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

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Thimerosal is a preservative that has been used in manufacturing vaccines since the 1930s. Reports have indicated that infants can receive ethylmercury (in the form of thimerosal) at or above the U.S. Environmental Protection Agency guidelines for methylmercury exposure, depending on the exact vaccinations, schedule, and size of the infant. In this study we compared the systemic disposition and brain distribution of total and inorganic mercury in infant monkeys after thimerosal exposure with those exposed to MeHg. Monkeys were exposed to MeHg (via oral gavage) or vaccines containing thimerosal (via intramuscular injection) at birth and 1, 2, and 3 weeks of age. Total blood Hg levels were determined 2, 4, and 7 days after each exposure. Total and inorganic brain Hg levels were assessed 2, 4, 7, or 28 days after the last exposure. The initial and terminal half-life of Hg in blood after thimerosal exposure was 2.1 and 8.6 days, respectively, which are significantly shorter than the elimination half-life of Hg after MeHg exposure at 21.5 days. Brain concentrations of total Hg were significantly lower by approximately 3-fold for the thimerosal-exposed monkeys when compared with the MeHg infants, whereas the average brain-to-blood concentration ratio was slightly higher for the thimerosal-exposed monkeys (3.5 ± 0.5 vs. 2.5 ± 0.3). A higher percentage of the total Hg in the brain was in the form of inorganic Hg for the thimerosal-exposed monkeys (34% vs. 7%). The results indicate that MeHg is not a suitable reference for risk assessment from exposure to thimerosal-derived Hg. Knowledge of the toxicokinetics and developmental toxicity of thimerosal is needed to afford a meaningful assessment of the developmental effects of thimerosal-containing vaccines. *Key words:* brain and blood distribution, elimination half-life, ethylmercury, infant nonhuman primates, methylmercury, thimerosal. *Environ Health Perspect* 113:1015–1021 (2005). doi:10.1289/ehp.7712 available via *http://dx.doi.org/* [Online 21 April 2005]

Public perception of the safety and efficacy of childhood vaccines has a direct impact on immunization rates (Biroscak et al. 2003; Thomas et al. 2004). The current debate linking the use of thimerosal in vaccines to autism and other developmental disorders [Institute of Medicine (IOM) 2001, 2004] has led many families to question whether the potential risks associated with early childhood immunizations may outweigh the benefits (Blaxill et al. 2004; SafeMinds 2005). Thimerosal is an effective preservative that has been used in the manufacturing of vaccines since the 1930s. Thimerosal consists of 49.6% mercury by weight and breaks down in the body to ethylmercury and thiosalicylate (Tan and Parkin 2000). Recent reports have indicated that some infants can receive ethylmercury (in the form of thimerosal) at or above the U.S. Environmental Protection Agency (EPA) guidelines for methylmercury exposure (U.S. EPA 2005), depending on the exact vaccinations, schedule, and size of the infant (Ball et al. 2001). Clements et al. (2000) calculated that children receive 187.5 μg of ethylmercury from thimerosal-containing vaccines given over the first 14 weeks of life. According to the authors, this amount approaches or, in some cases, exceeds the U.S. EPA guidelines for MeHg exposure during pregnancy (0.1 μg/kg/day). Other estimates (Halsey 1999) have indicated that the schedule could provide repeated doses of ethylmercury from approximately 5 to 20 μg/kg over the first 6 months of life. Studies in preterm infants indicate that blood levels of Hg after just one vaccination (hepatitis B) increase by > 10-fold to levels above the U.S. EPA guidelines (Stajich et al. 2000).

The U.S. EPA guidelines for MeHg (U.S. EPA 2005) are based on several decades of studies of humans and animal models of developmental toxicity (Burbacher et al. 1990a; National Research Council 2000). Because few data exist for ethylmercury, the use of the MeHg guidelines would seem appropriate if the two compounds have similar toxicokinetic profiles and neurodevelopmental effects. The results from the few studies that have provided a direct comparison of these two compounds have been reviewed recently by Magos (2003), who concluded that *a*) Hg clears from the body faster after the administration of ethylmercury than after the administration of MeHg; *b*) the brain-to-blood Hg concentration ratio established for MeHg will overestimate Hg in the brain after exposure to ethylmercury; and *c*) because ethylmercury decomposes faster than MeHg, the risk of brain damage is less for ethylmercury than for MeHg. These conclusions are based on only a few studies, none of which included measurements of both blood and brain Hg levels in infant subjects.

We initiated the present study in order to directly compare the blood and brain levels of Hg in infant nonhuman primates exposed orally to MeHg or via intramuscular (im) injections of vaccines containing thimerosal. Nonhuman primates have been used extensively in previous studies of MeHg toxicokinetics and developmental neurotoxicity (Burbacher et al. 1986, 1990b; Gunderson et al. 1986, 1988; Rice and Gilbert 1982, 1990, 1995; Stinson et al. 1989; Vahter et al. 1994, 1995). The routes of administration (oral for MeHg and im injection for thimerosal-containing vaccines) were chosen to mimic the two routes of Hg exposure for humans. The dosages and schedule of administration of Hg were chosen to be comparable with the current immunization schedule for human newborns, taking into consideration the faster growth (~ 4 to 1) of the macaque infant (Gunderson and Sackett 1984). The results of the present study provide important new information regarding the comparative toxicokinetics of these two compounds in newborns and infants.

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