



# Neurodevelopment of Amazonian children exposed to ethylmercury (from Thimerosal in vaccines) and methylmercury (from fish)



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## ABSTRACT

Few studies have addressed co-occurring methylmercury (MeHg) from maternal origin and ethylmercury (EtHg) from Thimerosal-containing vaccines (TCVs) during infant's neurodevelopment. We studied children ( $n = 1139$ ) from the Western Amazon based on combined (low, intermediate, and high) exposure to chronic MeHg from fish consumption and acute TCV- EtHg. Neurodevelopment outcomes were age of walking and age of talking, and the Bayley Scale of Infant Development (BSID). The Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) were measured at six and 24 months of age. Median hair-Hg (HHg) at birth was  $6.4 \mu\text{g g}^{-1}$  in mothers, and  $1.94 \mu\text{g g}^{-1}$  in newborns; total (pregnancy and infancy) EtHg exposure ranged from 0 to  $187.5 \mu\text{g}$ . The combined (MeHg + EtHg) exposure showed significant differences for MDI but not for PDI; however, there was a significant decrease in both MDI and PDI scores at 24 months. The increase in BSID delays (scores  $< 80$ ) between six and 24 months was not discernible with regards to EtHg or MeHg exposure. We found a statistically significant increase in neurodevelopmental (BSID) delays related to the combined exposure to Hg (MeHg  $>$  EtHg). Neurodevelopment delays due to low-doses of organic mercury (albeit undiscernible) are not predictable but can be avoided by choosing low-Hg fish and providing Thimerosal-free vaccines.

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## 1. Introduction

During developmental periods extending from prenatal stages, the brain is more vulnerable to the adverse effects of toxic insults than at more mature stages; however, experience-guided development drives neuro-cognition achievements. Early brain susceptibility to mercury toxicity (Clarkson et al., 2003) and adverse neurological outcomes have been reported in animal experiments (*in vivo* and *in vitro*) as well as in human epidemiological studies (Dórea, 2013; Grandjean et al., 2014). In fish-eating populations of the Amazon, during prenatal and postnatal life, not only methylmercury (MeHg) but also ethylmercury (EtHg) in Thimerosal-containing vaccines (TCV) are the main forms of organic mercury exposure to the developing human brain (Marques et al., 2013a).

The first indication of EtHg neurotoxic effects on development resulted from high doses during the accidental mass poisoning in Iraq (Clarkson et al., 1976). Children born to women exposed to

food contaminated with organic Hg (both MeHg and EtHg) showed impairment derived from neurological examination scores and milestone (age of first walking and first talking) delays (Marsh et al., 1987). Despite strong evidence of potential effects of low-doses of Thimerosal/EtHg (Geier et al., 2015), studies addressing only TCV-EtHg exposures and association with neurodevelopmental effects are conflicting in population studies conducted in developed countries (Dórea, 2010).

Despite a shorter residence time in the blood, compared with MeHg, Thimerosal-EtHg stays longer in the brain of monkeys (Burbacher et al., 2005). Thimerosal/EtHg toxicity tests conducted *in vitro* (molecular and cellular level) have shown perturbations of toxicity pathways of equal magnitude to that found for MeHg (Dórea, 2013). Experimental studies with Thimerosal/EtHg doses (simulating TCV) on tissue structure, function, and animal behavior have demonstrated neurotoxic effects in different species such as monkeys, hamsters, mice, and rats (Dórea, 2013); untoward effects of Thimerosal-EtHg on neurodevelopment have also been found in population studies (Dórea, 2013; Geier et al., 2015).

During pregnancy and lactation, subsistence fish-eating Amazonian mothers can pass relatively large amounts of Hg to fetuses and to breastfed infants (Marques et al., 2013a; Vieira et al., 2013).

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