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LETTER TO THE EDITOR

Modeling Neurodevelopment Outcomes and Ethylmercury Exposure from Thimerosal-Containing Vaccines

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Dear Editor,

The neurotoxic effects of ethylmercury (EtHg) accidentally consumed in Iraq were sufficient to withdraw ethylmercury-containing fungicides as seed dressing. Despite that, not only did thimerosal continue to be used in pharmaceutical preparations but also toxicological interest in EtHg-derived substances diminished considerably and was never addressed with regard to the small quantities used as a vaccine preservative. Thimerosal-containing vaccines (TCV) have no record of overt clinical neurological consequences due to EtHg, and the plausibility of subtle neurotoxic effects in children has been recognized only recently by the United States and other industrialized countries. In this context, we welcome the interesting work of Berman *et al.* (2008); it is clear that this assiduous study (in immunologically susceptible mice) took into consideration doses and schedules of TCV-Hg concentrations that had been used in infants in the United States. Their mice model does not, however, cover the full extent of modifying factors associated with TCV-Hg exposure in the majority of immature and newborns around the world that still have to depend on TCV.

According to Berman *et al.* (2008), the United States vaccination scheduled exposed a total of 125 μgHg distributed at 2, 2, and 6 months through TCV (hepatitis B and DTP). This type of vaccine is no longer used in industrialized countries but it is still used all over the world. We know that thimerosal concentrations vary among brands of vaccines and also that immunization schedules vary depending on a country's health policy; not only that but new outbreaks of disease introduce additional new vaccines (which may contain thimerosal) during the first year of life. As an example, the public health services of Brazil, like other countries, still uses several brands of hepatitis B vaccine (containing thimerosal as preservative) with concentrations ranging from 12.5 to 50 μgHg per 0.5 ml shot. Another salient difference between countries that use TCV (like Brazil) and the United States is that in the former country hepatitis B inoculation starts within the first 12–24 h after birth (Marques *et al.*, 2007) and is administered to low-birth weight $\geq$2000 g (Ministério, da Saúde, 2006 and premature babies who are also recommended a fourth shot as an additional booster (DI/DH/CVE, 2006). In such situations, not only toxicokinetics (TK) but especially toxicodynamics (TD) of EtHg are entirely different between a 1-day-old (with different stages of immaturity and birth weight) and a 60-day-old child (as modeled).

The newborn presents several physiological degrees of immaturity in the excretory system (kidneys and bile formation) and target organ (central nervous system, CNS) that are important modifiers of EtHg TK and TD. These features are inversely accentuated by gestational age and birth weight. Under such circumstances, unbound circulating EtHg in a newborn (and immature) may not be eliminated as fast as in a 2-month-old baby and thus will be readier to cross the more vulnerable blood-brain barrier (BBB). The newborn BBB increases in effectiveness with age; therefore, the free EtHg can more easily penetrate the immature CNS (Dorea, 2007). As a consequence, the smaller the body size and blood volume, the more altered the TD and TK of EtHg. Indeed, Stajich *et al.* (2000) showed that preterm infants do not metabolize Hg efficiently. Collectively, studies show that larger babies have significantly higher mean liver metallothionein than smaller babies (Dorea, 2007).

Factors associated with protein-binding capacity, excretion mechanisms, and enzyme activities are immature in the neonate and modulate differences in adverse effects between newborns and infants exposed to neurotoxic substances. During the period of immaturity, not only plasma albumin but also total protein concentrations decrease (Dorea, 2007). The best example in differences between neurotoxic effects is the type of albumin and competition for binding sites (due to increased circulatory concentrations of bilirubin). Albumin binding (to bilirubin) is less effective during the first postnatal days and, as a consequence, excess free bilirubin can cross the BBB at early stages of the postnatal CNS immaturity

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and cause brainstem abnormalities; albumin priming can be effective in attenuating effects caused by unbound bilirubin (Dorea, 2007).

We do not dispute the conclusions drawn by Berman *et al*. regarding Hg and the neurobiology of autism; however, we think it is possible to take their findings one step further in regards to thimerosal neurotoxicity. We contend that these findings are appropriate for U.S.-like scenarios (as intended by the authors) but are not sufficient to address the current TCV schedules in the majority of newborns and infants around the world. TCV are used worldwide in vaccination schedules that include more of these vaccines at an earlier age. Unfortunately, the differences that set newborns (especially low-birth-weights and prematures) apart from 2-month-old infants have not yet been modeled in experimental studies and remain neglected in TK and TD knowledge of TCV-EtHg exposure. We hope that studies like Berman *et al*. (2008) can inspire conventional toxicology to address uncertainties regarding current serial EtHg exposure in newborns and infants that have to take TCV.

REFERENCES

Berman, R. F., Pessah, I. N., Mouton, P. R., Mav, D., and Harry, J. (2008). Low-level neonatal thimerosal exposure: Further evaluation of altered neurotoxic potential in SJL mice. *Toxicol. Sci.* **101,** 294–309.

Dórea, J. G. (2007). Exposure to mercury during the first six months via human milk and vaccines: Modifying risk factors. *Am. J. Perinatol.* **24,** 387–400.

Marques, R. C., Dórea, J. G., Manzatto, A. G., Bastos, W. R., Bernardi, J. V., and Malm, O. (2007). Time of perinatal immunization, thimerosal exposure and neurodevelopment at 6 months in breastfed infants. *Acta Paediatr.* **96,** 864–868.

MS—Ministério da Saúde. (2006). *Manual dos centros de referência para imunobiológicos especiais. Série A.* Normas e Manuais Técnicos. 188.

DI/DH/CVE—Divisao de Imunizacao, Divisão de Hepatites, Centro de Vigilancia Epidemiologica "Prof. Alexandre Vranjac". (2006). Hepatitis B vaccine. *Rev. Saúde Púb.* **40,** 1137–1140.

Stajich, G. V., Lopez, G. P., Harry, S. W., and Sexson, W. R. (2000). Iatrogenic exposure to mercury after hepatitis B vaccination in preterm infants. *J. Pediatr.* **136,** 679–681.