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Review or Mini-review

Examining the evidence that ethylmercury crosses the blood-brain barrier

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ABSTRACT

Scientific research can provide us with factual, repeatable, measurable, and determinable results. As such, scientific research can provide information that can be used in the decision-making process in the care of patients and in public policy. Although it has been suggested that ethylmercury ($C_2H_5Hg^+$)-containing compounds do not cross the blood-brain barrier (BBB), this review examines the literature that addresses the question as to whether ethylmercury-containing compounds cross the BBB. The review will begin with cellular studies that provide evidence for the passive and active transport of mercury species across the BBB. Then, animal and clinical studies will be presented that specifically examine whether mercury accumulates in the brain after exposure to ethylmercury-containing compounds or Thimerosal (an ethylmercury-containing compound used as a preservative in vaccines and other drugs that metabolizes or degrades to ethylmercury-containing compounds and thiosalicylate). The results indicate that ethylmercury-containing compounds are actively transported across membranes by the L (leucine-preferring)-amino acid transport (LAT) system, the same as methylmercury-containing compounds. Further, 22 studies from 1971 to 2019 show that exposure to ethylmercury-containing compounds (intravenously, intraperitoneally, topically, subcutaneously, intramuscularly, or intranasally administered) results in accumulation of mercury in the brain. In total, these studies indicate that ethylmercury-containing compounds and Thimerosal readily cross the BBB, convert, for the most part, to highly toxic inorganic mercury-containing compounds, which significantly and persistently bind to tissues in the brain, even in the absence of concurrent detectable blood mercury levels.

1. Introduction

Scientific research can provide us with factual, repeatable, measurable, and determinable results. As such, scientific research can provide information that can be used in the decision-making process in the care of patients and in public policy.

In 2018, Boom et al. published a review in the *Journal of Family Strengths* stating that, "*Ethyl mercury does not cross the blood-brain barrier and is structurally different from methyl mercury*…" This statement by Boom et al. (2018) was in the context of describing ethylmercury as being safer than methylmercury.

Factual truth in science is part of the role of science and adherence to the evidence is critical. The evidence indicates that ethylmercury ($C_2H_5Hg^+$) -containing compounds do cross the blood-brain barrier (BBB). In this current review, the evidence supporting the notion that ethylmercury-containing compounds cross the BBB will be presented and discussed. The review will begin with a summary of cellular studies showing the passive and active transport of mercury species across the BBB. Then, animal and clinical studies that specifically examine whether mercury accumulates in the brain after exposure to ethylmercury-containing compounds or Thimerosal (an ethylmercury-containing compound used as a preservative that metabolizes or degrades to ethylmercury-containing compounds and thiosalicylate) will be presented from a historical perspective.

2. Cellular studies – showing passive and active transport across the BBB

Some mercury species, such inorganic mercury-containing compounds, do not readily cross the BBB. However, organic mercury is fat soluble and has a high affinity for thiol groups and as such, it can easily penetrate the BBB (Dewi et al., 2014). It has been accepted for decades that methylmercury-containing compounds, an organic form of mercury, cross the BBB (Kerper et al., 1992). First, methylmercury-

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containing compounds can passively cross the BBB because, as mentioned, they are fat soluble and have a high affinity for thiol groups. However, methylmercury-containing compounds also enter the brain as a cysteine complex via the L (leucine-preferring)-amino acid transport (LAT) system. Methylmercury binds to cysteine and the complex of methylmercury with L-cysteine is structurally similar to L-methionine, a substrate for the LAT system. Mercury then enters the brain as a methylmercury-cysteine (MeHg-S-Cys) complex via the LAT system by being mistaken for L-methionine (Zimmerman et al., 2013).

As early as 1987, Aschner and Clarkson (1987) found that methylmercury-containing compounds were translocated across the BBB by the LAT system. That finding was confirmed by other studies in the 1990s, e.g., Kerper et al. (1992). So, for many years, until about 2013, many believed the paradigm that methylmercury-containing compounds were actively transported across membranes by the LAT system, but ethylmercury-containing compounds were not. This assumption was found to be wrong in a study by Zimmermann et al. (2013).

Zimmermann et al. (2013) compared the toxicities induced by methylmercuric chloride and ethylmercuric chloride, as well as by their complexes with cysteine (MeHg-S-Cys and EtHg-S-Cys) in neuronal cells. They reported that L-methionine, a substrate for the LAT system, significantly protected against the toxicities induced by both complexes (MeHg-S-Cys and EtHg-S-Cys), but not the toxicities of methylmercuric chloride and ethylmercuric chloride. Moreover, L-methionine significantly decreased mercurial uptake when cells were exposed to MeHg-S-Cys or EtHg-S-Cys, but not to methylmercuric chloride or ethylmercuric chloride. These investigators concluded that uptake of MeHg-S-Cys and EtHg-S-Cys into neuronal cells is mediated, at least in part, through the LAT system. So, the LAT system that functions to actively increase neuronal uptake of for MeHg-S-Cys also functions to actively increase neuronal uptake of EtHg-S-Cys. This finding is critically important in the understanding of the ability of ethylmercury-containing compounds to actively be transported across the BBB.

Later, another cellular study by Lohren et al. (2016) examined the transfer of methylmercury chloride, Thimerosal, and mercuric chloride across the BBB. Using a primary porcine in vitro model of the BBB, Lohren et al. (2016) reported that all three species of mercury had cytotoxic effects in the barrier building cells; however, the most damage was caused by the organic species. They found that methylmercury chloride and Thimerosal crossed the barrier in both directions, with a slight accumulation in the basolateral, brain-facing compartment, after simultaneous incubation in both compartments.

2.1. Animal studies – showing accumulation in the brain after exposure to ethylmercury

In addition to the important finding indicating that ethylmercury-containing compounds are actively transported across membranes, including the BBB, there are many studies that specifically examined whether mercury accumulates in the brain after exposure to ethylmercury-containing compounds or Thimerosal. The following section examines animal model studies from a historical perspective.

Beginning as early as 1963, Suzuki et al. (1963) compared the bodily distribution of mercury in mice after subcutaneous administration of methyl-, ethyl- and propyl-mercury acetates. They found that ethylmercury-compounds were proportionally higher in the liver and kidneys and lower in the brain when compared with methylmercury. However, once ethylmercury-containing compounds entered the brain, it did not decrease as observed in other organs (Suzuki et al., 1963). They concluded that their results indicated the stability of the mercury-carbon bond in ethylmercury-containing compounds is lower than that of methylmercury-containing compounds, and hence, it was more easily converted to inorganic mercury-containing compounds that persisted in organs such as the brain.

In 1971, Takahashi et al. (1971) conducted a study in rats and monkeys using ^{203}Hg-ethylmercuric chloride and ^{203}Hg-mercuric chloride (intravenously and intraperitoneally administered). They studied the distribution of the mercury throughout the body. They stated that the evidence indicated that ethylmercury-containing compounds migrated into the brain through the BBB because the radioactivity first appeared in the choroid plexi, intracranial, and extra cerebral arteries, and then into the cerebrum and cerebellum, with no notable mercury in the lateral ventricles. Ethylmercury-containing compounds were found to significantly persist in the brain following administration.

Wright et al. (1973) conducted a study funded by the United States Department of Agriculture using an ethylmercury-containing fungicide, Ceresan M (ethylmercury p-toluene sulfonamide), that was designed to not be water soluble (so it would bind to plant seeds and be less likely to be washed off). Using cattle and sheep, the animals were administered Ceresan M on a daily basis using various doses and periods of time (6–12 days). Using atomic absorption spectrophotometry, they studied these animals for 20 weeks. It started out that most of the mercury went to the kidney and liver, but over time mercury levels increased in the brain and were still present in the brain for some animals 20 weeks after administration the last dose of Ceresan M.

Also in 1973, Tryphonas and Nielsen (1973) conducted a study sponsored by the Medical Research Council of Canada to evaluate the impact of chronic low-dose ethylmercuric chloride administration in young pigs. They observed that extensive neurotoxicity, renal toxicity, and hepatotoxicity was observed with high concentrations of mercury present in many tissues, including the brain. They also reported that tissue concentrations of mercury were directly dose-dependent.

In 1975, two studies showed that Thimerosal administered topically, subcutaneous, or intranasally, accumulates in the brain. First, Blair et al. (1975) intranasally dosed squirrel monkeys with saline or Thimerosal. Mercury concentrations were significantly raised over control values in the brain, liver, muscle and kidney, and yet, interestingly, not in the blood. Second, Gasset et al. (1975) conducted a comparison of topical and subcutaneous administration of Thimerosal to rabbits and their offspring. They reported that the results indicated that Thimerosal crossed both the BBB and placental barrier.

In addition, Yonaha et al. (1975), from the National Institute of Hygienic Sciences, studied uptake, retention, and toxicity of ethylmercury chloride in mice in several organs. These researchers found that ethylmercury chloride was highly incorporated into the brain.

Magos et al. (1985) compared the neurotoxicity of methyl- or ethylmercuric chloride given to rats by gastric gavage. Three or 10 days after the last treatment day, rats treated with ethylmercuric chloride had higher total and organic mercury concentrations in the blood and lower concentrations in kidneys and brain than methylmercuric chloride treated rats. However, inorganic mercury-containing compound concentrations were higher in all tissues, including the brain, after administration of ethylmercuric chloride than methylmercuric chloride.

Also, in 1985, Brzeźnicka and Chmielnicka studied rat liver, kidneys, blood, and brain tissue after a 2-week administration of methylmercuric chloride or ethylmercuric chloride in rats. Similar to Magos et al. (1985), just mentioned, the brain concentration of inorganic mercury-compounds were always higher in the rats treated with ethylmercuric chloride as compared to methylmercuric chloride (Brzeźnicka and Chmielnicka, 1985). Results from these two studies suggest that ethylmercury-containing compounds are more easily converted to inorganic mercury-containing compounds than methylmercury-containing compounds (Dórea et al., 2013).

Harry et al. (2004) examined mercury concentrations in the brain and kidney following ethylmercury chloride (injection), methylmercurychloride (gavage or injection), or Thimerosal (injection) administration to neonatal mice. They determined total mercury concentrations in blood, kidney, brain, and muscle. All three forms of mercury made their way into the brain. Importantly, by day 7, they found that even though mercury levels were decreased in the blood, mercury levels were unchanged in the brain. This finding is important, because it

shows that even if mercury has left the blood stream, it does not mean that it has left the body or the brain.

In 2005, Burbacher et al. (2005) published a study that examined the systemic disposition and brain distribution of total and inorganic mercury-containing compounds in infant monkeys after exposure to Thimerosal as compared to methylmercury hydroxide. Total mercury and inorganic mercury-containing compound brain concentrations were assessed at 2, 4, 7, or 28 days after the last exposure. Results showed that exposure to injected Thimerosal resulted in the presence of significant mercury concentrations in the blood and brain. Importantly, it was observed that significant declines were observed in blood mercury levels within 21 days post the last injection of Thimerosal (approaching undetectable levels), whereas significant levels of mercury were still present in the brain 28 days post the last injection of Thimerosal. This indicates that blood mercury concentrations are not necessarily indicative of brain mercury concentrations. Furthermore, it was reported that a significant fraction of mercury in the brain following Thimerosal injection was in the form of inorganic mercury-containing compounds. It was observed in this study that the half-life for inorganic mercury-containing compounds in the brain following Thimerosal injection was in excess of 120 days.

Orct et al. (2006) compared the distribution of subcutaneously administered Thimerosal or mercuric chloride in rats. They administered mercury on days 7, 9 and 11 of pups age, imitating the vaccination of infants. Total mercury was analyzed in blood and organs (kidney, liver and brain). The results showed that mercury was higher in the liver and kidney of the mercuric chloride group than in the Thimerosal exposed group. The brain and blood concentrations of mercury were higher in the Thimerosal exposed group.

Zareba et al. (2007) compared tissue distribution and different rates of mercury decomposition from Thimerosal exposure to a methylmercury-containing compound exposure in neonatal mice (10 days postnatal). Mice were given a single intramuscular injection of either Thimerosal or a methylmercury-containing compound. Tissue samples were collected daily on postnatal day 11-14. In the brain, Thimerosal-exposed mice showed a steady decrease of organic mercury levels following the initial peak, whereas in the methyl mercury-containing compound exposed mice, concentrations peaked on day 2 after exposure. With regards to inorganic mercury-compound concentrations, the young mice treated with Thimerosal had inorganic mercury-containing compound concentrations in the brain that were higher than in the methylmercury-treated animals.

In 2008, Berman et al. (2008) injected mice on postnatal days 7, 9, 11, and 15 with 14.2, 10.8, 9.2, and 5.6 μg mercury/Kg from Thimerosal, respectively. Mercury was found in blood, brain, and kidneys 24 h following the last Thimerosal injection. In addition, they observed 7 days after the last Thimerosal injection that undetectable levels of mercury were found in the blood, but similar levels of mercury were present in the brain and kidneys as were observed 24 h following the last injection of Thimerosal. Once again, revealing that even if mercury has left the blood stream, it does not mean that it has left the body or the brain.

In 2009, Olczak et al. (2009) injected Thimerosal in suckling rats on postnatal days 7, 9, 11 and 15 in four equal doses. They reported that toxicokinetic analysis revealed that mercury from Thimerosal injections accumulated in the rat brain in significant amounts and remained there longer than 30 days after the injection.

Rodrigues et al. (2010) examined the distribution of methyl-, ethyl- and inorganic mercury-containing compounds in rat tissues (brain, heart, kidney, and liver) and in blood following administration of Thimerosal or a methylmercury-containing compound. Mercury was found in the brain after Thimerosal exposure, and the speciation breakdown found was 63% inorganic mercury-containing compounds, 13.5% ethylmercury-containing compounds, and 23.7% methylmercury-containing compounds. Just as in the Burbacher et al. (2005) study mentioned earlier, most of the mercury from Thimerosal had accumulated in the brain as inorganic mercury-containing compounds.

Later in 2012, Blanuša et al. (2012) compared the mercury distribution and rate of excretion in the early period of life following exposure to either Thimerosal or mercuric chloride in suckling rats. Thimerosal or mercuric chloride were administered subcutaneously three times during the suckling period (on the days of birth 7, 9, and 11) to mimic the vaccination schedule in infants. Following day 6, the mercury retention was higher in the brain in the Thimerosal group, whereas the enteral excretion rate was similar, and urinary excretion was much lower compared to mercuric chloride. Importantly, despite decreasing blood mercury levels in the 6-days post Thimerosal administration, and ongoing enteral excretion of mercury, and to a significantly lesser extent in urinary excretion of mercury, no significant decrease in brain mercury levels were observed.

In 2015, Niehoff et al. (2015) using the model organism, *Drosophila melanogaster*, examined uptake of mercury species for mercuric chloride, methylmercury chloride, and Thimerosal. They reported that no mercury was detected in the cerebral region for mercuric chloride, however both organic species showed the ability to cross the BBB. In addition, the mercury level in the brain exceeded the fed concentration indicating mercury enrichment (more for methylmercury chloride than for Thimerosal).

And most recently, Afsordeh et al. (2019), assessed in the prefrontal lobe of rat brains exposed to Thimerosal. In this study, experimental groups received a single dose of Thimerosal (300 μg/kg) postnatally at 7, 9, 11, and 15 days (the control group received nothing). Prefrontal cortex samples were collected and prepared. Microglia and mast cells were increased significantly, and the pro-inflammatory cytokines were significantly increased. Moreover, Thimerosal caused abnormal neurogenic inflammatory reactions and alterations in the neuroimmune cells that lasted for a longer period in the brain than in the blood.

3. Clinical studies-– showing accumulation in the brain after exposure to ethylmercury-containing compounds

Clinical studies were found that show accumulation of mercury in the brain after exposure to ethylmercury-containing compounds. Mal'tsev (1972) commented that, upon autopsy of children who died of ethylmercury-containing compound exposure, degenerative, inflammatory, and necrotic alterations were seen, as well as hemorrhages in the central nervous system, kidney, liver, heart, and intestines.

Between 1969 and 1975 there were 13 cases of exomphalos treated with topically applied Thimerosal (Fagan et al., 1977). Ten of the infants died. Mercury assays were repeated on the formalin-fixed tissues of the 3 cases in which fresh tissue assays had been performed. These three infants all had significant amounts of mercury in their brain that were well in excess of the minimum toxic levels in adults and fetuses.

Later, in 1980, Cinca et al. (1980) reported on four cases of accidental ethylmercury chloride poisoning. Two of the patients showed that this organic mercury compound was very toxic to the brain and spinal cord. All over the entire cerebral cortex (but mostly in the caudal end of the medial surface of the brain), there was nerve cell loss and a diffuse proliferation of neuroglia on microscopic examination of the brain. The midbrain and bulbar (especially the lateral nucleus) reticular formation showed neuroglia activation and neuronal loss. In the cerebellum, the granular layer was also diseased.

3.1. The misconception of ethylmercury-containing compound retention and excretion time

The misconception that ethylmercury-containing compounds do not cross the BBB comes, in part, from the notion, as promoted by the US Centers for Disease Control and Prevention (CDC), that ethylmercury-containing compounds do not stay in the body long enough to cause harm. As stated by the CDC, "…*ethylmercury, which is cleared from the human body more quickly than methylmercury…therefore [it is] less likely*

to cause any harm" (CDC, 2015) Or, as further stated by the CDC, *Thimerosal does not stay in the body a long time so it does not build up and reach harmful levels. When thimerosal enters the body, it breaks down to ethylmercury and thiosalicylate, which are readily eliminated."* (CDC, 2015).

The CDC relies on two studies conducted by Pichichero et al. (2008), (2009) to support this claim. In the Pichichero et al. (2008) study, they obtained blood, stool, and urine samples before vaccination and 12 h to 30 days after vaccination from 216 healthy children. They reported that blood mercury half-life was calculated to be 3.7 days and returned to prevaccination levels by day 30, and that increased mercury levels were detected in stools after vaccination. Similarly, in the Pichichero et al. (2009) study in premature infants, blood mercury half-life was calculated to be 6.3 days, and mercury levels returned to prevaccination levels by day 30. In both studies the authors stated that the blood mercury half-life following injection of Thimerosal-containing vaccines to infants is substantially shorter than that of oral methylmercury in adults.

From the Pichichero et al. studies, the CDC concluded that ethylmercury-containing compounds quickly leave the body and that they are most likely eliminated in the stools (although the amount of mercury found in the stools in the Pichichero et al. (2008) study was a fraction of what was injected). These researchers did not perform 'mass balance' calculations, based on the amount of mercury eliminated in the stools, and it is hard to find information on stool volume in newborns, so it is difficult to estimate whether the whole dose was actually eliminated or not over 30 days, despite returning to background levels. It is also important to mention that there were background levels of methylmercury in the newborns in that study. Hence, Thimerosal injection causes a worrying spike (roughly six-fold increase in blood levels) of mercury entering the children's bodies on top of background mercury exposure.

Further, the assumption that once mercury is no longer in the blood and that stool mercury excretion is sufficient to rapidly eliminate the total mercury dose received is not supported by any of the aforementioned research. For instance, the Harry et al. (2004) study, as mentioned earlier, examined mercury concentrations in the brain and kidney following ethylmercury-containing compound (injection), methylmercury chloride (gavage or injection), or Thimerosal (injection) administration to neonatal mice. Similar to Pichichero et al., Harry et al. found that by day 7 mercury levels were decreased in the blood; however, even though mercury was decreased in the blood stream, the mercury levels were unchanged in the brain. Burbacher et al. (2005), also mentioned earlier, found that Thimerosal exposure had, for the most part, resulted in the accumulation of inorganic mercury-compounds in the brain, which explains how the levels in the brain in the Harry et al. study remained the same. It is very difficult for mercury to leave the brain once it has converted to inorganic mercury-compounds. The finding that ethylmercury-containing compounds are converted to inorganic mercury-containing compounds once entering the brain is also supported by the Rodrigues et al. (2010) study, also mentioned earlier. These investigators found that the percentages for the forms of mercury in brain after Thimerosal exposure were 63% inorganic mercury-containing compounds, 13.5% ethylmercury-containing compounds, and 23.7% methylmercury-containing compounds.

It is important to note that once ethylmercury-containing compounds enter the brain, evidence indicates ethylmercury-containing compounds easily cross cellular membranes and concentrate inside of cells. For example, ethylmercury-containing compounds were observed to concentrate by a factor of 5-5.6-fold along the inner membrane of astrocytes, and by a factor of 1,000-fold inside the mitochondrial membrane (Sharpe et al., 2012; Wehe et al., 2014; Clayton et al., 2005). Once ethylmercury-containing compounds concentrate in this fashion within cells, the relatively weaker carbon-mercury bond in ethylmercury-containing compounds allows it to be more easily broken-down into inorganic mercury-containing compounds than occurs with methymercury-containing compounds. Once mercury is in an inorganic state, it has a very low potential to exit and it can exert a direct toxic effect on cells (Geier et al., 2009).

4. Current use of Thimerosal

Although Thimerosal has been removed from some childhood vaccines in the United States (US), Thimerosal is still used in many childhood vaccines in the developing world. In the US, Thimerosal is still used in the meningococcal vaccine which is recommended for young adults going to college. Thimerosal was also in the tetanus-toxoid vaccine until a few years ago and it is given to individuals of all ages (Johns Hopkins Bloomberg School of Public Health, 2019). Further, in the US, over half of influenza-vaccine doses (> 75 million) still contain a preservative level of Thimerosal.

5. Current opinion on the safety of Thimerosal

Whether Thimerosal exposure has any impact on children's development is a controversial issue. As stated by DeSoto and Hitlan (2010) in their review of the controversy, *"This particular controversy does have truly high stakes for many reasons."* There are claims that Thimerosal is safe for use in children (Boom et al., 2018) and there are claims that it is not (Geier et al., 2017), and there is research to support both claims. To add to the confusion, the US CDC claims that Thimerosal is safe (CDC, 2015) and yet there are three CDC sponsored studies that find Thimerosal exposure is associated with tic disorder in children (Thompson et al., 2007; Verstraeten et al., 2003; Barile et al., 2012). Sometimes, even the same researchers have found conflicting results. For example, Mrozek-Budzyn et al. (2012) reported an adverse effect from neonatal Thimerosal containing vaccines on psychomotor development index scores. Then later, Mrozek-Budzyn et al. (2015) conducted another study in Poland (using different developmental tests from their first study) that did not find a relationship between exposure to Thimerosal and children's development. It should be mentioned many developing countries (where Thimerosal is still used) may have a higher background mercury contamination than in the US or Europe (such as in the Polish study). Hence, the combination of a significant background presence of mercury in newborn babies coupled with mercury in vaccinations could compound the problem and more likely impact development (Dórea, 2018).

In its totality, a review of the studies on the issue of safety of mercury exposure in children reveals that the vast majority of studies find that mercury, in all its forms, is harmful (Kern et al., 2016). Unfortunately, the Precautionary Principle, in this instance, has not been adopted because both the CDC and the US Food and Drug Administration (US FDA) promote the notion that methylmercury is harmful and ethylmercury is safe (CDC, 2015; US FDA, 2018).

6. Conclusion

As mentioned, scientific research can provide us with factual, repeatable, measurable, and determinable results. It can provide researchers and clinicians with evidenced-based information by asking important questions in healthcare, such as, do ethylmercury-containing compounds cross the BBB, particularly Thimerosal, which is used as a preservative in some medical products such as in vaccines and allergy testing. The aforementioned studies address this question and their research provides an answer that is biologically plausible, consistent, measurable, and repeatable. Although the article published by Boom et al. (2018) was most likely well-intentioned, adherence to evidence in science is important.

Thimerosal is an ethylmercury-containing pharmaceutical compound that is 49.55% mercury. Thimerosal was developed in 1927 (Geier and Geier, 2007). Thimerosal was designed in the 1920s to solve problems with the use, at that time, of elemental mercury and mercury

chloride as a bactericide and fungicide. Elemental mercury was observed to have only limited toxicity and mercuric chloride (which was more toxic) was minimally capable of penetrating membranes. Thimerosal is a designer mercury compound with unique features, including: (1) high water solubility, (2) high ability to penetrate cellular members, and (3) intracellular release of highly toxic inorganic mercury-containing compounds that persist from many days to many years following exposure.

Since, Thimerosal was designed to penetrate membranes and release intracellular inorganic mercury-containing compounds, it should not be surprising that the evidence regarding Thimerosal indicates that its ethylmercury-containing breakdown compounds readily cross the BBB and result in significant and persistent inorganic mercury-containing compounds within the brain. This review indicates that following an initial phase of a few days or weeks during which time mercury levels in the blood are significantly increased by Thimerosal exposure, on a more long-term basis, mercury levels in the blood return to background levels (and ongoing fecal excretion of mercury is occurring), but, yet, significant inorganic mercury-compounds were observed to persist in the brain for months or even potentially years following Thimerosal exposure. As a result, Thimerosal studies clearly establish its significant toxicity and the long-term persistence of its intracellular inorganic mercury breakdown compounds.

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Declaration of Competing Interest

This work has not been published previously. It is not under consideration for publication elsewhere. It is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

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