

# Integrating Experimental (In Vitro and In Vivo) Neurotoxicity Studies of Low-dose Thimerosal Relevant to Vaccines

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**Abstract** There is a need to interpret neurotoxic studies to help deal with uncertainties surrounding pregnant mothers, newborns and young children who must receive repeated doses of Thimerosal-containing vaccines (TCVs). This review integrates information derived from emerging experimental studies (in vitro and in vivo) of low-dose Thimerosal (sodium ethyl mercury thiosalicylate). Major databases (PubMed and Web-of-science) were searched for in vitro and in vivo experimental studies that addressed the effects of low-dose Thimerosal (or ethylmercury) on neural tissues and animal behaviour. Information extracted from studies indicates that: (a) activity of low doses of Thimerosal against isolated human and animal brain cells was found in all studies and is consistent with Hg neurotoxicity; (b) the neurotoxic effect of ethylmercury has not been studied with co-occurring adjuvant-AI in TCVs; (c) animal studies have shown that exposure to Thimerosal-Hg can lead to accumulation of inorganic Hg in brain, and that (d) doses relevant to TCV exposure possess the potential to affect human neuro-development. Thimerosal at concentrations relevant for infants' exposure (in vaccines) is toxic to cultured human-brain cells and to laboratory animals. The persisting use of TCV (in developing countries) is counterintuitive to global efforts to lower Hg exposure and to ban Hg in medical products; its continued use in TCV requires evaluation of a sufficiently nontoxic level of ethylmercury compatible with repeated exposure (co-occurring with adjuvant-AI) during early life.

**Keywords** Children · Infants · Neurodevelopment · Pregnancy · Ethylmercury · Thimerosal

## Introduction

The prevalence of emerging neuro-developmental disabilities has been directly linked to environmental neurotoxic substances which are estimated to affect 3% of children [1]; environmental mercury exposure, mainly methylmercury from seafood [1] and elemental mercury from coal combustion (used in electrical utilities) as well as municipal and medical waste incinerators [2], is at the center of concerns. However, a considerable part of these disabilities (25%) may arise as a result of interaction with individual genetic susceptibilities [1]. Indeed it is known that Hg neurotoxicity involves long latencies and atypical responses between low and high doses [3]; additionally, it has now been shown that exposure to different forms of mercury (such as methylmercury and Hg vapor) can act synergistically in increasing neurotoxic risks [3].

Organic and inorganic forms of mercury have a long history of use in medicine and pediatrics. Until the 1950s mercury preparations were part of the therapeutic resources to deal with common childhood ailments [4]. Because of its role in pink disease and also with the advent of more specific therapeutic drugs, mercury formulations have been withdrawn from children's medication [4]. Nevertheless, Thimerosal (sodium ethyl mercury thiosalicylate) has remained in wide use as a preservative in pharmaceutical products. Thimerosal in topical formulations has been eliminated in many parts of the world but its use in vaccines for pregnant women, newborns and young children continues in developing countries [5]. Although breast-fed infants can be exposed to elemental Hg from maternal

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