

## Appendix 2

### Case Study: Thimerosal and Mercury Toxicity in Humans

#### The Preservative Thimerosal

Thimerosal is a preservative that was invented in 1920 by the chemist, Eli Lilly, the founder of the pharmaceutical company of the same name (Kirby 2005 p48). It is an organomercurial compound that is almost 50% mercury by weight and metabolises to *ethylmercury* and *thiosalicylate*. Its brand name is Merthiolate and it is a cream-coloured water soluble crystalline powder (Kirby 2005). This preservative has never been tested for safety and effectiveness since it was first used in the 1930's (FDA p1). The first requirement for preservatives to be included in the US Code of Federal Regulations (CFR) was in 1968 but preservatives were present in many products prior to this time. The CFR requires that 'the preservative shall be sufficiently non-toxic so that the amount present in the recommended dose of the product will not be toxic to the recipient...' (FDA p1). Yet the FDA does not test preservatives for safety and efficacy. FDA safety and effectiveness standards only apply to collecting safety and effectiveness data on the product that is being licensed not on the preservative that is in the product for licensing.

Whilst the FDA states that the concentration of thimerosal in vaccines meets the *preservative* standards set by the *United States Pharmacopeia* these standards do not refer to the safety of the preservative – only to its effectiveness. In other words, it kills the specified challenge organisms and is able to prevent the growth of the fungi when it is at a concentration in the range of 0.001% - 0.01%. Thimerosal at a concentration of 0.01% contains 50 micrograms of thimerosal per 0.5 ml dose or 25 micrograms of mercury in a 0.25 ml dose. A trace amount of thimerosal is considered to contain 1 microgram or less of mercury per dose. Whilst the FDA claims several studies have indicated thimerosal has a 'long record of safe and effective use' (p2) these studies are mostly for the effectiveness of thimerosal in topical products and not for the safety and effectiveness of thimerosal injected into the tissues (FDA p7). During the 1990's many thimerosal-containing vaccines were added to the childhood schedule in all countries. Yet there is no safety data on the health effects of trace amounts of thimerosal in vaccines or accumulated or synergistic effects of thimerosal with other vaccine

ingredients (FDA 2012 p3). It is also known that organomercurial compounds have the potential for neurotoxicity even at low levels in the human body.

Cases of mercury poisoning that occurred from the administration of thiomersal-containing products in the 1970-1990's (including the administration of immune globulin) reported necrosis, acute hemolysis, disseminated intravascular coagulation, acute renal tubular necrosis and central nervous system injury including obtundation, coma and death (IOM in FDA p3). Animal studies prior to 1990 demonstrated that the maximum dose of thimerosal that could be tolerated without causing death was 20 micrograms of thimerosal/kg in rabbits and 45 micrograms/kg in rats (FDA p3). There is no mention of the health effects that occur in these animals (prior to death) when exposed to these levels of mercury. In addition, the FDA has not established definitive data on the time it takes to remove ethyl mercury from the body of animals or humans. The FDA uses the Magos et al (1985) study of rats to make the claim that 'ethylmercury is less neurotoxic than methylmercury', the organomercury compound that the safety guidelines are based on. There is no evidence provided by the FDA to support this statement and no description of the health effects in the rats after exposure to 5 daily doses of ethyl and methyl mercury to illustrate the conclusion that 'it is less neurotoxic' (FDA p3). Instead the FDA uses other studies to observe that there are differences in the way thimerosal and methyl mercury are distributed, metabolized and excreted in the body, therefore the FDA concludes 'Thimerosal appears to be removed from the blood and body more rapidly than methyl mercury' (FDA p3). This is not a definitive statement about the removal of thimerosal.

The guidelines that do exist for the health effects of mercury in humans have been established from accidents with the related organomercury compound, methylmercury and its consumption in the diet - not injection into the body (FDA p2; TEACH). The FDA states that ethyl and methyl mercury are expected to have different toxicological profiles but as there is a 'lack of definitive data on the comparative toxicities' the FDA has considered them equivalent in its risk evaluation (p2). It is also known that exposure from ingestion is very different to exposure from injection of the substances into the tissues (Gilbert 2004). Ethyl and methylmercury are both organic compounds which mean they contain carbon and are easily absorbed by lipids and fatty membranes (Kirby 2005 p48). The difference between the compounds is that ethylmercury has one extra carbon molecule making it a larger structure (Kirby 2005). Organomercury is more

dangerous than inorganic mercury because inorganic mercury can dissolve in water and be more easily excreted by the kidneys in urine (Gilbert 2004). Ethylmercury is less readily eliminated from the body because it is an organic mercury compound.

### **FDA Guidelines for the Use of Methyl and Ethyl Mercury**

Several agencies have developed guidelines for safe exposure to methyl mercury including the US Environmental Protection Agency (EPA) (1997) 0.1 mg/kg/day, the Agency for Toxic Substances and Disease Registry (ATSDR) (1999) 0.3 mg/kg/day, the FDA (1979) 0.4 mg/kg/day and WHO (1996) 0.47 mg/kg/day (FDA p2). These exposure levels range from 0.1 micrograms/kg body weight/day (EPA) to 0.47 micrograms/kg body weight /day (WHO). The FDA claims that the figures vary between agencies due to:

- I. Varying safety margins
- II. The different emphasis placed upon various sources of data
- III. The different missions of the agencies and
- IV. The population that the guideline is intended to protect. For example, adult or child.

The FDA's guideline has been based partly on an adult who ingests 30 micrograms/day of methyl mercury in the diet. This is equivalent to 0.43 micrograms/kg/day for a 70kg adult. Although there are variations in the guidelines between the different agencies the FDA considers that they all fall within the same order of magnitude. However, if this data is assessed in the perspective in which it is used i.e. the safety of toxins in a new born infant compared to a mature adult of 70kg then these guidelines vary considerably between the agencies. The 0.1 mg/kg body weight recommended by the EPA is significantly less than 0.43 (FDA) and 0.47 mg/kg body weight (WHO) – particularly as the FDA's standard is based on a 70 kg adult. Toxins are known to have a 10 fold increased effect in infants compared to adults (Gilbert 2004).

Ideally the guidelines should also describe the route of entry of the exposure: ingestion (diet), inhalation or injection. This is essential because injection ensures that most of the substance is absorbed into the circulatory system and is accessible to all organs whereas ingestion via the diet results in a large proportion of the mercury being excreted in the faeces (Gilbert 2004). In animal studies methylmercury has been shown to cross the

placenta and accumulate in foetal brain, kidney and liver of mice, hamsters, rats and monkeys. Methyl mercury is transferred to infants via breast milk in both rats and hamsters but it transfers more efficiently across the placenta (TEACH p8).

Based on the FDA's guidelines it recommends that pregnant women, nursing mothers and young children do not consume certain kinds of fish that may contain high levels of methyl mercury (FDA p7; TEACH p1), in particular, shark, swordfish, king mackerel and tilefish which are the higher order consumers. In contrast, governments in 2013 are recommending the influenza vaccine to pregnant women (DHA IAP 2013) even though some influenza vaccines contain thimerosal and other non-inert excipients that are injected into the tissues and have access to the foetus and body organs. Every dose of influenza vaccine that comes from a multi-dose vial contains 24.5 micrograms of mercury (CSL PI). This is recommended even though the FDA has not established a safe dose of ethyl mercury in the foetus, infants, adults or pregnant women (FDA p3).

### **The Health Effects of Ethyl and Methyl Mercury**

Ethyl and methyl mercury are classified as neurotoxins that destroy cells in key centers of the brain and nervous system. Mercury is especially hazardous to foetuses and small children. This is of concern when it is also known that the majority of substances that are taken in by a pregnant woman will cross the placental membrane ensuring that the foetus will experience the same level of any drug that the mother is exposed to (Gilbert 2004 p28). However, compounds such as methylmercury are found in higher concentrations in the foetus than in the mother because the developing infant is a storage site for maternal mercury (Gilbert 2004 p28). Further protection is provided to the adult brain by the blood-brain barrier to filter out hazardous substances however the foetus and infant up to 6 months of age do not have this protection (Gilbert 2004). The blood-brain barrier is able to prevent large molecules from passing into the brain tissue but it cannot stop water soluble agents from entering the brain (Gilbert 2004 p28). Mercury is known to affect the central nervous system, skin and kidneys (FDA; NCIRS THIM FS p1). As the body systems of infants are still developing even a 'trace' amount of a toxin (particularly in combination with other substances) could affect the proper development of the kidneys and therefore inhibit the removal of mercury from an infant's body. The NCIRS states that 'ethyl mercury is rapidly converted in the body to inorganic mercury which is excreted in the stool' (p1). This statement is unreferenced

and may not apply to infants whose systems are still developing. In addition, it may also give the mercury greater access to the brain when the blood-brain barrier is not developed. The effects of mercury exposure in adults include kidney damage and digestive tract problems including diarrhea, nausea and ulcers (TEACH p4).

Mercury is known to inhibit cell division and migration within the forming brain and has been shown to bind to DNA thereby interrupting chromosomal reproduction and blocking several essential proteins (Kirby 2005 p48). The uptake of a chemical by different tissues and organs is also known to be affected by exposure to multiple chemicals at the same time (Gilbert 2004 p28). A combination of chemicals (such as the excipients in multiple vaccines or exposures to pesticides and other chemicals in the environment) can interact to affect absorption of the substance or to affect the body's reaction to a specific chemical. Knowledge of these interactions on the metabolism and elimination of substances from the human body is limited (Gilbert 2004 p28). This is particularly the case for the foetus and infants because their body systems are still developing. Most detoxification occurs in the liver by breaking down toxic substances into less toxic substances. Heavy metals such as mercury are unable to be degraded so removal is dependent upon the functioning of the kidneys (Gilbert 2004 p29). Mercury is removed from the body by the kidneys which concentrate the toxin in the urine ready for excretion. A significant factor in the ability of a toxin to cause harm is the half-life of the substance.

Methyl mercury has a half life of approximately 70 days but it is believed to be slightly less for ethyl mercury (PHAC 2002 p6). This is not a definitive statement supported with evidence. The Australian NCIRS states that the half-life of methyl mercury is 50 days and for ethyl mercury is considerably less at 7-10 days but this statement is not referenced (NCIRS THIM p1). The half-life of any substance will be influenced by the genetics of the individual and the variations that occur in physiology at different ages or under different conditions. For example, metabolism varies considerably between individuals and in response to hormonal changes at different stages in life – infant, adult or pregnant mother (Gilbert 2004 p29). The half-life of a toxin can increase considerably during pregnancy due to physiological changes that affect the absorption, distribution and metabolism of an agent (Gilbert 2004 p 31). A compromised immune system or genetic trait can result in low level exposures being completely intolerable to some individuals (Gilbert 2004 p31). In addition, rapid weight loss can cause excess

toxins to be redistributed into the blood as fat is metabolised. Young people are particularly susceptible to health effects from toxins because the organs are rapidly developing and the dividing cells are more easily harmed than mature cells (Gilbert 2004 p31).

The brain grows rapidly in the first 7 years of life and mercury is a neurotoxin that specifically targets the nervous system and brain (TEACH). When children have been exposed to methyl mercury during pregnancy (in utero) it has been associated with delays in reaching developmental milestones and decreases in intelligence (TEACH p2). The foetus is found to be more sensitive to the effects of mercury and conditions such as severe neurologic injury including a condition similar to cerebral palsy have been acquired even when the mother has shown few or no symptoms (FDA p2). The larger the dose the greater the severity of the neurological condition (TEACH). When children in utero were exposed to low levels of methyl mercury they experienced sensory and motor neurological dysfunction and developmental delays (FDA p2). Children exposed to high doses of methyl mercury may experience mental retardation, cerebral palsy, reduced muscle coordination, blindness, deafness, seizures, muscle weakness and an inability to speak (TEACH p2 and 4). Studies from the Faroe Islands reported subtle cognitive disabilities including, impaired performance on attention, language and memory tests, associated with levels of methyl mercury that were previously thought to be safe (Grandjean et al 1997 in FDA p3).

Children and adults exposed to high levels of methylmercury can also develop a disorder called *acrodynia* or *pink disease* (TEACH p4). Symptoms of this disorder include leg cramps, irritability, redness, peeling of hands and skin, nose and soles of feet, fever, itching, sweating, salivating, rashes, sleeplessness, weakness and neurological tics (TEACH). Pink disease is another name for mercury poisoning and the symptoms are consistent with autism spectrum disorders (American Psychiatric Assoc in PHAC 2002 p3).

## **Mercury Toxicity and Autism**

Some epidemiological studies have also linked ethylmercury exposure with autism and other neurological disorders in children (TEACH p4; PHAC 2002 p3). However, due to variations in methodology the results from different studies have been inconsistent.

Evidence is also available that demonstrates autism is a common disorder in vaccinated children but a rare disorder in unvaccinated children (Vaccine Injury). This evidence is consistent with the fact, that neurodevelopmental disorders such as autism have similar symptoms to those of mercury poisoning (Coulter 1990; Kirby 2005 p73; PHAC 2002 p3; US Congressional Record).

Autism is characterised by impaired social interaction and communication, repetitive and stereotypic behaviours, interests and activities (PHAC 2002 p3). Symptoms generally appear at 18 to 30 months of age and range from mild to severe resulting in the term Autism Spectrum Disorders (ASD) (PHAC 2002 p3). Causes that have been implicated in this disorder are genetics, exposure to heavy metals such as lead and mercury, nutritional deficiencies and metabolic disease. One theory is that a genetic predisposition to metallothionein protein dysfunction could cause autism in children after exposure to heavy metals (PHAC 2002 p3). Some children have a genetic problem with expelling mercury from the body and these predisposed children are more at risk of permanent neurological damage particularly when exposed to the live-virus MMR vaccine at eighteen months of age (Kirby 2005). This genetic predisposition appears to be four times more common in boys than girls (El-Dahr in 2001 in Kirby 2005 p143) This correlates with the statistics on autism, Attention Deficit Disorder (ADD), tics, speech delay and most other neurological disorders, which are also higher in boys compared to girls in the same ratio (American Psychiatric Association 1994 in PHAC 2002). The sulfur-based protein metallothionein (MT) which performs many key functions in the human body is dysfunctional or depleted in autistic children.

### **The History of Mercury as a Preservative in Vaccines**

In 1982, the FDA Register stated *mercury compounds used in medicinal products should be classified as 'not generally recognized as safe and effective'* (Burton 2003). At this time, the FDA independent panel also described mercury as an unreliable preservative. It was described as more bacteriostatic than bactericidal – it slowed the growth of new bacteria but did not kill them altogether. In fact, it was found to be more deadly to healthy cells than it was to harmful bacteria e.g. 35.3 times more toxic for embryonic heart tissue than for *Staphylococcus aureus* (FDA 1982 in Kirby 2005 p83).

Studies indicated that thimerosal was one of the most toxic and highly allergenic of twenty or more mercury compounds that the panel examined (FDA 1982 in Kirby 2005). Whilst the FDA knew in 1982 of mercury's potential to cause cell damage and delayed allergic responses, it did not use caution by insisting that it was removed from vaccines (Burton 2003). Instead the FDA called for the removal of all mercury-based preservatives, including thimerosal from over-the-counter topical products, such as eardrops, eyedrops, nasal sprays and mercurochrome but it did not call for its removal from vaccines that are injected into the tissues of infants. It wasn't required to be removed from vaccines until 1998 after parents began investigating the ingredients of vaccines. Many parents were associating the escalation of chronic illness in children during the 1990's with the increase in the number of vaccines being used and the increase in the vaccination rates in children (Bernard et al 2001 in FDA p3; Burton 2003). In particular the reported cases of autism increased dramatically in the 1990's (10 to 17 percent per year) and the exposure of infants to ethylmercury increased threefold (Burton 2003).

It was estimated that children in the 1990's were receiving many times more than the daily limit of mercury because of the addition of many new thimerosal-containing vaccines (FDA p1). When Hepatitis B and Haemophilus Influenza Type B vaccines were added to the schedule in the early 1990's the cumulative levels of ethylmercury that children were exposed to increased almost 3 fold (Burton 2003). Parents informed Congress of these concerns in 1997 and the FDA was mandated to evaluate the human exposure to mercury that children were receiving (Burton 2003). Due to the variations in safety standards that existed between agencies the National Academy of Sciences was asked by Congress to provide a recommendation for a justifiable level of mercury for protecting human health (FDA p3). It was agreed that the EPA's guide of 0.1 microgram/kg/day was considered scientifically justifiable (Burton 2003; FDA p3). Consequently the FDA discovered that the amount of ethyl mercury that infants were exposed to in the first 6 months of life through mandatory vaccinations was higher than the recommended standard for organomercury compounds (Burton 2003).

A 'safe' cumulative level of mercury in infants depends upon the standard that is used and the size of the infant (Gilbert 2004; Halsey 1999). Halsey (1999) observed that using the EPA guideline of 0.1 microgram/kg/day 'many children at 2 months of age received almost 90 times the daily limit in a single doctor's visit. And the smallest



babies were given approximately eight months worth of daily exposures (240 times the daily limit) in a single day' (Halsey 1999 in Kirby 2005 p81). Halsey (1999) the Director of Vaccine Safety in America, is quoted as saying in an American Academy of Pediatrics (AAP) committee report 'doctors should be told soon about the amount of mercury in vaccines and the conflict with a federal health guideline' (Halsey 1999 (57 and 59) in Kirby D 2005 p70). Halsey N, (1999) also stated 'no-one knows what dose of mercury, if any is safe, and we can claim there is no evidence of harm but the truth is no-one has looked' (Kirby 2005 p71).

After parents and researchers highlighted the correlation between vaccines and increased neurodevelopmental disorders in children the FDA reviewed the list of regulated products containing mercury that were listed under the *FDA Modernization Act of 1997*. The review was conducted in 1999 and concluded that 'there was no evidence of harm from the use of thimerosal as a vaccine preservative, other than local hypersensitivity reactions (Bell et al 2001 in FDA p4). The FDA stated that as a precaution vaccines would be reformulated without thimerosal. In 2001 the Institute of Medicine (IOM) stated that an association between mercury exposure and neurodevelopmental disorders including autism, attention deficit hyper-activity disorder (ADHD) and speech or language delay was biologically plausible (FDA p3). However it was considered that further studies were needed to prove a causal link. After assessing further epidemiological studies, the IOM in 2004 rejected a causal relationship between thiomersal containing vaccines and neurodevelopmental disorders (FDA p3). Many of the epidemiological studies conducted or funded by the CDC have been claimed to be of poor design, under-powered and fatally flawed (Burton 2003).

The statement made by the Institute of Medicine (IOM) Immunisation Safety Review Committee in 2004 made the following conclusion:

The body of evidence favoured rejection of a causal relationship between thimerosal-containing vaccines and autism and that the hypothesis generated to date, concerning the biological mechanism for such causality, are theoretical only. The committee also stated that the benefits of vaccination are proven and the hypothesis of susceptible populations is presently speculative and that widespread rejection of vaccines would lead to increases in incidences of serious infectious diseases (FDA p3).

It is claimed by the FDA that ‘there is only a theoretical potential of toxicity from trace amounts of thimerosal in vaccines’ (IOM, FDA, NCIRS THIM). This is a value judgment made without definitive knowledge of a safe level of mercury in children or adults. Mercury is classified as a neurotoxin and exposure to organic mercury is known to target the nervous system resulting in a disease similar to autism (TEACH p4; PHAC 2002 p3). Whilst the FDA considered that it was unethical to determine a safety profile of ethyl mercury in infants it did not consider it unethical to use ethyl mercury in vaccines for many years without knowing what level was harmful to an infant.

The FDA has used ethylmercury in vaccines for many years and it has been detected in the blood, urine, and faeces of vaccinated infants (PHAC 2002; Kirby 2005). These infants present a good opportunity to study the effects of different levels of mercury in children but the FDA has not used this opportunity to systematically study the health outcomes of ethyl mercury after 60 years of using thimerosal-containing vaccines. In 1999 the US Federal health officials conceded that the amount of thimerosal in vaccines exceeded 2 safety thresholds (Burton 2003). They also conceded that the amount of mercury in one dose of DTaP or Hepatitis B vaccines (25 micrograms each) was many times above the threshold set by the EPA (Burton 2003). Whilst there is inadequate research on the neurotoxicity and nephrotoxicity of ethyl mercury in infants, there is a large body of evidence indicating the dangers to health of ethyl mercury in animals and humans. Yet the FDA did not consider it unethical to use this preservative in numerous vaccines for children when it did not have empirical evidence of its safety.