disease and mortality in acquired murine lupus. Environ. Health Perspect. 111 (10), 1273–1277.
116. Vimercati, L., Santarelli, L., Pesola, G., Drago, I., Lasorsa, G., Valentino, M., Vacca, A., Soleo, L., 2001. Leukocytes in workers exposed to low levels of Monocyte-macrophage system and polymorphonuclear metallic mercury. Sci. Total Environ. 10 270 (1–3), 157–163.
117. Vimercati, L., Santarelli, L., Pesola, G., Drago, I., Lasorsa, G., Valentino, M., Vacca, A., Soleo, L., 2001. Leukocytes in workers exposed to low levels of Monocyte-macrophage system and polymorphonuclear metallic mercury. Sci. Total Environ. 10 270 (1–3), 157–163.
118. Ware GW, ed. (1989). Mercury; USEPA Office of Drinking Water health advisories. *Reviews of Environmental Contamination and Toxicology*, 107:93–102.
119. Westphal, G., Hallier, E., 2003. Mercury in infants given vaccines containing thiomersal. Lancet 361 (93–58), 699.
120. Wilkinson, L.J., Waring, K.H., 2002. Cysteine dioxygenase: modulation of expression in human cell lines by cytokines and control of sulphate production. Toxicol. In Vitro 16 (4), 481–483.
121. World Health Organisation, 2005. Mercury in Health Care, Policy Paper, August 2005, www.healthcarewaste.org
122. Yasutake, A., Nakano, A., Miyamoto, K., Eto, K., 1997. Chronic effects of methylmercury in rats. I. Biochemical aspects. Tohoku J. Exp. Med. 182 (3), 185–196.
123. Yokoo, E.M., Valente, J.G., Grattan, L., Schmidt, S.L., Platt, I., Silbergeld, E.K., 2003. Low level methylmercury exposure effects neuropsychological function in adults. Environ. Health 2 (1), 8.
124. Zalpus, R.K., 2000. Mol. interact. Mercury Kidney 52 (1), 113–144.
125. Zhang, M.Q., Zhu, Y.C., Deng, R.W., 2002. Evaluation of mercury emissions to the atmosphere from coal combustion, China. Ambio 31 (6), 482–484.