Toxic Effects Of Mercury: A Review Of Contemporary Understanding

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Abstract: The danger of methylmercury poisoning appears to be slight when the environment is not directly contaminated with methylmercury. Sediments rapidly bind mercury and decrease its availability to aquatic organisms. Sediments further have a greater propensity to demethylate than to methylate mercury. In noncontaminated aquatic ecosystems, the concentrations of methylmercury and inorganic mercury are many times lower than those that have been found to cause toxicity, even in the most sensitive organisms. Methylmercury bound to protein is comparatively less toxic than methylmercury salts, and selenium present in this protein appear to be one of the major detoxifying agents for methylmercury. This is particularly important in seafood, where there is an excess of selenium compared to methylmercury. Neurotoxicity induced by methylmercury (MeHg) increases the formation of reactive radicals and accelerates free radical reactions. This review summarizes recent findings in the MeHg- induced formation of free radicals and the role of oxidative stress in its neurotoxicity. Oxidative stress on CNS can produce damage by several interacting mechanisms, including mitochondrial damage with increase in intracellular free Ca2+, activation and inhibition of enzymes, release of excitatory amino acids, metallothioneins expression, and microtubule disassembly.

[Shabnum Nabi**. Toxic Effects Of Mercury: A Review Of Contemporary Understanding.** *Researcher* 2015;7(2):28-43]. (ISSN: 1553-9865). http://www.sciencepub.net/researcher. 6

Keywords: Methylmercury, Toxicity, Review

Introduction

The leperous distilment; whose effect
Holds such an enmity with blood of man
That swift as quicksilver it courses through
The natural gates and alleys of the body,
And with a sudden vigor it doth posset
And curd, like eager droppings into milk,
he thin and wholesome blood:so did it mine;

[W. Shakespeare: Hamlet, Prince Of Denmark. Act I, Scene 5 (1600)]

The use of mercury in manufacturing and medical purposes has been recorded since classical times in china, Egypt, Greece and Rome. Concomitantly, poisoning by this metal has also been reported since at 2000 years ago, such as in Pliny the Elder's (23-79 AD) *Naturae Historiarum Libri,* which refers to cinnabar (HgS) poisoning among miners at Almaden, Spain **(Rackham, 1952)**. Mercury as a poison has been documented for many centuries.

Historically, mercury poisoning has been mainly occupational and iatrogenic. In 18^{th} century Ramazinni described the occupational diseases developed by workers exposed to mercury **(Goldwater, 1936)**. Elemental and inorganic mercury both continue to be widely used in industrial applications. In 16^{th} century, calomel (Hg_2Cl_2, mercurous chloride) was introduced as a treatment for syphilis **(De Laguna, 1955 and Sigerest, 1996)**. Medical administration of mercury was largely practiced until 20^{th} century. It was present in cathartic, antisyphilitic, antihelminthic, diuretic, and many other preparations. It is still used in Chinese herbal medicines, in the form of calomel or even cinnabar, according to the traditional pharmacopoeia **(Ernst and Coon, 2001)**. Some of these preparations which have become popular in western countries exceed the maximum concentrations permitted by regulatory bodies **(World Health Organization, 1991)**. Dental mercury amalgam, which releases low amounts of mercury (elemental mercury vapor and inorganic ions), was first recorded in china in 600 AD. The safety of mercury amalgam has long been a source of controversy **(Dodes, 2001 and Clarkson, 2002)**.

Mercury is a ubiquitous contaminant, and a range of chemical species is generated by human activity and natural environmental change. Elemental mercury and its inorganic and organic compounds have different toxic properties, but all of them are considered hazardous in human exposure. In an equimolecular exposure basis, organomercurials with a short aliphatic chain are the most harmful compounds and they may cause irreversible damage to the nervous system. Methylmercury (CH_3Hg+) is the most studied following the neurotoxic out breaks identified as Minimata disease and the Iraq poisoning. The first description of CNS pathology dates from 1954. Since then, the clinical neurology, the neuropathology and the mechanisms of neurotoxicity

of organomercurials have been widely studied. The high thiol reactivity of CH_3Hg+, as well as all mercury compounds, has been suggested to be basis of their harmful biological effects.

Thiol poisons, especially mercury and its compounds, reacting with SH groups of proteins lead to the lowered activity of various enzymes containing sulfhydryl groups. This produces a series of disruptions in the functional activity of many organs and tissues of the organism (Trakhtenberg, 1964)

Methylmercury Exposure

Methylmercury is a commonly encountered form of environmental mercury due both to its widespread use as well as to biomethylation by aquatic organisms. Exposure to methylmercury in the food chain has lead to catastrophic episodes of intoxication **(Takeuchi *et al*., 1962 and Bakir *et al*., 1973)**, and exposure to inorganic and organomercurials still poses a significant toxicological problem **(Adams *et al*., 1983 and Hansen, 1990)**. Poisoning has occurred after both acute and chronic exposure to MeHg. Chronic poisoning with MeHg typically results in ataxia, disturbances of sensory and visual function, and extremity weakness **(Chang, 1980)**. Mercury leads the pack in the potency of its toxicity and in the pervasiveness of its presence in the environment, medicine and dentistry. Doctors who administer mercury laden vaccines and dentists who plant highly toxic mercury in people's mouths in the form of dental amalgam cannot seem to see the forest from the trees and curb their use of it. It is reasonable to assume a direct correlation between rising environmental mercury levels, mercury exposure through dental amalgam, heavy fish consumption and exposure to mercury in vaccines with the rapidly expanding diabetic pandemic, not to mention the host of drugs and even chemicals put in to foods that are part of the diabetic equation.

Because Glycemic Regulation Is One Of The Body'S Most Central Homeostatic Mechanisms, Mercury'S Attack Is Most Problematic, Even At Low Concentrations, And Indicates That It Is Playing A Great Role In The Dramatic Rise In Diabetes. (IMVA, 2006)

In contrast to the historical exposure to mercury, in the mid-20th century there appeared a new and unexpected form of mercury poisoning resulting from the environmental exposure to short-chain alkyl mercury compounds. Although organomercurials had been known since the 19th century, important poisoning outbreaks occurred in the 20th century. These organic forms of mercury were widely used as anti-fungicides for seed and cereal crop preservation and affected the general population mainly through contaminated food. Furthermore, organomercury compounds synthesized for various purposes have also exposed the population to these new agents **(World Health Organization, 1989; 1990 and 1991)**.

Sources Of Exposure

According to the Agency for Toxic Substances and Disease Registry (ATSDR) of the U.S. Department of Health Services, mercury is listed as the third-most frequently found (lead and arsenic are first and second), and the most toxic substance in the United States **(ATSDR, 2001)**. This figure originates from the U.S. Government's Priority List of Hazardous Substances. This list includes, in order of priority, substances that have been at hazardous waste sites on the National Priorities List (Superfund sites) that "pose the most significant potential threat to human health due to their known or suspected toxicity and the frequency of exposure." Of 1,467 hazardous waste sites listed on the National Priorities List in 1998, toxic levels of mercury were identified in 714. Mercury toxicity is also considered the second-most common cause of acute heavy metal poisoning, with 3,596 cases reported in 1997 by the American Association of Poison Control Centers **(Ozuah, 2000)**.

Annual worldwide emissions of mercury into the atmosphere have been estimated at 2,200 metric tons **(Ferrara *et al*., 2000)**. One-third of these emissions are estimated to originate from natural sources (volcanic eruptions and decay of mercury-containing sediments) and two-thirds from man-made sources. Twenty-five percent of worldwide emissions come from fossil fuel combustion. In the United States, 26 percent (64.7tons/year) of atmospheric mercury emissions come from medical waste incineration, such as cremation **(ATSDR, 1999)**.

There are currently 1,782 advisories (one per body of water) issued by the U.S.Environmental Protection Agency (EPA) in 41 states in the united states restricting the consumption of any locally caught fish or shellfish due to their mercury content. Sixteen states have issued statewide or statewide-coastal advisories recommending restricting the consumption of fish caught in the state or along the coastline due to methylmercury contamination **(ATSDR, 1999)**. The Environmental Working Group, in a presentation to the Food Advisory Committee of the U.S. Food and Drug Administration (FDA), recently presented data warning of the consequences for fetuses of women who follow the current FDA'S fish consumption advisory and eat 12 ounces of "safe" fish per week. The Environmental Working Group estimates that more than 25 percent of children *in utero* in the United States would be exposed to levels

of mercury above the EPA safe reference dose (0.1µg methylmercury/kg body weight/day) for at least 30 days during gestation and would have an increased risk for neurological damage **(EWG, 2001)**.

The ATSDR considers anyone who lives in close proximity to a former mercury mining site, recycling facility, municipal or medical incinerator, or coal-fired electric generating plant to be at risk for mercury toxicity. Anyone who routinely consumes contaminated fish, subsistence hunters who consume meat or organ tissues of marine mammals or feral wildlife, individuals with a "large number" of dental amalgams, pregnant or nursing women (and their developing fetuses and breast-fed babies), those who use consumer products containing mercury (skin-lightening creams or antiseptic facial products, mercury-containing diuretics or laxatives, and teething powders), or those living or working in buildings painted with mercury-containing latex paint are also considered at significant risk. Mercury-containing latex paint was removed from paint manufacturing in 1991 but may still be available in the reserve inventories of contractors and warehouses **(ATSDR, 1999)**.

Inspite Of Manifold Privilege Of Consistent Fish Gobbling, It Oddments A Grave Informant Of Mercury Exposure To Man Leading To Cataclysm Happenings Of Intoxication (Rizvi, Et Al., 2005)

Methylmercury In The Environment

Mercury is found in the environment in three basic states: elemental mercury or mercury vapor, inorganic mercury, and organic mercury (ethyl-, methyl-, alkyl-, or phenylmercury). Each form has an individual toxicological profile and metabolic fate. The most frequent sources of mercury exposure are open to debate. On an individual exposure basis, the estimated intake and retention of elemental mercury vapor (from dental amalgams and atmospheric pollution) in non-occupationally exposed individuals has a much broader range (3.9-21.0 µg/day) than either inorganic (4.3 µg/day) or methylmercury (1-6µg/day) exposure **(National Research Council, 2000)**.

1. **Mercury In Sediments**

When mercury is first deposited in sediment, it is rapidly and strongly complexed to various components of the sediment. Mercury is most strongly bound to sulfur-containing organic and inorganic particles. In surface sediments, up to 62% of the mercury present is bound to these types of particles **(Walters and Wolery, 1974)**. To a lesser extent, mercury is also bound strongly to clays, mineral sediments containing iron and manganese oxides, and to fine sands **(Reimers and Krenkel, 1974)**. Only a small portion of mercury in sediments is released into the pore water. In this interstitial water, mercury appears to be associated primarily with organic acids such as fulvates and humates with little or none of the mercury in the unbound form **(Fitzgerald and Lyons, 1973)**. Of mercury present in deeper sediments, 65-75% is also bound to organic acids **(Walters and Wolery, 1974)**.With or without agitation; the rate of release of mercury from sediments is hardly measurable **(Reimers and Krenkel, 1974)**.

2. **Methylation**

Because of the greater toxicity of methylmercury as compared to nonalkylmercury compounds, great attention has been directed toward the formation and passage of methylmercury in aquatic sediments. Organisms present in many types of sediments are able to methylate inorganic mercury under ideal laboratory conditions **(Jernelov, 1969 and Gillespie, 1972)**. Methylating organisms that have been isolated grow only under very strict conditions: they are microaerophilic, being killed if the sediment is agitated; they grow only in a narrow pH range; and, even under ideal conditions, they are slow growers **(Spangler *et al.*, 1972)**. Methylation appears to occur only in the top 1-2 cm of sediment. Burrowing sediment organisms, however, can expose mercury present at deeper layers to the methylating process **(Jernelov, 1970)**. When the pH of sediment is raised, mercury is bound less tightly to organic acids and sulfide complexes and is more readily available for methylation **(Matsumura *et al.*, 1972)**. When mercury is bound to sulfides, there is little demonstrable methylation under anaerobic conditions. Even under aerobic conditions the rate of methylation is only about 0.001% that for mercuric chloride under the same conditions **(Fagerstrom and Jernelov, 1971)**. Methylation even under ideal conditions can at best convert less than 1.5% of the inorganic mercury present per month **(Jensen and Jernelov, 1969 and Jacobs and Keeney, 1974)**.

3. **Demethylation**

Little or no methyl mercury, however, is found in sediments **(Andren and Harriss, 1973)**. This might be explained by methylmercury's lesser tendency to be absorbed by sediment constituents and greater tendency to be desorbed than inorganic mercury. Methylmercury tends to be bound only to sulfur containing sediment particles, and, even in sulfur-containing sediments, the rate of absorption is one half to one third that for inorganic mercury salts. The rate of desorption of methylmercury from any type of sediment is from 10-1000 times that for inorganic mercury **(Reimers and Krenkel, 1974)**.

Another possible explanation for not finding appreciable amounts of methyl mercury in sediments is that there is a greater tendency for sediments to

demethylate than to methylate mercury compounds. As much as 15% of bacterial isolates from mercury containing sediments have been found to demethylate mercury **(Spangler *et al*., 1973)**. These organisms are hardly, being able to demethylate both aerobically and anaerobically. The demethylation process is rapid, with 100% of any methylmercury added to the cultures being demethylated within 4 days and, in some cases, within 1 day **(Spangler *et al*., 1972 and Spangler *et al*., 1973)**. A majority of the organisms isolated that demethylate mercury have been identified as belonging to the *Pseudomonas species* **(Spangler *et al*., 1972)**.

4. **Methylmercury In Aquatic Food Chains**

Mercury is avidly taken up by lower biologic orders in aquatic ecosystems **(Huckabee and Goldstein, 1973, Fagerstrom and Jernelov, 1974 and Biesinger, 1974)**. Greater than 75% of methylmercury present in these lower orders is taken up directly from water. Even in higher orders, such as predatory fish, as much as 60% of methylmercury present is taken up from water **(Jernelov and Lann, 1971)**. At each higher trophic level the concentration of methylmercury usually increases **(Matida and Kumada, 1969 and Jernelov and Lann, 1971)**. In fish this might be explained by methymercury's prolonged half-life. Methylmercury is rapidly cleared from the aquatic environment and bound mostly to muscle tissue. When exposedto similar concentrations of methylmercury and inorganic mercury, fish are able to absorb methylmercury from water 100 times as fast as the inorganic mercury and are able to absorb five times as much methylmercury from food as compared to inorganic mercury **(De Freitas *et al*., 1974)**. Once absorbed, methylmercury is retained two to five times as long as inorganic mercury. With increased fish size, both the uptake of methylmercury from the environment and the clearance of methylmercury from the fish are decreased. Because, however, methylmercury is strongly bound to muscle, methylmercury does accumulate appreciably with increased muscle mass and increased duration of exposure. With fish of the same size and with similar conditions of exposure, the rate of uptake and clearance of methylmercury is approximately the same in all species **(De Freitas *et al*., 1974)**.

Direct methylation of inorganic mercury by members of higher biologic orders has been postulated to account for the higher methylmercury levels found in these orders. For instance, liver homogenates of certain species of tuna and trout have been found to methylate mercury **(Imura *et al*., 1972)**. In vivo experiments, however, where fish and rats have been exposed to methylmercury, have suggested the occurrence of demethylation, with a larger fraction of the mercury in the liver and kidneys being in the form of inorganic mercury **(Burrows *et al*., 1974 and Norseth and Clarkson, 1970)**.

Methylmercury Toxicity

The studies about Methylmercury toxicity became ubiquitous and diversified since the outbreak of environmental catastrophes such as those in Minamata (1950s) and Niigata (1960s). In such episodes, as a consequence of Methylmercury exposure, the exposed individuals exhibit severe forms of neurological disease which include a collection of cognitive, sensory, and motor disturbance **(Eto, 2000 and Takeuchi *et al*., 1979)**.

The studies on Methylmercury toxicity have tried to evaluate its impact on several ecosystems around the world including places in Japan, Iraq, Canada, Africa, Brazilian Amazon and India **(Malm, 1998, Harada *et al*., 2001 and Agarwal *et al*., 2007)**, as well as to understand its toxicological effect on biological systems. Methylmercury was firstly recognized as a potent neurotoxicant for the adult nervous system in studies performed on exposed workers of a chemical factory in England **(Hunter *et al*., 1940 and Hunter and Russell, 1954)**. Later, its importance as a neurotoxicant for the nervous system during development was recognized in the Minimata's outbreak **(Eto, 2000 and Takeuchi *et al*, 1979)**. Since then, several studies of exposed human populations as well as experiments with laboratory animals demonstrated that exposure to toxic levels of Methylmercury during pre- and post-natal life causes neurological abnormalities, cognitive impairment, and behavioral disturbance **(Steuerwald *et al*., 2000 and Cordier *et al*., 2002)**. Methylmercury vulnerability of the developing brain reflects the ability of lipophilic methylmercury to cross the placenta and to concentrate in the central nervous system (CNS) once the blood-brain barrier is not fully developed in the prenatal period **(Castoldi *et al*., 2001 and Lepham *et al*., 1995)**.

1. **Membrane Interactions And Transporter Mediated Methylmercury Toxicity**

Methylmercury quickly diffuses across membranes without significant partitioning in lipid bilayers. Thus, it has been proposed that Methylmercury toxicity is mediated by Methylmercury membrane leakage **(Lakowicz and Anderson, 1980)**. However, it has also been suggested that the potential of Methylmercury to increase oxidative events leading to cell damage is controlled by Methylmercury binding to membrane transporters. Methylmercury absorption, distribution, and excretion are commonly mediated by plasma membrane protein transporters **(Sekine *et al*., 2000)**. In addition, it has been possible to investigate at molecular level the mechanisms of Methylmercury transport through membrane transporters with broad

substrate selectivity. These transporters are known as "Multispecific". The main route for Methylmercury transmembrane transport seems to be the amino acid transport system L, which transports large amino acids **(Aschner and Aschner, 1990)**.

It has been proposed that Methylmercury-cystein conjugate is the pathway whereby Methylmercury exerts its toxicity **(Morkzan *et al*., 1995)**. Once the presence of such transporters is crucial for toxicity to occur at least through this mechanism, transporter inhibition is expected to be beneficial to prevent disorders caused by Methylmercury toxicity.

2. **Cellular Mechanism To Methylmercury Intoxication**

Calcium homeostasis: Calcium ion (Ca^{2+}) plays a critical role in CNS cell death. Ca^{2+} increase beyond physiological levels activates catabolic enzymes such as phospholipases, proteases and endonucleases, causes mitochondrial dysfunction, and disturbs cytoskeletal organization. Several lines of evidence indicate that at low concentrations MeHg disrupts Ca^{2+} homeostasis, increasing its intracellular level in a number of experimental situations, including primary culture of cerebellar granule cells **(Limke *et al*., 2003)**. This effect has all the potential to disrupt the synaptic function and impair the neural development **(Marty and Atchison, 1998)**.

3. **Mitochondrial Damage Induced By Methylmercury**

Mercury Can Induce Apoptosis In Human T Lymphocytes. The Target Organelle Was The Mitochondrion And That Induction Of Oxidative Stress Led To Activation Of Death-Signaling Pathways (Shenker Et Al., 1999)

Mitochondria are the main intracellular sites for reactive oxygen production and one of the most susceptible targets for radical species to exert their actions. Importance of mitochondria for Methylmercury toxicity was recognized from studies performed both in vivo and in vitro. In vivo exposure to Methylmercury causes its accumulation inside mitochondria followed by a series of biochemical changes in these organelles **(Denny and Atchison, 1994)**. These effects are similar to those observed in studies of mitochondrial respiratory chain inhibition **(Mori *et al*., 2007)**.

Rats exposed to Methylmercury in vivo display neurological symptoms after a latent period. Mitochondrial function (as measured by oxygen consumption of brain slices) is impaired during the symptomatic phase but not during the latent phase **(Yoshino *et al*., 1966B)**. Although MeHg concentrations are maximal during the latent phase, the effects of MeHg on mitochondria may be indirect as they are preceded by inhibition of protein synthesis **(Yoshino *et al*., 1966A and Yoshino *et al*., 1966B)**.

Synaptosomes from rats treated with MeHg and from naive rats exposed to MeHg in vitro have reduced rates of respiration **(Verity *et al*., 1975)**. This effect is blocked by removal of K^+, suggesting that there is an increase in the K^+ permeability of the inner mitochondrial membrane. Alterations in respiration are also observed in guinea pig brain slices at slightly higher concentrations of MeHg **(Fox *et al*., 1975)**. The decrease in respiratory rates may be due to MeHg-induced inhibition of the tricarboxylic acid cycle. This is consistent with earlier work in which in vivo Methylmercury exposure reported decreased succinate dehydrogenase activity **(Yoshino *et al*., 1966B)**. High MeHg levels cause impairment of mitochondrial function as the organelle exhibits a membrane permeability transition state. MeHg exposure induces a decrease in the activity of enzymes of the mitochondrial energy metabolism such as cytochrome C oxidase (CCO), superoxide dismutase (SOD) and succinate dehydrogenase (SDH) **Yoshino *et al*., 1966B**. This is probably due to the decrease in the respiratory rate caused by MeHg-induced inhibition of the tricarboxylic acid cycle. This is consistent with previous work showing that MeHg exposure decreases succinate dehydrogenase activity **(Naganuma *et al*., 1998)**. In vitro MeHg exposure of isolated mitochondria from rat liver inhibits electron transport and phosphorylation, increases K^+ permeability, and dissipates the mitochondrial membrane potential (MMP) **Sone *et al*., 1977**. Loss of MMP results in efflux of mitochondrial Ca^{+2} and inhibition of mitochondrial Ca^{+2} uptakes **(Levesque and Atchison, 1991)**. In addition, MeHg exposure in isolated rat brain mitochondria causes ATP-dependent and independent decrease in Ca^{+2} uptake and increase in Ca^{+2} effluxes from mitochondria (Denny *et al*., 1993). Although mitochondria participate in Ca^{+2} buffering at relatively elevated Ca^{+2}, the affinity of the uniport carrier for Ca^{+2} is low, and mitochondria may play only a minor role in buffering Ca^{+2} under normal conditions **(Levesque and Atchison, 1991)**.

4. **Microtubule Network**

MeHg seems to interact with cytoplasmic cytoskeletal components, including microtubules **(Sager *et al*., 1983)**. In vitro studies demonstrated that MeHg presents high affinity for tubulin sulphydryl groups (-SH), depolymerizing cerebral microtubules and directly inhibiting their assembly **(Sager *et al*., 1983 and Vogel *et al*., 1989)**. In addition, several works reported that MeHg promotes microtubule disruption in a number of cell models, including human fibroblasts **(Sager *et al*., 1983)**, neuroblastoma, and glioma cells **(Prasad *et al*., 1979 and Miura *et al*., 1984)**.

***5.* Methylmercury And Neurotransmitter System**

Several metal compounds have been shown to interfere with neurotransmission. MeHg directly affects the mechanisms of neurotransmission, including release and uptake of neurotransmitters, enzymatic neurotransmitter metabolic inactivation, and post-synaptic events associated with receptor activation **(Atchison, 2005)**. Some neurotoxicants indirectly interfere with neurotransmission by interacting, for example, with energy metabolism, sodium channels, or ATPases. Furthermore, changes of any parameter of neurotransmission can be the result of neuronal death due to cytotoxic effects of the neurotoxicants **(Orrenius and Nicotera, 1994)**.

The rising of extracellular glutamate levels is responsible for the constant activation of metabotropic and ionotropic glutamate receptors thus elevating Na^+ influx and Ca^{2+} release from intracellular organelles that may trigger a biochemical cascade which increases the production of ROS **(Orrenius and Nicotera, 1994)**. Oxidative stress by itself inhibits the astrocytic glutamate uptake through a direct action on the transporter proteins **(Park *et al*., 1996 and Volterra *et al*., 1994)**.

Although the toxic damage caused by MeHg might be intrinsically prevalent in neurons, many of the published evidences suggest that neuronal damage in response to MeHg most likely represent aberrant control of the extracellular milieu by the astrocytes **(Shanker *et al*., 2001)**. On line with this argument it should be remarked that the neurotoxic effect of MeHg could be reverted with antagonists of N-methyl- D-aspartate (NMDA) receptor **(Park *et al*., 1996)**.

Moreover, MeHg has been described to produce increases in the spontaneous release of other neurotransmitters such as dopamine, GABA, acetylcholine, and serotonin from rat brain synaptosomes **(Komulainen and Tuomisto, 1981, Minema *et al*., 1989 and Juarez *et al*., 2002)**. MeHg also inhibits astrocytic uptake of cystine and cysteine, the key precursors for glutathione biosynthesis **(Shanker *et al*., 2001)**.

***6.* Methylmercury And Metallothioneins**

Metallothioneins (MTs) constitute a family of proteins characterized by unusual cystein abundance **(Hidalgo *et al*., 2001)**. Under physiological conditions, MTs are unusually rich in multiple cysteine residues allowing their binding to metal centers and enabling them to serve as a heavy–metal detoxification system **(Gonzalez-Duarte, 2003)**. MTs are predominantly expressed in the central nervous system and it is important to gain new insight into how MTs are regulated in the brain in pathological injury, such as that produced by MeHg intoxication.

Some studies have reported the potential role of MTs in attenuating the cytotoxicity induced by MeHg **(Hidalgo *et al*., 2001 and Aschner *et al*., 1997)**. Although the interaction of MTs with MeHg ions has long been established, elucidation of the binding features of MeHg-MT species has been hampered by the inherent difficulties of MeHg- thiolate chemistry, which mainly arise from the diverse coordination preferences of Hg (II) and the various ligation modes of the thiolate ligands **(Wright *et al*., 1990)**. Nevertheless, the analysis of MeHg binding to MTs has been intensively studied. In contrast, the chemistry of MeHg-MT complexes has attracted much less attention. Earlier reports demonstrated the inability of MT in the detoxification of MeHg and that it is unable to bind to MeHg either in vivo or in vitro **(Wright *et al*., 1990 and Rising *et al*., 1995)**. Subsequent attempts to induce brain MT by exposure to MeHg+ gave inconsistent results: MT concentrations remained unchanged in rats, whereas MT and mRNA concentrations increased in MeHg –treated rat neonatal astrocyte cultures **(Rising *et al*., 1995)**. However, there is increasing evidence that induction of MTs in astrocytes attenuates and even reverses the cytotoxicity caused by MeHg, indicating binding of MeHg by an astrocyte-specific MT isoform, MT1 **(Yao *et al*., 1999)**.

***7.* Methylmercury In Human Body**

Methylmercury is almost completely absorbed (95-100 percent) in the human gastrointestinal tract **(Ozuah, 2000 and Clarkson, 2002)**, 90 percent of which is eventually eliminated through the feces. Methylmercury is present in the body as a water-soluble complex, mainly with the sulfur atom of thiol ligands **(Clarkson, 2002)**, and crosses the blood-brain barrier complexed with L-cystein in a molecule resembling methionine. Methylmercury is absorbed into the placenta and stored in the fetal brain in concentrations that exceed maternal blood levels **(Cernichiari *et al*., 1995)**. After being released from cells in a complex with reduced glutathione, methylmercury is degraded in the bile duct to an L-cystein complex. Only 10 percent of methylmercury is eliminated through the kidneys. The rest either undergoes enterohepatic recycling or demethylation by microflora in the intestine and immune system and eventual elimination through the feces.

Most methylmercury in animal exposure studies is degraded to, and eliminated as, inorganic mercury at the rate of one percent per day **(Clarkson, 2002)**. At least one study has demonstrated the capacity of two common forms of gastrointestinal yeast to convert inorganic mercury to methylmercury **(Yannai *et al*., 1991)**. Demethylation by intestinal microflora is a crucial step in the elimination of methylmercury from the body, but research has not yet identified the

mechanisms or the microbes responsible for this detoxification system **(Clarkson, 2002)**. Enterohepatic reabsorption is also a significant event in the metabolism of methylmercury; more than 70 percent is reabsorbed from the gut and returned to the liver **(Clarkson, 2002 and Alexander and Aaseth, 1982)**.

Inorganic mercury has been found as the major form of mercury in brain tissue in humans fatally exposed to methylmercury **(Davis *et al*., 1994)**. The conversion of methylmercury to inorganic mercury is thought to take place in phagocytic cells in the liver or in the astroglial cells of the brain **(Clarkson, 2002)**.

***8*. Methylmercury Toxicity In Man**

Recently, more has been elucidated about the toxicity of methyl mercury in man. Although chromosomal breaks have been found in onion root tips exposed to concentrations of methylmercury that cause neurotoxicity in animals **(Ramel, 1969)**, no genetic defects or excessive chromosomal abnormalities have been found in children with congenital methylmercury poisoning **(RCMD, 1974)**. With severe long-term methylmercury poisoning, brain atrophy with associated presenile dementia and atrophy of the Islets of Langerhans of the pancreas with associated diabetes mellitus have resulted **(RCMD, 1974)**. Methylmercury poisoning has yet to be demonstrated in human populations not exposed directly to methylmercury or to food contaminated with methylmercury. Recent studies of populations who subsist mainly on seafood that is naturally high in methylmercury have failed to demonstrate any evidence of methylmercury poisoning, even with whole blood methylmercury levels that average three to eight times that a comparative non-fish-eating population **(Turner *et al*., 1980 and Marsh *et al*., 1974)**.

***9*. Cns Damage Induced By Methylmercury**

The majority of toxicity due to methylmercury exposure involves the central nervous system. Methylmercury can cause demyelination, autonomic dysfunction, sensory nerve conduction delay, abnormal neuronal migration, and abnormal central nervous system cell division. Chronic toxicity symptoms include paresthesia, peripheral neuropathy, cerebellar ataxia, akathisia, spasticity, memory loss, dementia, constricted vision, dysarthria, impaired hearing, smell and taste, tremors, and depression **(Ozuah, 2000 and Clarkson, 2002)**.

***10*. Cardiovascular Damage Induced By Methylmercury**

Methylmercury exposure also appears to increase risk for cardiovascular disease. In a long-term prospective study, both intake of nonfatty freshwater fish and hair mercury content demonstrated a statistically significant correlation with increased risk for acute myocardial infarction **(Salonen *et al*., 1995)**. Men with the highest hair mercury had a 2.9-fold increased risk for cardiovascular death. An examination of the same cohort found a significant correlation between hair mercury and increased risk for progression of carotid atherosclerosis **(Salonen *et al*., 2000)**. Prenatal exposure to methylmercury has been correlated with significant blood pressure elevations in seven year old children as a result of maternal fish intake **(Sorensen *et al*., 1999**

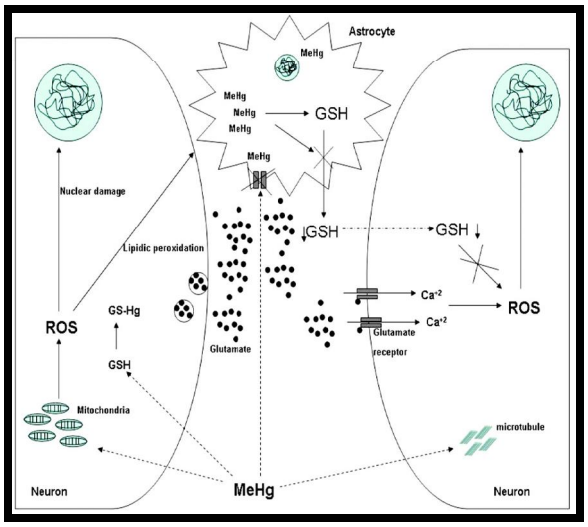

Figure 1: A schematic model of some of the currently proposed mechanism for cellular damage induced by MeHg in the CNS. In the extracellular environment, MeHg inhibits glutamate uptake, as well as a number of the amino acids that are associated with the synthesis of astrocytic glutathione (GSH). Accumulation of glutamate in the extracellular space and the resulting excessive activation of NMDA receptors can result in excitotoxicity, and, ultimately, cell death. Other proposed mechanisms are related with mitochondrial MeHg -associated dysfunction, including impaired cytoplasmatic Ca2+ homeostasis and release of ROS, metabolic inhibition that leads to impaired ATP production, lipid peroxidation and nuclear damage. MeHg also can provoke microtubules chain disruption decreasing vesicular migration or genotoxicity (Do Nascimento *et al.*, 2008).

***11*. Mercury Toxicity In Food Chain Organisms**

In aquatic ecosystems, mercury is quite toxic to lower biological orders and to juveniles of certain species. At concentration of less than 0.1 ppb, methylmercury causes a decrease in the growth rate of phytoplankton and a decreased reproduction of daphnia **(Biesinger, 1974 and Harada *et al*., 1970)**. At similar levels inorganic mercury causes a decreased long term survival of fiddler crab larvae **(Matida *et al*., 1971)**. In fish toxicity has been noted

at 3ppb for both methylmercury and mercuric chloride **(Matida *et al.*, 1971 and Weir and Hine, 1970)**. These toxic levels of mercury compare with normal methylmercury levels in surface water of less than 0.001 ppb and inorganic mercury levels of less than 0.05 ppb **(Andren and Harriss, 1973 and Hartung, 1973)**.

12. **Mercury In Vaccines**

Mercury is currently mixed with DTaP, HIB, and hepatitis B vaccines or is used in the manufacturing process for vaccines, with resultant trace amounts being present in the final product. Based on existing Centers for Disease Control (CDC) recommendations for vaccinations, a typical six month old child , if receiving all thimerosal (49.6 % ethylmercury) containing vaccines, could potentially be injected with as much as 187.5-200 µg of methylmercury; the equivalent of more than 1.0 µg per day. This amount exceeds the reference limits for exposure to mercury set by the EPA of 0.1µg/kg/day **(Halsey, 1999)**. In the united states, at the FDA's request, all the vaccines are currently being produced as thimerosol-free or thimerosol-reduced (>95% reduction) vaccines. Thimerosol-preserved vaccines are still available and used in clinical practice.

Medical And Health Officials Seem To Live In An Unconscious Fog When It Comes To Mercury Even Though Methyl Mercury Induces Oxidative Stress And Cell Cytotoxicity Through Mitochondrial Apoptosis Pathways (IMVA, 2006)

Someday it will dawn on both dentists and doctors who use mercury that they are actually poisoning children and people.

Ethyl mercury (fungicides, thimerosal in vaccines, and gamma-globulin) also causes renal and central nervous system toxicity and is deposited in the liver, kidneys, skin, brain, spleen, and plasma **(Clarkson, 2002)**. Ethyl mercury, like methylmercury, is metabolized to the inorganic form and accounts for 50 percent of the mercury eliminated in urine. Ethyl mercury may actually be converted to inorganic mercury in the tissues in greater amounts and more rapidly than methylmercury **(Clarkson, 2002)**. As with methylmercury, the feces are the main natural route of elimination.

Methylmercury And Oxidative Stress

Mehg Triggers Ros Production, Suppresses Insulin Secretion, And Induces Apoptosis In-Cell-Derived H1t-T15 Cells And Isolated Mouse Pancreatic Islets (Chen Et Al., 2006)

ROS are generally very small molecules and are highly reactive due to the presence of unpaired valence shell electrons. ROS form as a natural by-product of the normal oxygen metabolism and have important roles in cell signaling. These molecules are generated continuously during oxidative metabolism and consist of inorganic molecules, such as superoxide radical anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radicals (OH^-), as well as organic molecules such as alkoxyl and peroxyl radicals **(Schulz *et al.*, 2000)**. Some evidences suggest that the disturbance in the balance between oxidative and reductive cell processes is involved in the pathogenesis of many neurodegerative conditions such as Alzheimer disease, amyotrophic lateral sclerosis (ALS), and Parkinson disease. Other conditions such as autoimmune and inflammatory diseases, cancer, and diabetes mellitus also seemed to be related to this disturbance **(Schulz *et al.*, 2000)**.

MeHg has been thought to induce ROS and generation of oxidative events leading to cell damage. Previous studies have suggested that there is a relationship between these events with dysfunction of the cellular energetic metabolism and disruption of the electron transport chain. These phenomena generate oxidative stress **(Clarkson, 1997 and Shanker *et al.*, 2002)**. MeHg exposure increases the rate of ROS in the cerebellum (in vivo) and in the brain synaptosomes as well as in the cerebellum neuronal cultures, hypothalamic neuronal cell line, and mixed reaggregating cell cultures **(Ali *et al.*, 1992, Sarafian *et al.*, 1994 and Sarafian, 1999)**. The formation of these species was critical to determine the damage and the cell death in distinct cell types such as astrocytes and neurons.

It seems that the intensity of MeHg exposure is a crucial factor to establish whether the neuronal death occurs by necrosis or apoptosis **(Kunimoto, 1994 and Castoldi *et al.*, 2000)**. However, the mechanism of cell death induced by oxidative stress via MeHg has not been well characterized.

1. **Inhibition Of Protein Synthesis**

Disruption of protein synthesis may be an early manifestation of MeHg toxicity in vitro and in vivo, and has been proposed to be the proximal event and primary mechanism of action of MeHg in the nervous system **(Yoshino *et al.*, 1966B and Verity *et al.*, 1977)**. However, no direct relationship between the inhibition of protein synthesis and neuropathologic changes in MeHg poisoning has been established.

MeHg alters protein phosphorylation, although the patterns of alteration differ somewhat from study to study. **Sarafian and Verity, 1990** reported stimulation of protein phospholabeling in primary cultures of cerebellar granule cells exposed to low concentrations of MeHg 24 h, whereas cerebellar glial cells had decreased in protein phosphorylation under identical exposure conditions.

Methylmercury And Antioxidant Defenses

Many studies have already established that MeHg neurotoxicity evokes oxidative stress with formation of ROS in the CNS and that the increase of ROS induces cell damage and death in the CNS. In order to avoid the damage caused by ROS, such as DNA strand breaks, lipid peroxidation, and protein modification, mechanisms have been developed during evolution which dispose or prevent the generation of ROS **(Dringen, 2000)**. However, the underlying mechanisms responsible for the protection of CNS against MeHg neurotoxicity are still poorly understood.

It is well known that cell defenses against free radicals such as ROS include scavenger compounds such as glutathione, cysteine, melatonin, and enzymes with antioxidant activities as superoxide dismutase, catalase and glutathione peroxidase **(Olivieri *et al.*, 2000)**.

It was demonstrated that MeHg induces a concentration-dependent increase in: ROS formation in rat neonatal neuronal culture and astrocyte culture **(Park *et al.*, 1996, Sorg *et al.*, 1998 and Shanker and Aschner, 2003)**. It was also shown that this effect can be reverted by the use of n-propyl gallate (PG), a free radical scavenger, superoxide dismutase (SOD), an antioxidant enzyme, and α-phenyl-tert-butyl nitrone (PBN), a lipophilic hydroxyl radical spin trapping agent **(Shanker and Aschner, 2003 and Gasso *et al.*, 2001)**.

Endogenous glutathione (GSH) is one of the most abundant and essential thiol tripeptide present in mammalian cells for scavenging reactive oxygen species **(Dringen, 2000)**. The involvement of GSH in the neurotoxicity of MeHg was also evaluated, showing that the increased oxidative stress is related with the depleted intracellular GSH levels **(Lee *et al.*, 2001 and Shanker *et al.*, 2005)**. The excessive formation of ROS induced by MeHg exposure can be reverted under treatment with L-2-oxothiazolidine-4-carboxylic acid (OTC), which increases the amount of intracellular GSH, as well as the depletion of GSH by treatment with buthionine-L-sulphoxane (BSO) can potentiate the production of ROS induced by MeHg in rat primary cerebral astrocytes **(Do Nascimento *et al.*, 2008)**.

Recently a human population study in the Amazon correlated the MeHg exposure with the levels of glutathione and catalase activity. Surprisingly, it was demonstrated that high blood levels of glutathione in woman exposed to high concentrations of MeHg may be explained by the increase of glutathione peroxidase activity **(Pinheiro *et al.*, 2007)**. In the same population the inhibition of catalase activity was also observed. These changes likely reflect adaptive responses of the Amazonian population to oxidative stress induced by MeHg.

Other studies revealed that the GSH content may vary in different regions of the CNS, demonstrating that the GSH amount is higher in cerebral cells than in cerebellar cells **(Kaur *et al.*, 2007 and Adachi and Kunimoto, 2005)**. This may explain the higher susceptibility of cerebellar cells to MeHg toxicity in comparison with cerebral cells, but the reason why certain areas of CNS showed different sensitivity to MeHg toxicity, remains unclear.

In addition, MeHg poisoning can induce sympathetic ganglia toxicity and neurite outgrowth inhibition **(Soderstrom and Ebendal, 1995 and Miura *et al.*, 2000)**. Compounds that possess sulphydryl (-SH) groups attenuate MeHg neurotoxicity, once at least part of MeHg effects occurs through interaction with -SH groups in cellular proteins **(Mullaney *et al.*, 1994)**. In this context, primary neuronal cultures from avian sympathetic ganglion were used to evaluate the protective role of antioxidant agents with –SH group such as L-cysteine against MeHg toxicity. It was reported that MeHg induces massive cell death (neurite death) and that L-cysteine could fully protect (nearly 100%) the sympathetic neuron against this damage. The effect of GSH was also tested showing the same properties of cysteine **(De Melo Reis *et al.*, 2007)**.

The use of methionine, an antioxidant agent which does not possess –SH groups, fails to promote cell protection against MeHg intoxication, proving the relevance of –SH groups to this effect **(De Melo Reis *et al.*, 2007)**. Another antioxidant that protects the brain from oxidative stress is vitamin E, which maintains the integrity of membrane by inhibiting lipid peroxidation **(Ricciarelli *et al.*, 2001)**. Recent findings reported the protective effect of the antioxidants tocopherols and tocotrienols (analogs to vitamin E) against MeHg neurotoxicity **(Osakada *et al.*, 2004 and Khanna *et al.*, 2006)**. In cerebellar granule cells (CGC), these compounds effectively prevent cell death caused by MeHg intoxication as well as cell migration **(Shichiri *et al.*, 2007)**.

Evidences also suggest that the treatment with trolox (6-hydroxy-2, 5, 7, 8,-tetramethylchroman-2-carboxylic acid), other antioxidant derivative from vitamin E, might provide prevention against oxidative stress. In MeHg-treated rats, it detected many apoptotic cells in the cerebellar granule layers and the treatment with trolox clearly repressed the appearance of these apoptotic processes **(Usuki *et al.*, 2001)**.

A number of different hypotheses have been suggested to explain the mechanism by which the antioxidant defenses protect CNS against MeHg neurotoxicity, which include scavenging and removal of free radicals, reversal of glutamate uptake

impairment, inhibition of cytochrome c release, and caspase activation **(Aschner *et al*., 2007)**.

It has been established that MeHg inhibits glutamate transport by astrocytes by an unknown mechanism which leads to the increase of ROS generation **(Aschner *et al*., 2007)**. It was demonstrated that a variety of antioxidants can prevent the overproduction of ROS, in this way attenuating MeHg neurotoxicity. Some workers have focused on the effect of antioxidant agents in the impairment of EAA transport elicited by MeHg **(Do Nascimento *et al*., 2008)**.

Mechanisms Of Mercury Toxicity

Mercury can cause biochemical damage to tissues and genes through diverse mechanisms, such as interrupting intracellular calcium homeostasis, disrupting membrane potential, altering protein synthesis, and interrupting excitatory amino acid pathways in the central nervous system **(Yee and Choi, 1996)**. Mitochondrial damage, lipid peroxidation, microtubule destruction **(National Research Council, 2000)**, and the neurotoxic accumulation of serotonin, aspartate, and glutamate are all mechanisms of methylmercury neurotoxicity **(Yee and Choi, 1996)**.

One of the major mechanisms behind MeHg-induced toxicity is via generation of reactive oxygen species (ROS) and depletion of glutathione (GSH).The balance between the oxidative and reductive cellular processes is critical for MeHg-induced neurotoxicity. Over time, both methylmercury and elemental mercury vapor in the brain are transformed to inorganic mercury, and become firmly bound to sulfhydryl-containing macromolecules **(National Research Council, 2000)**. Both methylmercury and inorganic mercury bind to various molecular weight thiol containing proteins (glutathione, cysteine, albumin, etc.). The binding and dissociation of these mercury-thiol complexes are believed to control the movement of mercury and its toxic effects in the body **(Clarkson, 2002)**.

Mitochondrial damage from oxidative stress may be the earliest sign of neurotoxicity with methylmercury. A study in neural tissue indicates the electron transport chain appears to be the site where free radicals are generated, leading to oxidative damage induced by methylmercury **(Yee and Choi, 1996)**.

Concluding Remarks

The molecular mechanisms of MeHg damage in both adult and developing CNS is not fully understood. Early reports have described a number of possible cellular mechanisms to explain the neurotoxicity induced by MeHg. Most of these studies reported the high affinity of MeHg for thiol groups (-SH) which are present in cytoskeletal proteins, enzymes, and peptides that contain the amino acid cysteine **(Kaur *et al*., 2007)**.

The effects of MeHg on the normal functioning of the nervous system are numerous. It is unlikely that any single event is responsible for the neurotoxicity of MeHg. Rather, MeHg likely causes disruptions in cellular processes including synaptic function, excitability, ion regulation, and protein synthesis.

There have been discrepancies in the outcomes of epidemiological studies estimating the effect of MeHg from fish diet. The availability of nutritional factors such as docosahaxaenoic acid (DHA) might influence MeHg toxicity and may explain the discrepancies from the different studies.

Antioxidants (both enzymatic and non enzymatic) provide protection against deleterious metal-mediated free radical attacks. Vitamin E and melatonin can prevent the majority of MeHg – mediated damage both in vitro systems and in metal loaded animals. Toxicity produced by MeHg showed that the protective effect of vitamin E against lipid peroxidation may be associated rather with the level of non-enzymatic antioxidants than the activity of enzymatic antioxidants. Molecular and cellular approaches can be a strategy to critically examine the possibility of therapeutic actions such as antioxidants or chelating agents in the treatment of neurodegeneration produced by MeHg. The rising tonnage (approximately 20 tons a day) put into the air everyday by human activity.

Because Mercury Is Increasingly Becoming Elevated In All Forms Of Life, We Can Assume That More People Will Have Some Defects In Pancreatic Function. Pancreatic Support Is Increasingly Necessary For Optimal Health (IMVA, 2006)

In short, the challenges posed by methylmercury poisoning nowadays can be summarized in the following points:

- The need for a definition and description of the effects of low-level exposure to methylmercury through seafood and fresh water fish, particularly in relation to neurodevelopment, i.e. in vitro and prenatal exposure. This would require a definition of the non-effect range, *lowest observed adverse effect level* (LOAEL) for MeHg concentrations in the most vulnerable populations. Furthermore, even if the fetal brain has been identified as the most vulnerable target, many sensitivity factors still remain to be investigated.
- The need for an improved understanding of MeHg neurotoxicity mechanisms. Although a wealth of information is available on the subject, what is required is a clear explanation that takes the phenomena underlying specific clinical and

neuropathological toxicity manifestations fully into account.

- A better knowledge of the above mentioned points will undoubtedly lead to more effective preventative public health measures.
- At last four courses of action now seem warranted. First, toxic mercurial in agriculture and industry should be replaced by less toxic substitutes. Second, controls should be applied at the point of origin to prevent the discharge of potentially harmful Hg wastes. Third, continued periodic monitoring of Hg in fish and wildlife is needed for identification of potential problem areas, and for evaluation of ongoing mercury curtailment programs. And fourth, additional research is merited on mechanisms of mercury accumulation and detoxification in comparatively pristine ecosystems.

The present study was, therefore plotted by us to scrutinize aftermath of methylmercury chloride on certain areas of the rat brain, spinal cord, heart, lung and pancreas using biochemical techniques. The present investigation is the first to observe biochemical effects of methylmercury chloride on heart, lung and pancreas. The work set out deals with:-

1) Biochemical Parameters

i) Lipid peroxidation and their products.
ii) Antioxidant systems.
iii) Protein.

***2)* Behavioral Parameters**

I) Open Field Behavior.
II) Tail Suspension Test.
III) Force Swim Test.
IV) Righting Reflex Test
V) Elevated plus maze.

***3)* Cytogenetic Parameters**

I) Micronucleus Test
II) Chromosomal Aberration.

An endeavor has been made to appraise the biochemical swing inside the rat body after methylmercury toxicity. Though it is not professed that every organ of the rat has been probed in all respects it is tried that relevant organs may not be overlooked. However, as mercury is a deadly global pollutant, causing damage to living organisms, including human beings, it is a diminutive stride in the colossal field of mercury research.

From the results of our study it was found that oxidative stress is present during methylmercury intoxication. The concentrations of MDA in tissues were observed to increase significantly in rats treated with this metal. Treatment with vitamin-E and Acetyl-L-Carnitine reduced sensitivity to oxidative stress. On the other hand, vitamin-E plus Acetyl-L-Carnitine could cause complex alterations in the antioxidant system and could minimize the oxidative stress induced by methylmercury chloride.

Don'T Treat The Symptoms. Treat The Cause. Discover Why Heavy Metals May Be Causing Your Unexplained Health Problems. [Ian M. Solley]

Acknowledgements:

Author is grateful to the Department of Zoology, Aligarh Muslim University for financial support to carry out this work.

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