

Statement of Dr. Thomas Burbacher
Subcommittee on Labor, HHS Appropriations
October 5, 2004

Comparison of Blood and Brain Mercury Levels in Infant Monkeys Exposed to Methylmercury or Vaccines Containing Thimerosal

Our study was initiated to provide a direct comparison of the blood and brain levels of mercury in infant nonhuman primates exposed orally to methylmercury or via i.m. injections of vaccines containing thimerosal. Nonhuman primates have been used extensively in previous studies of methylmercury toxicokinetics and developmental neurotoxicity. The routes of administration (oral for methylmercury and i.m. injection for thimerosal-containing vaccines) were chosen to mimic the two routes of mercury exposure for humans. The dosages and schedule of administration of mercury were chosen to be comparable to the current immunization schedule for human newborns, taking into consideration the faster growth (approximately 4 to 1) of the macaque infant. The results of this study provide important new information regarding the comparative toxicokinetics of these two compounds in newborns and infants. We used normal birth weight monkeys.

Infants were assigned to 1 of 3 exposure groups at birth. Seventeen infants assigned to the thimerosal group were given the typical schedule of vaccines for human infants. Seventeen infants assigned to the methylmercury group were given methylmercury in an oral dose.

Another seven were assigned to a control group. These infants did not receive any gavages or i.m. injections. Infants were assigned to the three groups on a semi-random basis, in order to balance gender ratios and average birth weights across groups.

We drew blood samples from the infants at birth and at 2, 4 and 7 days after the initial Hg exposure. After subsequent exposures we drew their blood at 7 and 14 days. Depending on the sacrifice group (see below) blood was drawn up to 28 days after the final exposure on day 21 to further characterize the washout kinetics of Hg. Autopsies were performed on the animals to determine the mercury levels.

Results

All infants were healthy and there were no significant differences in the weight gain across the 3 groups. We observed similar peak (day 2) levels of total Hg in the blood were observed for methylmercury exposed and thimerosal exposed infants after the first exposure (at birth). This showed that the initial distribution of total Hg to the blood following oral methylmercury exposure is a good predictor of the initial distribution of total Hg to the blood following i.m. injections of thimerosal.

The peak (day 2) levels of total Hg in the blood after subsequent exposures (weeks 1, 2, and 3), however, were very different. Hg accumulated in the blood of the methylmercury exposed infants with subsequent doses.

Total blood Hg levels declined rapidly in between doses for the thimerosal exposed infants. This resulted in minimal accumulation in blood Hg levels during the subsequent weekly doses. The elimination of total Hg in the blood of the thimerosal exposed infants was biphasic with an initial fast half-life and a slower terminal half-life.

On the basis of these results we concluded that the half-life of total mercury in the blood following repeated oral methylmercury exposure will significantly overestimate the levels of total Hg in the blood of infants exposed to repeated i.m. injections of thimerosal.

We found that the half-life of total Hg in the brain of thimerosal-exposed infants was considerably shorter than the half-life of total Hg in the brain of methylmercury exposed infants. Thus the half-life of total mercury in the brain following repeated oral methylmercury exposure will significantly overestimate the levels of total Hg in the brain

of infants exposed to repeated i.m. injections of thimerosal.

The level of total Hg in the brain of the methylmercury-exposed infants was approximately 2.5 times the level of mercury in their blood. For the thimerosal-exposed infants, the level of Hg in the brain was approximately 3.5 times the level of mercury in their blood. This leads to the conclusion that the brain to blood ratio of total mercury following repeated oral methylmercury exposure will significantly underestimate the level of Hg in the brain of infants exposed to repeated i.m. injections of thimerosal.

The half-lives of total Hg in the brain of thimerosal-exposed and methylmercury-exposed infants were considerable longer than the corresponding estimated half-life of total Hg in blood. Thus total Hg in the blood is a poor predictor of target organ (brain) total Hg levels following repeated exposures to methylmercury or thimerosal.

In addition to total Hg levels in the brain, levels of both organic and inorganic Hg were obtained during the washout period. The half-life for organic Hg in the brain was close to the half-life for total Hg. The half-life for organic Hg is significantly shorter than the half-life for total Hg in brain. This leads to the conclusion that the half-life of organic Hg in the brain following repeated oral methylmercury exposure will significantly overestimate the levels of organic Hg in the brain of infants exposed to repeated i.m. injections of thimerosal.

The concentration of inorganic Hg in the brain samples was below the quantifiable limit of the assay (7 ppb) in 8 of 17 methylmercury-exposed infants. The average concentration of inorganic Hg for those infants with values above the detection limit (N=10) was approximately 7 to 8 ppb. Inorganic Hg represented only 6% to 10% of total Hg in the brain. The half-life of inorganic Hg in the brain could not be estimated because levels did not change over the 28 days of washout.

The inorganic form of Hg was readily measurable in the brains of the thimerosal-exposed infants. The average concentration of inorganic Hg was approximately 16 ppb. This

level of inorganic Hg represented 21 % to 86% of the total Hg in the brain. These values are considerably higher than the inorganic fraction observed in the brain of methylmercury infants. Again, the half-life of inorganic Hg in the brain could not be estimated because levels did not change over 28 days of washout. These findings lead to the conclusion that the demethylation rate of Hg following repeated oral methylmercury exposure will significantly underestimate the levels of inorganic Hg in the brain of infants exposed to repeated i.m. injections of thimerosal. Furthermore, inorganic Hg in the brain has a long half-life (over 120 days) that could not be estimated in this study.

General conclusions (and some recommendations):

1). Methylmercury is not a suitable reference for risk assessment from exposure to thimerosal derived Hg. There are significant differences in the toxicokinetics of Hg following repeated oral exposure to methylmercury when compared to exposure to repeated i.m. injections of thimerosal.

Thimerosal Hg clears the blood and brain much faster than Hg following oral methylmercury exposure. Levels of Hg in blood and brain are 3 to 4 times lower following repeated equal doses of thimerosal Hg when compared to oral methylmercury.

The conversion of organic Hg to inorganic Hg is much more extensive following repeated i.m. injections of thimerosal than repeated oral methylmercury exposure. The significance of this increased demethylation rate and the resulting inorganic Hg levels in the brain is unknown and should be investigated.

2). The elimination of total Hg in the blood of the thimerosal exposed infants has 2 phases. Studies of blood Hg clearance in human infants receiving vaccines should be sure to use data collection and analysis techniques to examine the slower terminal phase of clearance in addition to the faster initial phase.

3). Blood Hg may not be a good indicator of risk of adverse effects on the brain, particularly under conditions of rapidly changing blood levels such as those observed

following vaccinations. Data from the current study indicate that while little accumulation of Hg in the blood occurs over time with repeated vaccinations, accumulation of Hg in the brain does occur. Thus, conclusions drawn from blood Hg clearance data in human infants receiving vaccines may not be a good indicator of risk, given the significantly slower half-life of Hg in the brain.

4). There is much we do not know about thimerosal derived Hg. Knowledge of the biotransformation of thimerosal, the chemical identity of the Hg-containing species in the blood and brain, and the neurotoxic potential of intact thimerosal and its various biotransformation products are urgently needed to afford a meaningful interpretation of the potential developmental effects of immunizations with thimerosal-containing vaccines in newborns and infants. This information is critical if we are to respond to public concerns regarding the safety of childhood immunizations.