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ScienceDirect
Toxicology in Vitro 22 (2008) 927–934
Toxicology in Vitro
www.elsevier.com/locate/toxinvit

Genotoxicity of thimerosal in cultured human lymphocytes with and without metabolic activation sister chromatid exchange analysis proliferation index and mitotic index

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Received 5 July 2007; accepted 20 January 2008
Available online 1 February 2008

Abstract

Thimerosal is an antiseptic containing 49.5% of ethyl mercury that has been used for years as a preservative in many infant vaccines and in flu vaccines. Thimerosal is an organic mercurial compound used as a preservative in biomedical preparations. In this study, we evaluated the genotoxic effect of thimerosal in cultured human peripheral blood lymphocytes using sister chromatid exchange analysis in culture conditions with and without S9 metabolic activation. This study is the first report investigating the genotoxic effects of thimerosal in cultured human peripheral blood lymphocyte cells using sister chromatid exchange analysis. An analysis of variance test (ANOVA) was performed to evaluate the results. Significant induction of sister chromatid exchanges was seen at concentrations between 0.2 and 0.6 μg/ml of thimerosal compared with negative control. A significant decrease ($p < 0.001$) in mitotic index (MI) and proliferation ındex (PRI) as well as an increase in SCE frequency ($p < 0.001$) was observed compared with control cultures. Our results indicate the genotoxic and cytotoxic effect of TH in cultured human peripheral blood lymphocytes at tested doses in cultures with/without S9 fraction.

Keywords: Genotoxicity; Thimerosal; S9 activation system; Mitotic index; Proliferation index

1. Introduction

Thimerosal (TH, sodium ethylmercury-thiosalicylate,) was developed by Eli Lilly in the 1930 s as an effective bacteriostatic, fungistatic preservative and has been widely used in multidose vials of vaccines and in ophthalmic, otic, nasal, and topical products. (Ball et al., 2001). TH contains 49.6% mercury by weight and releases ethylmercury as a metabolite. In the body, ethylmercury can be converted to inorganic mercury. Inorganic mercury is known to induce membrane and DNA damage (Ferrat et al., 2002; Ben-Ozer et al., 2000), and in cell culture conditions it was shown to be mutagenic and generate DNA breaks. Due to possible adverse health effects, investigations on its metabolism and toxicity are urgently needed. An *in vivo* study on chronic toxicity of TH in rats was inconclusive and reports on genotoxic effects in various *in vitro* and/or *in vivo* systems were contradictory. Little is known about the reactions of human peripheral blood lymphocyte at low concentrations, which can occur after using TH containing products.

In addition, there were reports on genotoxic effects of TH *in vivo*. A weak but significant increase in micronuclei and chromosome aberrations was seen in male Swiss CD–1 mice at doses between 10 and 20 mg/kg (Marrazzini et al., 1994); another study in used male and female (102/E1·C3H/E1) F1 mice and Swiss albino mice reported negative results (Adler et al., 1991).

Possible carcinogenic effects were investigated in one study on the chronic toxicity of TH in Fischer 344 rats (Mason et al., 1971). However, this study does not meet

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doi:10.1016/j.tiv.2008.01.012