

## Evidence for Thimerosal Risk

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Evidence for Thimerosal Risk - Page 1

[Neurochem Res.](#) 2011 Feb 25. [Epub ahead of print]

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.

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#### **Study of some biomarkers in hair of children with autism**

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Abstract

**Introduction:** Autism is a severe developmental disorder, which involves social withdrawal, communication deficits, and stereotypic repetitive behavior. The possible etiologies that precipitate autism symptoms remain controversial in many cases, but both genetic and environmental factors have been implicated. Mercury has gained much attention for a considerable period of time before other exacerbating or protective factors were suggested. The aim of this study was to investigate the relationship between autism and the level of some metals (namely mercury, lead, and copper) or zinc as a counteracting antioxidant element.

**Methods:** The study recruited 32 autistic children and 32 normal controls and all of them were subjected to KID-SCID, Childhood Autism Rating Scale (CARS), Stanford Binet intelligence test, and biochemical analysis of hair samples for the level of mercury, copper, lead and zinc.

**Results:** There were highly significant differences between the level of these substances in the hair of children with autism compared with controls, positive correlation of CARS score with both mercury and copper, while intelligence quotient has significant negative correlation with the level of lead in the hair. The level of zinc does not correlate with either CARS score or intelligence quotient.

**Conclusion:** These preliminary results suggest a complementary role for the studied elements in the pathogenesis of autistic disorder, which should be considered in the management plane.

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[Folia Neuropathol.](#) 2010;48(4):258-69.

Lasting neuropathological changes in rat brain after intermittent neonatal administration of thimerosal.

[Olczak M](#), [Duszczak M](#), [Mierzejewski P](#), [Wierzba-Bobrowicz T](#), [Majewska MD](#).

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### **Abstract**

Thimerosal, an organomercurial added as a preservative to some vaccines, is a suspected iatrogenic factor, possibly contributing to paediatric neurodevelopmental disorders including autism. We examined the effects of early postnatal administration of thimerosal (four i.m. injections, 12 or 240 µg THIM-Hg/kg, on postnatal days 7, 9, 11 and 15) on brain pathology in Wistar rats. Numerous neuropathological changes were observed in young adult rats which were treated postnatally with thimerosal. They included: ischaemic degeneration of neurons and "dark" neurons in the prefrontal and temporal cortex, the hippocampus and the cerebellum, pathological changes of the blood vessels in the temporal cortex, diminished synaptophysin reaction in the hippocampus, atrophy of astroglia in the hippocampus and cerebellum, and positive caspase-3 reaction in Bergmann astroglia. **These findings document neurotoxic effects of thimerosal, at doses equivalent to those used in infant vaccines or higher, in developing rat brain, suggesting likely involvement of this mercurial in neurodevelopmental disorders.**

PMID: 21225508 [PubMed - in process]Free Article

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[Int J Immunopathol Pharmacol.](#) 2010 Oct-Dec;23(4):1015-20.

Luteolin and thiosalicylate inhibit HgCl<sub>2</sub> and thimerosal-induced VEGF release from human mast cells.

[Asadi S](#), [Zhang B](#), [Weng Z](#), [Angelidou A](#), [Kempuraj D](#), [Alysandratos KD](#), [Theoharides TC](#).

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## Abstract

HgCl<sub>2</sub> is a known environmental neurotoxin, but is also used as preservative in vaccines as thimerosal containing ethyl mercury covalently linked to thiosalicylate. We recently reported that mercury chloride (HgCl<sub>2</sub>) can stimulate human mast cells to release vascular endothelial growth factor (VEGF), which is also vasoactive and pro-inflammatory. Here we show that thimerosal induces significant VEGF release from human leukemic cultured LAD2 mast cells (at 1 microM 326±12 pg/10<sup>6</sup> cells and 335.5±12 pg/10<sup>6</sup> cells at 10 microM) compared to control cells (242±21 pg/10<sup>6</sup> cells, n=5, p less than 0.05); this effect is weaker than that induced by HgCl<sub>2</sub> at 10 microM (448±14 pg/10<sup>6</sup> cells) (n=3, p less than 0.05). In view of this finding, we hypothesize that the thiosalicylate component of thimerosal may have an inhibitory effect on VEGF release. Thimerosal (10 microM) added together with the peptide Substance P (SP) at 2 microM, used as a positive control, reduced VEGF release by 90 percent. Methyl thiosalicylate (1 or 10 microM) added with either SP or HgCl<sub>2</sub> (10 microM) inhibited VEGF release by 100 percent, while sodium salicylate or ibuprofen had no effect. Pretreatment for 10 min with the flavonoid luteolin (0.1 mM) before HgCl<sub>2</sub> or thimerosal completely blocked their effect. Luteolin and methyl thiosalicylate may be useful in preventing mercury-induced toxicity.

PMID: 21244751 [PubMed - in process]

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[Acta Neurobiol Exp \(Wars\)](#). 2010;70(2):147-64.

Influence of pediatric vaccines on amygdala growth and opioid ligand binding in rhesus macaque infants: A pilot study.

[Hewitson L](#), [Lopresti BJ](#), [Stott C](#), [Mason NS](#), [Tomko J](#).

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## Abstract

This longitudinal, case-control pilot study examined amygdala growth in rhesus macaque infants receiving the complete US childhood vaccine schedule (1994-1999). Longitudinal structural and functional neuroimaging was undertaken to examine central effects of the vaccine regimen on the developing brain. Vaccine-exposed and saline-injected control infants underwent MRI and PET imaging at approximately 4 and 6 months of age, representing two specific timeframes within the vaccination schedule. Volumetric analyses

showed that exposed animals did not undergo the maturational changes over time in amygdala volume that was observed in unexposed animals. After controlling for left amygdala volume, the binding of the opioid antagonist [(11)C]diprenorphine (DPN) in exposed animals remained relatively constant over time, compared with unexposed animals, in which a significant decrease in [(11)C]DPN binding occurred. **These results suggest that maturational changes in amygdala volume and the binding capacity of [(11)C]DPN in the amygdala was significantly altered in infant macaques receiving the vaccine schedule.** The macaque infant is a relevant animal model in which to investigate specific environmental exposures and structural/functional neuroimaging during neurodevelopment.

PMID: 20628439 [PubMed - indexed for MEDLINE]Free Article

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[Arch Toxicol.](#) 2010 Nov;84(11):891-6. Epub 2010 Apr 13.

Identification and distribution of mercury species in rat tissues following administration of thimerosal or methylmercury.

[Rodrigues JL](#), [Serpeloni JM](#), [Batista BL](#), [Souza SS](#), [Barbosa F Jr.](#)

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### **Abstract**

Methylmercury (Met-Hg) is one the most toxic forms of Hg, with a considerable range of harmful effects on humans. Sodium ethyl mercury thiosalicylate, thimerosal (TM) is an ethylmercury (Et-Hg)-containing preservative that has been used in manufacturing vaccines in many countries. Whereas the behavior of Met-Hg in humans is relatively well known, that of ethylmercury (Et-Hg) is poorly understood. The present study describes the distribution of mercury as (-methyl, -ethyl and inorganic mercury) in rat tissues (brain, heart, kidney and liver) and blood following administration of TM or Met-Hg. Animals received one dose/day of Met-Hg or TM by gavage (0.5 mg Hg/kg). Blood samples were collected after 6, 12, 24, 48, 96 and 120 h of exposure. After 5 days, the animals were killed, and their tissues were collected. Total blood mercury (THg) levels were determined by ICP-MS, and methylmercury (Met-Hg), ethylmercury (Et-Hg) and inorganic mercury (Ino-Hg) levels were determined by speciation analysis with LC-ICP-MS. Mercury remains longer in the blood of rats treated with Met-Hg compared to that of TM-exposed rats. Moreover, after 48 h of the TM treatment,

most of the Hg found in blood was inorganic. Of the total mercury found in the brain after TM exposure, 63% was in the form of Ino-Hg, with 13.5% as Et-Hg and 23.7% as Met-Hg. In general, mercury in tissues and blood following TM treatment was predominantly found as Ino-Hg, but a considerable amount of Et-Hg was also found in the liver and brain. Taken together, our data demonstrated that the toxicokinetics of TM is completely different from that of Met-Hg. Thus, Met-Hg is not an appropriate reference for assessing the risk from exposure to TM-derived Hg. It also adds new data for further studies in the evaluation of TM toxicity.

PMID: 20386881 [PubMed - indexed for MEDLINE]

In other words, it is not settled....

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[Cell Biol Toxicol.](#) 2010 Apr;26(2):143-52. Epub 2009 Apr 9.

Induction of metallothionein in mouse cerebellum and cerebrum with low-dose thimerosal injection.

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### **Abstract**

Thimerosal, an ethyl mercury compound, is used worldwide as a vaccine preservative. We previously observed that the mercury concentration in mouse brains did not increase with the clinical dose of thimerosal injection, but the concentration increased in the brain after the injection of thimerosal with lipopolysaccharide, even if a low dose of thimerosal was administered. Thimerosal may penetrate the brain, but is undetectable when a clinical dose of thimerosal is injected; therefore, the induction of metallothionein (MT) messenger RNA (mRNA) and protein was observed in the cerebellum and cerebrum of mice after thimerosal injection, as MT is an inducible protein. MT-1 mRNA was expressed at 6 and 9 h in both the cerebrum and cerebellum, but MT-1 mRNA expression in the cerebellum was three times higher than that in the cerebrum after the injection of 12 microg/kg thimerosal. MT-2 mRNA was not expressed until 24 h in both organs. MT-3 mRNA was expressed in the cerebellum from 6 to 15 h after the injection, but not in the cerebrum until 24 h. MT-1 and MT-3 mRNAs were expressed in the cerebellum in a dose-dependent manner. Furthermore, MT-1 protein was detected from 6 to 72 h in the cerebellum after 12 microg/kg of thimerosal was injected

and peaked at 10 h. MT-2 was detected in the cerebellum only at 10 h. In the cerebrum, little MT-1 protein was detected at 10 and 24 h, and there were no peaks of MT-2 protein in the cerebrum. In conclusion, MT-1 and MT-3 mRNAs but not MT-2 mRNA are easily expressed in the cerebellum rather than in the cerebrum by the injection of low-dose thimerosal. It is thought that the cerebellum is a sensitive organ against thimerosal. **As a result of the present findings, in combination with the brain pathology observed in patients diagnosed with autism, the present study helps to support the possible biological plausibility for how low-dose exposure to mercury from thimerosal-containing vaccines may be associated with autism.**

PMID: 19357975 [PubMed - indexed for MEDLINE]

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[Toxicol Appl Pharmacol.](#) 2010 Mar 15;243(3):283-91. Epub 2009 Sep 2.

Mercury toxicokinetics--dependency on strain and gender.

[Ekstrand J](#), [Nielsen JB](#), [Havarinasab S](#), [Zalups RK](#), [Söderkvist P](#), [Hultman P](#).

Molecular and Immunological Pathology, Department of Clinical and Experimental Medicine, Linköping University, SE-58185 Linköping, Sweden.

### **Abstract**

Mercury (Hg) exposure from dental amalgam fillings and thimerosal in vaccines is not a major health hazard, but adverse health effects cannot be ruled out in a small and more susceptible part of the exposed population. Individual differences in toxicokinetics may explain susceptibility to mercury. Inbred, H-2-congenic A.SW and B10.S mice and their F1- and F2-hybrids were given HgCl<sub>2</sub> with 2.0 mg Hg/L drinking water and traces of (203)Hg. Whole-body retention (WBR) was monitored until steady state after 5 weeks, when the organ Hg content was assessed. Despite similar Hg intake, A.SW males attained a 20-30% significantly higher WBR and 2- to 5-fold higher total renal Hg retention/concentration than A.SW females and B10.S mice. A selective renal Hg accumulation but of lower magnitude was seen also in B10.S males compared with females. Differences in WBR and organ Hg accumulation are therefore regulated by non-H-2 genes and gender. Lymph nodes lacked the strain- and gender-dependent Hg accumulation profile of kidney, liver and spleen. After 15 days without Hg A.SW mice showed a 4-fold higher WBR and liver Hg concentration, but 11-fold higher renal Hg concentration, showing the key role for the kidneys in explaining the slower Hg elimination in A.SW mice. The trait causing higher mercury accumulation was not

dominantly inherited in the F1 hybrids. F2 mice showed a large inter-individual variation in Hg accumulation, showing that multiple genetic factors influence the Hg toxicokinetics in the mouse. The genetically heterogeneous human population may therefore show a large variation in mercury toxicokinetics.

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PMID: 19732784 [PubMed - indexed for MEDLINE]

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[Clin Chim Acta](#). 2010 Nov 11;411(21-22):1580-6. Epub 2010 Jul 16.

Making sense of epidemiological studies of young children exposed to thimerosal in vaccines.

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### **Abstract**

**OBJECTIVE:** To compare epidemiological studies dealing with neurological issues (compatible with Hg toxicity) linked to exposing newborns and infants to intramuscular doses of preservative-Hg resulting from vaccination with thimerosal-containing vaccines (TCV).

**METHODS:** Major databases were searched for studies that addressed neurodevelopment outcomes other than autism. Eight studies were identified and compared.

**RESULTS:** Information extracted from the studies done in the USA, the UK, and Italy is important in understanding the complex interplay of variables but insufficient to establish non-toxicity for infants and young children still receiving TCV: a) there is ambiguity in some studies reporting neurodevelopment outcomes that seem to depend on confounding variables; b) the risk of neurotoxicity due to low doses of thimerosal is plausible at least for susceptible infants; c) there is a need to address these issues in less developed countries still using TCV in pregnant mothers, newborns, and young children.

**CONCLUSIONS:** Since the use of TCV is still inevitable in many countries, this increases the need to protect vulnerable infants and promote actions that strengthen neurodevelopment. Developing countries should intensify campaigns that include breastfeeding among efforts to help prime the central nervous system to tolerate exposure to neurotoxic substances, especially thimerosal-Hg.



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PMID: 20638374 [PubMed - indexed for MEDLINE]

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[Acta Neurobiol Exp \(Wars\)](#). 2010;70(2):196-208.

Age-dependent lower or higher levels of hair mercury in autistic children than in healthy controls.

[Majewska MD](#), [Urbanowicz E](#), [Rok-Bujko P](#), [Namyslowska I](#), [Mierzejewski P](#).

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### **Abstract**

An association between autism and early life exposure to mercury is a hotly debated issue.

In this study, 91 autistic Polish children, male and female, 3-4 and 7-9 years old, were compared to 75 age- and sex-matched healthy children with respect to: demographic, perinatal, clinical and developmental measures, parental age, birth order, morphometric measures, vaccination history, and hair mercury content. In demographic and perinatal measures there were no consistent differences between the autistic and control groups. Autistic children had a significantly greater prevalence of adverse reactions after vaccinations and abnormal development than controls. Between 45 and 80% of autistic children experienced developmental regress. Autistic children significantly differed from healthy peers in the concentrations of mercury in hair: younger autistics had lower levels, while older - higher levels than their respective controls. The results suggest that autistic children differ from healthy children in metabolism of mercury, which seems to change with age.

PMID: 20628443 [PubMed - indexed for MEDLINE]Free Article

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[Talanta](#). 2010 Jan 15;80(3):1158-63.

Methylmercury and inorganic mercury determination in blood by using liquid chromatography with inductively coupled plasma mass spectrometry and a fast sample preparation procedure.

[Rodrigues JL](#), [de Souza SS](#), [de Oliveira Souza VC](#), [Barbosa F Jr](#).

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## Abstract

Despite the necessity to differentiate chemical species of mercury in clinical specimens, there are a limited number of methods for this purpose. Then, this paper describes a simple method for the determination of methylmercury and inorganic mercury in blood by using liquid chromatography with inductively coupled mass spectrometry (LC-ICP-MS) and a fast sample preparation procedure. Prior to analysis, blood (250µL) is accurately weighed into 15-mL conical tubes. Then, an extractant solution containing mercaptoethanol, l-cysteine and HCl was added to the samples following sonication for 15min. Quantitative mercury extraction was achieved with the proposed procedure. Separation of mercury species was accomplished in less than 5min on a C18 reverse-phase column with a mobile phase containing 0.05% (v/v) mercaptoethanol, 0.4% (m/v) l-cysteine, 0.06molL<sup>-1</sup> ammonium acetate and 5% (v/v) methanol. The method detection limits were found to be 0.25µgL<sup>-1</sup> and 0.1µgL<sup>-1</sup> for inorganic mercury and methylmercury, respectively. Method accuracy is traceable to Standard Reference Material (SRM) 966 Toxic Metals in Bovine Blood from the National Institute of Standards and Technology (NIST). The proposed method was also applied to the speciation of mercury in blood samples collected from fish-eating communities and from rats exposed to thimerosal. With the proposed method there is a considerable reduction of the time of sample preparation prior to speciation of Hg by LC-ICP-MS. Finally, after the application of the proposed method, we demonstrated an interesting in vivo ethylmercury conversion to inorganic mercury.

PMID: 20006068 [PubMed - indexed for MEDLINE]

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[Neurotox Res.](#) 2010 Jul;18(1):59-68. Epub 2009 Sep 16.

Are neuropathological conditions relevant to ethylmercury exposure?

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## Abstract

Mercury and mercurial compounds are among the environmentally ubiquitous substances most toxic to both wildlife and humans. Once released into the environment from both natural and anthropogenic sources, mercury exists mainly as three different molecular species: elemental, inorganic, and organic. Potential health risks have been reported from

exposure to all forms; however, of particular concern for human exposure relate to the potent neurotoxic effects of methylmercury (MeHg), especially for the developing nervous system. The general population is primarily exposed to MeHg by seafood consumption. In addition, some pharmaceuticals, including vaccines, have been, and some continue to be, a ubiquitous source of exposure to mercurials. A significant controversy has been whether the vaccine preservative ethylmercury thiosalicylate, commonly known as thimerosal, could cause the development of autism. In this review, we have discussed the hypothesis that exposure to thimerosal during childhood may be a primary cause of autism. The conclusion is that there are no reliable data indicating that administration of vaccines containing thimerosal is a primary cause of autism. However, one cannot rule out the possibility that the individual gene profile and/or gene-environment interactions may play a role in modulating the response to acquired risk by modifying the individual susceptibility.

PMID: 19756911 [PubMed - indexed for MEDLINE]

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[J Environ Sci \(China\)](#). 2009;21(12):1716-21.

Effects of methyl-, phenyl-, ethylmercury and mercurychlorid on immune cells of harbor seals (*Phoca vitulina*).

[Kakuschke A](#), [Valentine-Thon E](#), [Fonfara S](#), [Kramer K](#), [Prange A](#).

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### **Abstract**

Mercury (Hg) is present in the marine environment as a natural metal often enhanced through human activities. Depending on its chemical form, Hg can cause a wide range of immunotoxic effects. In this study, the influence of methyl-, ethyl- and phenylmercury as well as mercurychloride on immune functions was evaluated. Two parameters of cellular immunity, proliferation and mRNA cytokine expression of interleukin-2, -4, and transforming growth factor beta, were investigated in harbor seal lymphocytes after in vitro exposure to Hg compounds. While all Hg compounds had a suppressive effect on proliferation, differences between juvenile and adult seals were found. Lymphocytes from juveniles showed a higher susceptibility to the toxic effect compared to lymphocytes from adults. Furthermore, the degree of inhibition of proliferation varied among the four Hg compounds. The organic compounds seem to be more immunotoxic than the inorganic

**compound.** Finally, for the cytokine expression of methylmercury-incubated lymphocytes, time-dependent changes were observed, but no dose-dependency was found. Marine mammals of the North Sea are burdened with Hg, and lymphocytes of harbor seals may be functionally impaired by this metal. The present in vitro study provides baseline information for future studies on the immunotoxic effects of Hg on cellular immunity of harbor seals.  
PMID: 20131603 [PubMed - indexed for MEDLINE]

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[Cases J.](#) 2009 Nov 18;2:199.

The usefulness of chelation therapy for the remission of symptoms caused by previous treatment with mercury-containing pharmaceuticals: a case report.

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### **Abstract**

**INTRODUCTION:** A great deal of data regarding the toxicology of mercury has been recently reported. Although the most common human exposures to mercury are currently mercury vapour from amalgam tooth fillings, methylmercury from seafood and ethylmercury as a preservative in vaccines, in the past mercury compounds have been used in the treatment of syphilis.

**CASE PRESENTATION:** Mercury intoxication was found in a 67 year-old Italian man affected by neurological symptoms of apparently unknown origin. The patient developed syphilis forty years ago and then underwent therapy with mercurials to treat his chronic bacterial infection. We treated the patient with disodium edetate chelation therapy. Six months after the beginning of the therapy, the patient's neurological symptoms began to decrease, and were completely cured after two years of therapy.

**CONCLUSION:** This case supports the use of chelation therapy with disodium edetate to remove damages caused by mercury intoxication.

**Don't know what kind of mercury, however. It may not have been ethylmercury.**

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[FASEB J.](#) 2009 Aug;23(8):2374-83. Epub 2009 Mar 23.

Cellular and mitochondrial glutathione redox imbalance in lymphoblastoid cells derived from children with autism.

[James SJ](#), [Rose S](#), [Melnyk S](#), [Jernigan S](#), [Blossom S](#), [Pavliv O](#), [Gaylor DW](#).

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### **Abstract**

Research into the metabolic phenotype of autism has been relatively unexplored despite the fact that metabolic abnormalities have been implicated in the pathophysiology of several other neurobehavioral disorders. Plasma biomarkers of oxidative stress have been reported in autistic children; however, intracellular redox status has not yet been evaluated.

Lymphoblastoid cells (LCLs) derived from autistic children and unaffected controls were used to assess relative concentrations of reduced glutathione (GSH) and oxidized disulfide glutathione (GSSG) in cell extracts and isolated mitochondria as a measure of intracellular redox capacity. The results indicated that the GSH/GSSG redox ratio was decreased and percentage oxidized glutathione increased in both cytosol and mitochondria in the autism LCLs. Exposure to oxidative stress via the sulfhydryl reagent thimerosal resulted in a greater decrease in the GSH/GSSG ratio and increase in free radical generation in autism compared to control cells. Acute exposure to physiological levels of nitric oxide decreased mitochondrial membrane potential to a greater extent in the autism LCLs, although GSH/GSSG and ATP concentrations were similarly decreased in both cell lines. These results suggest that the autism LCLs exhibit a reduced glutathione reserve capacity in both cytosol and mitochondria that may compromise antioxidant defense and detoxification capacity under prooxidant conditions.

PMID: 19307255 [PubMed - indexed for MEDLINE]PMCID: PMC2717775Free PMC Article

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[Biometals](#). 2009 Oct;22(5):697-700. Epub 2009 Feb 11.

Are toxic biometals destroying your children's future?

[Drum DA](#).

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### **Abstract**

Cadmium, arsenic, lead, and mercury have been linked to autism, attention deficit disorder, mental retardation and death of children. **Mercury in thimerosal found in many vaccines and flu shots contributes significantly to these problems. Decomposition of the thimerosal can produce more toxic compounds, either methylethylmercury or diethylmercury, in the body. These compounds have a toxicity level similar to dimethylmercury.** Within the human body, a mitochondrial disorder may release the more toxic form of mercury internally. **Young children and pregnant women must minimize internal exposure to the vaccines and flu shots containing mercury.**

PMID: 19205900 [PubMed - indexed for MEDLINE]

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[Exp Toxicol Pathol.](#) 2009 Mar;61(2):133-6. Epub 2008 Sep 3.

Gender-selective toxicity of thimerosal.

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### **Abstract**

A recent report shows a correlation of the historical use of thimerosal in therapeutic immunizations with the subsequent development of autism; however, this association remains controversial. Autism occurs approximately four times more frequently in males compared to females; thus, studies of thimerosal toxicity should take into consideration gender-selective effects. The present study was originally undertaken to determine the maximum tolerated dose (MTD) of thimerosal in male and female CD1 mice. However, during the limited MTD studies, it became apparent that thimerosal has a differential MTD that depends on whether the mouse is male or female. At doses of 38.4-76.8mg/kg using 10% DMSO as diluent, seven of seven male mice compared to zero of seven female mice tested succumbed to thimerosal. Although the thimerosal levels used were very high, as we were originally only trying to determine MTD, it was completely unexpected to observe a difference of the MTD between male and female mice. **Thus, our studies, although not directly addressing the controversy surrounding thimerosal and autism, and still preliminary due to small numbers of mice examined, provide, nevertheless, the first report of gender-selective toxicity of thimerosal and indicate that any future studies of thimerosal toxicity should take into consideration gender-specific differences.**

PMID: 18771903 [PubMed - indexed for MEDLINE]

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[Toxicol In Vitro](#). 2009 Sep;23(6):1092-9. Epub 2009 Jun 2.

Increase in intracellular Zn<sup>2+</sup> concentration by thimerosal in rat thymocytes: intracellular Zn<sup>2+</sup> release induced by oxidative stress.

[Hashimoto E](#), [Oyama TB](#), [Oyama K](#), [Nishimura Y](#), [Oyama TM](#), [Ueha-Ishibashi T](#), [Okano Y](#), [Oyama Y](#).

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### Abstract

Thimerosal (TMR), an ethylmercury-containing preservative in pharmaceutical products, was recently reported to increase intracellular Zn(2+) concentration. Therefore, some health concerns about the toxicity of TMR remain because of physiological and pathological roles of Zn(2+). To reveal the property of TMR-induced increase in intracellular Zn(2+) concentration, the effect of TMR on FluoZin-3 fluorescence, an indicator of intracellular Zn(2+), of rat thymocytes was examined. TMR at concentrations ranging from 0.3 microM to 10 microM increased the intensity of FluoZin-3 fluorescence in a concentration-dependent manner under external Ca(2+)- and Zn(2+)-free condition. The threshold concentration was 0.3-1 microM. The increase in the intensity was significant when TMR concentration was 1 microM or more. N,N,N',N'-Tetrakis(2-pyridylmethyl)ethylenediamine (TPEN), a chelator for intracellular Zn(2+), completely attenuated the TMR-induced augmentation of FluoZin-3 fluorescence. Hydrogen peroxide (H(2)O(2)) and N-ethylmaleimide, reducing cellular thiol content, significantly increased FluoZin-3 fluorescence intensity and decreased 5-chloromethylfluorescein (5-CMF) fluorescence intensity, an indicator for cellular thiol. The correlation coefficient between TMR-induced augmentation of FluoZin-3 fluorescence and attenuation of 5-CMF fluorescence was -0.882. TMR also attenuated the 5-CMF fluorescence in the presence of TPEN. Simultaneous application of H(2)O(2) and TMR synergistically augmented the FluoZin-3 fluorescence. It is suggested that TMR increases intracellular Zn(2+) concentration via decreasing cellular thiol content.

PMID: 19497362 [PubMed - indexed for MEDLINE]

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[J Ocul Pharmacol Ther](#). 2009 Apr;25(2):113-9.

Comparative toxicity of preservatives on immortalized corneal and conjunctival epithelial cells.

[Epstein SP](#), [Ahdoot M](#), [Marcus E](#), [Asbell PA](#).

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### Abstract

**PURPOSE:** Nearly all eye drops contain preservatives to decrease contamination.

Nonpreservatives such as disodium-ethylene diamine tetra-acetate (EDTA) and phosphate-buffered saline are also regularly added as buffering agents. These components can add to the toxicity of eye drops and cause ocular surface disease. To evaluate the potential toxicity of these common components and their comparative effects on the ocular surface, a tissue culture model utilizing immortalized corneal and conjunctival epithelial cells was utilized.

**METHODS:** Immortalized human conjunctival and corneal epithelial cells were grown. At confluency, medium was replaced with 100 microL of varying concentrations of preservatives: benzalkonium chloride (BAK), methyl paraben (MP), sodium perborate (SP), chlorobutanol (Cbl), and stabilized thimerosal (Thi); varying concentrations of buffer: EDTA; media (viable control); and formalin (dead control). After 1 h, solutions were replaced with 150 microL of MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazonium bromide). After 4 h, solutions decanted, 100 microL of acid isopropanol added, and the optical density determined at 572 nm to evaluate cell viability.

**RESULTS:** Conjunctival and corneal cell toxicity was seen with all preservatives. Depending upon concentration, BAK exhibited from 56% to 89% toxicity. In comparison, Cbl exhibited from 50% to 86%, MP from 30% to 76%, SP from 23% to 59%, and Thi from 70% to 95%. EDTA with minimal toxicity (from 6% to 59%) was indistinguishable from SP.

**CONCLUSIONS:** Generally, the order of decreasing toxicity at the most commonly used concentrations: Thi (0.0025%) > BAK (0.025%) > Cbl (0.25%) > MP (0.01%) > SP (0.0025%) approximately EDTA (0.01%). Even at low concentration, these agents will cause some degree of ocular tissue damage.

PMID: 19284328 [PubMed - indexed for MEDLINE]PMCID: PMC2958436Free PMC Article

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[J Med Food](#). 2009 Oct;12(5):1098-104.

Effects of glucan on immunosuppressive actions of mercury.



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### **Abstract**

Global cycling of mercury results in the presence of mercury salts in the environment. The well-established negative effects of mercury on the immune system led us to the study whether natural immunomodulator glucan can overcome the immunosuppressive effects of mercury. Two types of mercury, thimerosal and mercury acetate, were administered in a dose of 2-8 mg/L of drinking water to mice. After 2 weeks, all mice exhibited profound suppression of both cellular (phagocytosis, natural killer cell activity, mitogen-induced proliferation, and expression of CD markers) and humoral (antibody formation and secretion of interleukin-6, interleukin-12, and interferon-gamma) responses. The mice were then fed with a diet containing a standard dose of glucan. Our results showed that simultaneous treatment with mercury and glucan resulted in significantly lower immunotoxic effects of mercury, which suggests that glucans can be successfully used as a natural remedy of low-level exposure to mercury.

PMID: 19857075 [PubMed - indexed for MEDLINE]

Wonder what, if any, cell damage occurs when injected.

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[Curr Med Chem](#). 2008;15(28):3000-10.

Kawasaki's disease, acrodynia, and mercury.

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### **Abstract**

A superantigen or autoimmunity has been hypothesized to be the main cause of the Kawasaki's Disease but the etiology is unknown. Medical literature, epidemiological findings, and some case reports have suggested that mercury may play a pathogenic role. Several patients with Kawasaki's Disease have presented with elevated urine mercury levels compared to matched controls. Most symptoms and diagnostic criteria which are seen in children with acrodynia, known to be caused by mercury, are similar to those seen in

Kawasaki's Disease. Genetic depletion of glutathione S-transferase , a susceptibility marker for Kawasaki's Disease, is known to be also a risk factor for acrodynia and may also increase susceptibility to mercury . Coinciding with the largest increase (1985-1990) of thimerosal (49.6% ethyl mercury) in vaccines, routinely given to infants in the U.S. by 6 months of age (from 75microg to 187.5microg), the rates of Kawasaki's Disease increased ten times, and, later (1985-1997), by 20 times. Since 1990 88 cases of patients developing Kawasaki's Disease some days after vaccination have been reported to the Centers of Disease Control (CDC) including 19% manifesting symptoms the same day. The presented pathogenetic model may lead to new preventive- and therapeutic strategies for Kawasaki's disease. PMID: 19075648 [PubMed - indexed for MEDLINE]

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[Toxicol In Vitro](#). 2008 Jun;22(4):927-34. Epub 2008 Feb 1.

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

[Eke D](#), [Celik A](#).

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### **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 microg/ml of thimerosal compared with negative control. A significant decrease ( $p < 0.001$ ) in mitotic index (MI) and proliferation index (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.

PMID: 18321677 [PubMed - indexed for MEDLINE]

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[Chem Res Toxicol](#). 2008 Feb;21(2):483-93. Epub 2008 Jan 16.

Thiol-modulated mechanisms of the cytotoxicity of thimerosal and inhibition of DNA topoisomerase II alpha.

[Wu X](#), [Liang H](#), [O'Hara KA](#), [Yalowich JC](#), [Hasinoff BB](#).

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### **Abstract**

Thimerosal is an organic mercury compound that is widely used as a preservative in vaccines and other solution formulations. The use of thimerosal has caused concern about its ability to cause neurological abnormalities due to mercury accumulation during a normal schedule of childhood vaccinations. While the chemistry and the biological effects of methylmercury have been well-studied, those of thimerosal have not. Thimerosal reacted rapidly with cysteine, GSH, human serum albumin, and single-stranded DNA to form ethylmercury adducts that were detectable by mass spectrometry. These results indicated that thimerosal would be quickly metabolized in vivo because of its reactions with protein and nonprotein thiols. Thimerosal also potently inhibited the decatenation activity of DNA topoisomerase II alpha, likely through reaction with critical free cysteine thiol groups. Thimerosal, however, did not act as a topoisomerase II poison and the lack of cross-resistance with a K562 cell line with a decreased level of topoisomerase II alpha (K/VP.5 cells) suggested that inhibition of topoisomerase II alpha was not a significant mechanism for the inhibition of cell growth. Depletion of intracellular GSH with buthionine sulfoximine treatment greatly increased the K562 cell growth inhibitory effects of thimerosal, which showed that intracellular glutathione had a major role in protecting cells from thimerosal. Pretreatment of thimerosal with glutathione did not, however, change its K562 cell growth inhibitory effects, a result consistent with the rapid exchange of the ethylmercury adduct among various thiol-containing cellular reactants. Thimerosal-induced single and double strand breaks in K562 cells were consistent with a rapid induction of apoptosis. In conclusion, these studies have elucidated some of the chemistry and biological activities of the interaction of thimerosal with topoisomerase II alpha and protein and nonprotein thiols and with DNA.

PMID: 18197631 [PubMed - indexed for MEDLINE]

Apoptosis is “programmed cell death”.

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[Altern Ther Health Med](#). 2008 Nov-Dec;14(6):46-53.

A possible central mechanism in autism spectrum disorders, part 1.

[Blaylock RL](#).

Belhaven College, Jackson, Mississippi, USA.

### **Abstract**

The autism spectrum disorders (ASD) are a group of related neurodevelopmental disorders that have been increasing in incidence since the 1980s. Despite a considerable amount of data being collected from cases, a central mechanism has not been offered. A careful review of ASD cases discloses a number of events that adhere to an immunoexcitotoxic mechanism. This mechanism explains the link between excessive vaccination, use of aluminum and ethylmercury as vaccine adjuvants, food allergies, gut dysbiosis, and abnormal formation of the developing brain. It has now been shown that chronic microglial activation is present in autistic brains from age 5 years to age 44 years. A considerable amount of evidence, both experimental and clinical, indicates that repeated microglial activation can initiate priming of the microglia and that subsequent stimulation can produce an exaggerated microglial response that can be prolonged. It is also known that one phenotypic form of microglia activation can result in an outpouring of neurotoxic levels of the excitotoxins, glutamate and quinolinic acid. Studies have shown that careful control of brain glutamate levels is essential to brain pathway development and that excesses can result in arrest of neural migration, as well as dendritic and synaptic loss. It has also been shown that certain cytokines, such as TNF-alpha, can, via its receptor, interact with glutamate receptors to enhance the neurotoxic reaction. To describe this interaction I have coined the term immunoexcitotoxicity, which is described in this article.

PMID: 19043938 [PubMed - indexed for MEDLINE]

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[J Neurol Sci](#). 2008 Aug 15;271(1-2):110-8. Epub 2008 May 15.

Thimerosal exposure in infants and neurodevelopmental disorders: an assessment of computerized medical records in the Vaccine Safety Datalink.

[Young HA](#), [Geier DA](#), [Geier MR](#).

The George Washington University School of Public Health and Health Services, Department of Epidemiology and Biostatistics, United States.

### **Abstract**

The study evaluated possible associations between neurodevelopmental disorders (NDs) and exposure to mercury (Hg) from Thimerosal-containing vaccines (TCVs) by examining the automated Vaccine Safety Datalink (VSD). A total of 278,624 subjects were identified in birth cohorts from 1990-1996 that had received their first oral polio vaccination by 3 months of age in the VSD. The birth cohort prevalence rate of medically diagnosed International Classification of Disease, 9th revision (ICD-9) specific NDs and control outcomes were calculated. Exposures to Hg from TCVs were calculated by birth cohort for specific exposure windows from birth-7 months and birth-13 months of age. Poisson regression analysis was used to model the association between the prevalence of outcomes and Hg doses from TCVs. Consistent significantly increased rate ratios were observed for autism, autism spectrum disorders, tics, attention deficit disorder, and emotional disturbances with Hg exposure from TCVs. By contrast, none of the control outcomes had significantly increased rate ratios with Hg exposure from TCVs. Routine childhood vaccination should be continued to help reduce the morbidity and mortality associated with infectious diseases, but efforts should be undertaken to remove Hg from vaccines. Additional studies should be conducted to further evaluate the relationship between Hg exposure and NDs.

PMID: 18482737 [PubMed - indexed for MEDLINE]

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[Neurotoxicology](#). 2008 May;29(3):532-45. Epub 2008 Feb 23.

Immunologic and neurodevelopmental susceptibilities of autism.

[Pessah IN](#), [Seegal RF](#), [Lein PJ](#), [LaSalle J](#), [Yee BK](#), [Van De Water J](#), [Berman RF](#).

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### **Abstract**

Symposium 5 focused on research approaches that are aimed at understanding common patterns of immunological and neurological dysfunction contributing to neurodevelopmental disorders such as autism and ADHD. The session focused on genetic, epigenetic, and environmental factors that might act in concert to influence autism risk, severity and co-

morbidities, and immunological and neurobiological targets as etiologic contributors. The immune system of children at risk of autism may be therefore especially susceptible to psychological stressors, exposure to chemical triggers, and infectious agents. Identifying early biomarkers of risk provides tangible approaches toward designing studies in animals and humans that yield a better understanding of environmental risk factors, and can help identify rational intervention strategies to mitigate these risks.

PMID: 18394707 [PubMed - indexed for MEDLINE]PMCID: PMC2475601Free PMC

Article <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2475601/?tool=pubmed>

See Section VII – “Examination of Thimerosal Effects in neonatal SJL/J Mice at Vaccination-Associated Exposure Levels”

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[J Toxicol Environ Health A](#). 2007 Dec;70(24):2092-5.

Evaluation of cytotoxicity attributed to thimerosal on murine and human kidney cells.

[Park EK](#), [Mak SK](#), [Kültz D](#), [Hammock BD](#).

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### Abstract

Renal inner medullary collecting duct cells (mIMCD3) and human embryonic kidney cells (HEK293) were used for cytoscreening of thimerosal and mercury chloride (HgCl<sub>2</sub>).

Thimerosal and HgCl<sub>2</sub> acted in a concentration-dependent manner. In mIMCD3 cells the 24-h LC<sub>50</sub> values for thimerosal, thiosalicylic acid, 2,2-dithiosalicylic acid, and 2-sulfobenzoic acid were 2.9, 2200, >1000, and >10,000 microM, respectively. The 24-h LC<sub>50</sub> value for HgCl<sub>2</sub> in mIMCD3 cells was 40 microM. In HEK293 cells, the 24-h LC<sub>50</sub> value for thimerosal was 9.5 microM. These data demonstrate that the higher cytotoxicity produced by thimerosal on renal cells with respect to similar compounds without Hg may be related to this metal content. The present study also establishes mIMCD3 cells as a valuable model for evaluation of cytotoxicity of nephrotoxic compounds.

PMID: 18049999 [PubMed - indexed for MEDLINE]

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[Toxicol Sci](#). 2007 Nov;100(1):109-17. Epub 2007 Aug 13.

Thimerosal-induced apoptosis in human SCM1 gastric cancer cells: activation of p38 MAP kinase and caspase-3 pathways without involvement of [Ca<sup>2+</sup>]<sub>i</sub> elevation.

[Liu SJ](#), [Huang CC](#), [Huang CJ](#), [Wang BW](#), [Chang PM](#), [Fang YC](#), [Chen WC](#), [Wang JL](#), [Lu YC](#), [Chu ST](#), [Chou CT](#), [Jan CR](#).

Department of Surgery, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan 813.

### Abstract

Thimerosal is a mercury-containing preservative in some vaccines. The effect of thimerosal on human gastric cancer cells is unknown. **This study shows that in cultured human gastric cancer cells (SCM1), thimerosal reduced cell viability in a concentration- and time-dependent manner.** Thimerosal caused apoptosis as assessed by propidium iodide-stained cells and caspase-3 activation. Although immunoblotting data revealed that thimerosal could activate the phosphorylation of extracellular signal-regulated kinase, c-Jun NH2-terminal protein kinase, and p38 mitogen-activated protein kinase (p38 MAPK), only SB203580 (a p38 MAPK inhibitor) partially prevented cells from apoptosis. Thimerosal also induced [Ca<sup>2+</sup>]<sub>i</sub> increases via Ca<sup>2+</sup> influx from the extracellular space. However, pretreatment with (bis(o-aminophenoxy)ethane-N,N,N',N'-tetraacetate)/AM, a Ca<sup>2+</sup> chelator, to prevent thimerosal-induced [Ca<sup>2+</sup>]<sub>i</sub> increases did not protect cells from death. **The results suggest that in SCM1 cells, thimerosal caused Ca<sup>2+</sup>-independent apoptosis via phosphorylating p38 MAPK resulting in caspase-3 activation.**

PMID: 17698513 [PubMed - indexed for MEDLINE]Free Article

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[Toxicology](#). 2007 Feb 28;231(1):40-57. Epub 2006 Nov 25.

Cell death and cytotoxic effects in YAC-1 lymphoma cells following exposure to various forms of mercury.

[Yole M](#), [Wickstrom M](#), [Blakley B](#).

Department of Veterinary Biomedical Sciences, Western College of Veterinary Medicine, 52 Campus Drive, University of Saskatchewan, Saskatoon SK S7N 5B4, Canada.

yole@sask.usask.ca

Erratum in:

- [Toxicology](#). 2008 Jan 14;243(1-2):244-5.

### Abstract

The effects of 1 min-4 h exposures to four Hg compounds (mercuric chloride [HgCl<sub>2</sub>], methylmercuric chloride [CH<sub>3</sub>HgCl], p-chloromercuribenzoate [p-CMB] and thimerosal [TMS];

ethylmercurithiosalicylate]) on cell death, microtubules, actin, CD3 receptor expression, protein tyrosine phosphorylation (PTyr-P) and intracellular calcium ( $[Ca^{2+}]_i$ ) levels were investigated in YAC-1 lymphoma cells using flow cytometry. YOPRO-1 (YP) and propidium iodide (PI) dye uptake indicated all forms of Hg tested were toxic at concentrations ranging from 25.8-48.4  $\mu$ M, with two distinct patterns of effects. Early apoptosis was prolonged for CH<sub>3</sub>HgCl- and TMS-treated cells, with more than 50% remaining YP+/PI- after 4h. Both CH<sub>3</sub>HgCl and TMS induced complete loss of beta-tubulin fluorescence, indicative of microtubule depolymerization and inhibition of tubulin synthesis and/or beta-tubulin degradation, while F-actin fluorescence diminished to a lesser degree and only after loss beta-tubulin. CH<sub>3</sub>HgCl and TMS induced an almost immediate two-fold increase in CD3 fluorescence, with levels returning to baseline within minutes. With continued exposure, CD3 fluorescence was reduced to approximately 50% of baseline values. Both compounds also increased PTyr-P two- to three-fold immediately, with levels returning to baseline at 4h. Similarly, two- to three-fold increases in  $[Ca^{2+}]_i$  were noted after 1 min exposure.  $[Ca^{2+}]_i$  increased progressively, reaching levels five- to eight-fold greater than control values. In contrast, dye uptake was delayed with HgCl<sub>2</sub> and p-CMB, although cell death proceeded rapidly, with almost all non-viable cells being late apoptotic (YP+/PI+) by 4h. p-CMB produced early reductions in F-actin, and after 4h, complete loss of F-actin with only partial reduction of total beta-tubulin was seen with both p-CMB and HgCl<sub>2</sub>. HgCl<sub>2</sub> reduced CD3 expression and PTyr-P slightly within minutes, while p-CMB produced similar effects on CD3 only at 4h, at which time PTyr-P was increased two- to three-fold. Both compounds increased  $[Ca^{2+}]_i$  within minutes, though levels remained under twice the baseline concentration after 15 min exposure. With continued exposure,  $[Ca^{2+}]_i$  increased to levels two- to five-fold greater than control values. These findings indicate the two groups of Hg compounds may induce cell death by distinct pathways, reflecting interactions with different cellular targets leading to cell death.

PMID: 17210217 [PubMed - indexed for MEDLINE]

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[Toxicology](#). 2007 Jan 5;229(1-2):23-32. Epub 2006 Sep 24.

Dose and Hg species determine the T-helper cell activation in murine autoimmunity.

[Havarinasab S](#), [Björn E](#), [Ekstrand J](#), [Hultman P](#).

Molecular and Immunological Pathology (AIR), Department of Molecular and Clinical Medicine, Linköping University, SE-581 85 Linköping, Sweden. [saiha@imk.liu.se](mailto:saiha@imk.liu.se)



## Abstract

Inorganic mercury (mercuric chloride-- $\text{HgCl}_2$ ) induces in mice an autoimmune syndrome (HgIA) with T cell-dependent polyclonal B cell activation and hypergammaglobulinemia, dose- and H-2-dependent production of autoantibodies targeting the 34 kDa nucleolar protein fibrillarin (AFA), and systemic immune-complex deposits. The organic mercury species methylmercury (MeHg) and ethylmercury (EtHg--in the form of thimerosal) induce AFA, while the other manifestations of HgIA seen after treatment with  $\text{HgCl}_2$  are present to varying extent. Since these organic Hg species are converted to the autoimmunogen  $\text{Hg}(2+)$  in the body, their primary autoimmunogen potential is uncertain and the subject of this study. A moderate dose of  $\text{HgCl}_2$  (8 mg/L drinking water--internal dose 148 micro gHg/kg body weight [bw]/day) caused the fastest AFA response, while the induction was delayed after higher (25 mg/L) and lower (1.5 and 3 mg/L) doses. The lowest dose of  $\text{HgCl}_2$  inducing AFA was 1.5 mg/L drinking water which corresponded to a renal  $\text{Hg}(2+)$  concentration of 0.53 micro g/g. Using a dose of 8 mg  $\text{HgCl}_2$ /L this threshold concentration was reached within 24 h, and a consistent AFA response developed after 8-10 days. The time lag for the immunological part of the reaction leading to a consistent AFA response was therefore 7-9 days. A dose of thimerosal close to the threshold dose for induction of AFA (2 mg/L drinking water--internal dose 118 micro gHg/kg bw per day), caused a renal  $\text{Hg}(2+)$  concentration of 1.8 micro g/g. **The autoimmunogen effect of EtHg might therefore be entirely due to  $\text{Hg}(2+)$  formed from EtHg in the body.** The effect of organic and inorganic Hg species on T-helper type 1 and type 2 cells during induction of AFA was assessed as the presence and titre of AFA of the IgG1 and IgG2a isotype, respectively. **EtHg induced a persistent Th1-skewed response irrespectively of the dose and time used.** A low daily dose of  $\text{HgCl}_2$  (1.5-3 mg/L) caused a Th1-skewed AFA response, while a moderate dose (8 mg/L) after 2 weeks resulted in a balanced or even Th2-skewed response. Higher daily doses of  $\text{HgCl}_2$  (25 mg/L) caused a balanced Th2-Th1 response already from onset. In conclusion, while metabolically formed  $\text{Hg}(2+)$  might be the main AFA-inducing factor also after treatment with EtHg, the quality of the Hg-induced AFA response is modified by the species of Hg as well as the dose.

PMID: 17084957 [PubMed - indexed for MEDLINE]

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[J Matern Fetal Neonatal Med.](#) 2007 May;20(5):385-90.

A prospective study of thimerosal-containing Rho(D)-immune globulin administration as a risk factor for autistic disorders.

[Geier DA](#), [Geier MR](#).

The Institute of Chronic Illnesses, Silver Spring, MD, USA.

### Abstract

**BACKGROUND:** This study evaluated the relationship between prenatal mercury exposure from thimerosal (49.55% mercury by weight)-containing Rho(D)-immune globulins (TCRs) and autism spectrum disorders (ASDs).

**METHODS:** The Institutional Review Board of the Institute for Chronic Illnesses approved the present study. A total of 53 consecutive non-Jewish Caucasian patients with ASDs (Diagnostic and statistical manual of mental disorders, fourth ed. - DSM IV) born between 1987 and 2001 who presented to the Genetic Centers of America for outpatient genetic/developmental evaluations were prospectively collected from June 1, 2005 through March 31, 2006. Imaging and laboratory testing were conducted on each patient to rule out other causal factors for their ASDs. As race-matched controls, the frequency of Rh negativity was determined from 926 non-Jewish Caucasian pregnant women who had presented for outpatient prenatal genetics care to the Genetic Centers of America between 1980 and 1989.

**RESULTS:** Children with ASDs (28.30%) were significantly more likely (odds ratio 2.35, 95% confidence interval 1.17-4.52,  $p < 0.01$ ) to have Rh-negative mothers than controls (14.36%). Each ASD patient's mother was determined to have been administered a TCR during her pregnancy.

**CONCLUSION:** The results provide insights into the potential role prenatal mercury exposure may play in some children with ASDs.

PMID: 17674242 [PubMed - indexed for MEDLINE]

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[J Toxicol Environ Health A](#). 2007 May 15;70(10):837-51.

A case series of children with apparent mercury toxic encephalopathies manifesting with clinical symptoms of regressive autistic disorders.

[Geier DA](#), [Geier MR](#).

Institute of Chronic Illnesses, Inc., Silver Spring, Maryland, USA.

### Abstract

Impairments in social relatedness and communication, repetitive behaviors, and stereotypic abnormal movement patterns characterize autism spectrum disorders (ASDs). It is clear that while genetic factors are important to the pathogenesis of ASDs, mercury exposure can induce immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with ASDs. The Institutional Review Board of the Institute for Chronic Illnesses (Office for Human Research Protections, U.S. Department of Health and Human Services, IRB number IRB00005375) approved the present study. A case series of nine patients who presented to the Genetic Centers of America for a genetic/developmental evaluation are discussed. Eight of nine patients (one patient was found to have an ASD due to Rett's syndrome) (a) had regressive ASDs; (b) had elevated levels of androgens; (c) excreted significant amounts of mercury post chelation challenge; (d) had biochemical evidence of decreased function in their glutathione pathways; (e) had no known significant mercury exposure except from Thimerosal-containing vaccines/Rho(D)-immune globulin preparations; and (f) had alternate causes for their regressive ASDs ruled out. There was a significant dose-response relationship between the severity of the regressive ASDs observed and the total mercury dose children received from Thimerosal-containing vaccines/Rho (D)-immune globulin preparations. Based upon differential diagnoses, 8 of 9 patients examined were exposed to significant mercury from Thimerosal-containing biologic/vaccine preparations during their fetal/infant developmental periods, and subsequently, between 12 and 24 mo of age, these previously normally developing children suffered mercury toxic encephalopathies that manifested with clinical symptoms consistent with regressive ASDs. Evidence for mercury intoxication should be considered in the differential diagnosis as contributing to some regressive ASDs.

PMID: 17454560 [PubMed - indexed for MEDLINE]

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[Toxicol Sci.](#) 2006 Jul;92(1):246-53. Epub 2006 Apr 19.

Thimerosal induces apoptosis in a neuroblastoma model via the cJun N-terminal kinase pathway.

[Herdman ML](#), [Marcelo A](#), [Huang Y](#), [Niles RM](#), [Dhar S](#), [Kinningham KK](#).

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**Abstract**

The cJun N-terminal kinase (JNK)-signaling pathway is activated in response to a variety of stimuli, including environmental insults, and has been implicated in neuronal apoptosis. In this study, we investigated the role that the JNK pathway plays in neurotoxicity caused by thimerosal, an ethylmercury-containing preservative. SK-N-SH cells treated with thimerosal (0-10 microM) showed an increase in the phosphorylated (active) form of JNK and cJun with 5 and 10 microM thimerosal treatment at 2 and 4 h. To examine activator protein-1 (AP-1) transcription, cells were transfected with a pGL2 vector containing four AP-1 consensus sequences and then treated with thimerosal (0-2.5 microM) for 24 h. Luciferase studies showed an increase in AP-1 transcriptional activity upon thimerosal administration. To determine the components of the AP-1 complex, cells were transfected with a dominant negative to either cFos (A-Fos) or cJun (TAM67). Reporter analysis showed that TAM67, but not A-Fos, decreased AP-1 transcriptional activity, indicating a role for cJun in this pathway. To assess which components are essential to apoptosis, cells were treated with a cell-permeable JNK inhibitor II (SP600125) or transfected with TAM67, and the downstream effectors of apoptosis were analyzed. Cells pretreated with SP600125 showed decreases in activation of caspases 9 and 3, decreases in degradation of poly(ADP-ribose) polymerase (PARP), and decreased levels of proapoptotic Bim, in comparison to cells treated with thimerosal alone. However, cells transfected with TAM67 showed no changes in those same components. Taken together, these results indicate that thimerosal-induced neurotoxicity occurs through the JNK-signaling pathway, independent of cJun activation, leading ultimately to apoptotic cell death.

PMID: 16624850 [PubMed - indexed for MEDLINE]Free Article

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[Mol Carcinog.](#) 2006 Sep;45(9):657-66.

Thimerosal induces apoptosis and G2/M phase arrest in human leukemia cells.

[Woo KJ](#), [Lee TJ](#), [Bae JH](#), [Jang BC](#), [Song DK](#), [Cho JW](#), [Suh SI](#), [Park JW](#), [Kwon TK](#).

Department of Immunology, School of Medicine, Keimyung University, Taegu, South Korea.

### **Abstract**

Thimerosal is an organomercury compound with sulfhydryl-reactive properties. The ability of thimerosal to act as a sulfhydryl group is related to the presence of mercury. Due to its antibacterial effect, thimerosal is widely used as preservatives and has been reported to cause chemically mediated side effects. In the present study, we showed that the molecular

mechanism of thimerosal induced apoptosis in U937 cells. Thimerosal was shown to be responsible for the inhibition of U937 cells growth by inducing apoptosis. Treatment with 2.5-5 microM thimerosal but not thiosalicylic acid (structural analog of thimerosal devoid of mercury) for 12 h produced apoptosis, G(2)/M phase arrest, and DNA fragmentation in a dose-dependent manner. Treatment with caspase inhibitor significantly reduced thimerosal-induced caspase 3 activation. In addition, thimerosal-induced apoptosis was attenuated by antioxidant Mn (III) meso-tetrakis (4-benzoic acid) porphyrin (Mn-TBAP). These data indicate that the cytotoxic effect of thimerosal on U937 cells is attributable to the induced apoptosis and that thimerosal-induced apoptosis is mediated by reactive oxygen species generation and caspase-3 activation.

PMID: 16649253 [PubMed - indexed for MEDLINE]

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[Neurotoxicology](#). 2006 Sep;27(5):685-92. Epub 2006 Jun 16.

Cultured lymphocytes from autistic children and non-autistic siblings up-regulate heat shock protein RNA in response to thimerosal challenge.

[Walker SJ](#), [Segal J](#), [Aschner M](#).

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### **Abstract**

There are reports suggesting that some autistic children are unable to mount an adequate response following exposure to environmental toxins. This potential deficit, coupled with the similarity in clinical presentations of autism and some heavy metal toxicities, has led to the suggestion that heavy metal poisoning might play a role in the etiology of autism in uniquely susceptible individuals. Thimerosal, an anti-microbial preservative previously added routinely to childhood multi-dose vaccines, is composed of 49.6% ethyl mercury. Based on the levels of this toxin that children receive through routine immunization schedules in the first years of life, it has been postulated that thimerosal may be a potential triggering mechanism contributing to autism in susceptible individuals. One potential risk factor in these individuals may be an inability to adequately up-regulate metallothionein (MT) biosynthesis in response to presentation of a heavy metal challenge. To investigate this hypothesis, cultured lymphocytes (obtained from the Autism Genetic Resource Exchange, AGRE) from autistic children and non-autistic siblings were challenged with either 10 microM

ethyl mercury, 150 microM zinc, or fresh media (control). Following the challenge, total RNA was extracted and used to query "whole genome" DNA microarrays. Cultured lymphocytes challenged with zinc responded with an impressive up-regulation of MT transcripts (at least nine different MTs were over-expressed) while cells challenged with thimerosal responded by up-regulating numerous heat shock protein transcripts, but not MTs. Although there were no apparent differences between autistic and non-autistic sibling responses in this very small sampling group, the differences in expression profiles between those cells treated with zinc versus thimerosal were dramatic. Determining cellular response, at the level of gene expression, has important implications for the understanding and treatment of conditions that result from exposure to neurotoxic compounds.

PMID: 16870260 [PubMed - indexed for MEDLINE]

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Altern Ther Health Med. 2006 Jul-Aug;12(4):16-7.

Are mercury amalgam fillings safe for children? An evaluation of recent research results.

[Rode D.](#)

EcoNugenics Inc, Santa Rosa, California, USA.

**Abstract**

Two recent clinical trials on the safety of amalgam fillings in children found no evidence of harmful effects from mercury-containing dental fillings after following children for 5-7 years. This review suggests the studies' results are limited by (1) sample sizes that were too small to allow detection of genetic variations in mercury toxicity at a rate of 1 in 100 or lower, (2) a lack of control for other sources of mercury, and (3) a population that may have been skewed by excluding children with autism during a time when autism was escalating due, in part, to increased frequency of thimerosal-containing vaccine use.

PMID: 16862738 [PubMed - indexed for MEDLINE]

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[Neuro Endocrinol Lett.](#) 2006 Aug;27(4):401-13.

A meta-analysis epidemiological assessment of neurodevelopmental disorders following vaccines administered from 1994 through 2000 in the United States.

[Geier DA](#), [Geier MR](#).

The Institute for Chronic Illnesses, Inc., Silver Spring, MD 20905, USA. [mgeier@comcast.net](mailto:mgeier@comcast.net)

**Abstract**

**BACKGROUND:** Thimerosal is an ethylmercury-containing compound (49.6% mercury by weight) used as at the preservative level in vaccines (0.005% to 0.01%).

**METHODS:** Statistical modeling in a meta-analysis epidemiological assessment of the Vaccine Adverse Event Reporting System (VAERS) for neurodevelopment disorders (NDs) reported following Diphtheria-Tetanus-whole-cell-Pertussis (DTP) vaccines in comparison to Diphtheria-Tetanus-whole-cell-Pertussis-Haemophilus Influenzae Type b (DTPH) vaccines (administered: 1994-1997) and following Thimerosal-containing Diphtheria-Tetanus-acellular-Pertussis (DTaP), vaccines in comparison to Thimerosal-free DTaP vaccines (administered: 1997-2000), was undertaken.

**RESULTS:** Significantly increased adjusted (sex, age, vaccine type, vaccine manufacturer) risks of autism, speech disorders, mental retardation, personality disorders, thinking abnormalities, ataxia, and NDs in general, with minimal systematic error or confounding, were associated with TCV exposure.

**CONCLUSION:** It is clear from the results of the present epidemiological study and other recently published data associating mercury exposure with childhood NDs, additional ND research should be undertaken in the context of evaluating mercury-associated exposures, especially from Thimerosal-containing vaccines.

PMID: 16807526 [PubMed - indexed for MEDLINE]

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[Acta Microbiol Immunol Hung.](#) 2005;52(1):95-103.

Being on the track of thimerosal. Review.

[Mádi A.](#)

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### **Abstract**

The common preservative thimerosal is one of the most important organic mercury compounds human populations are exposed to. It has toxic effect on several cell lines, and it also induces programmed cell death in in vitro experiments. Association is suggested between application of thimerosal-containing vaccines and the occurrence of neurodevelopmental disorders, like autism. While specific recommendations were made to eliminate thimerosal from vaccines, consistent evidence is still lacking for an association of

exposure and disease. Unfortunately, it is very hard to study the molecular background of complex human diseases directly; however, investigations on more simple model organisms may lead to a better understanding of thimerosal as a possible disease inducing factor.

PMID: 15957237 [PubMed - indexed for MEDLINE]

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[Med Sci Monit.](#) 2005 Apr;11(4):CR160-70. Epub 2005 Mar 24.

A two-phased population epidemiological study of the safety of thimerosal-containing vaccines: a follow-up analysis.

[Geier DA](#), [Geier MR](#).

MedCon, Inc., USA.

### **Abstract**

**BACKGROUND:** Thimerosal is an ethylmercury-containing preservative in vaccines. Toxicokinetic studies have shown children received doses of mercury from thimerosal-containing vaccines (TCVs) that were in excess of safety guidelines. Previously, an ecological study showing a significant association between TCVs and neurodevelopmental disorders (NDs) in the US was published in this journal.

**MATERIAL/METHODS:** A two phased population-based epidemiological study was undertaken. Phase one evaluated reported NDs to the Vaccine Adverse Event Reporting System (VAERS) following thimerosal-containing Diphtheria-Tetanus-acellular-Pertussis (DTaP) vaccines in comparison to thimerosal-free DTaP vaccines administered from 1997 through 2001. Phase two evaluated the automated Vaccine Safety Datalink (VSD) for cumulative exposures to mercury from TCVs at 1-, 2-, 3-, and 6-months-of-age for infants born from 1992 through 1997 and the eventual risk of developing NDs.

**RESULTS:** Phase one showed significantly increased risks for autism, speech disorders, mental retardation, personality disorders, and thinking abnormalities reported to VAERS following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines. Phase two showed significant associations between cumulative exposures to thimerosal and the following types of NDs: unspecified developmental delay, tics, attention deficit disorder (ADD), language delay, speech delay, and neurodevelopmental delays in general.



**CONCLUSIONS:** This study showed that exposure to mercury from TCVs administered in the US was a consistent significant risk factor for the development of NDs. It is clear from these data and other recent publications linking TCVs with NDs that additional ND research should be undertaken in the context of evaluating mercury-associated exposures and thimerosal-free vaccines should be made available.

PMID: 15795695 [PubMed - indexed for MEDLINE]

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[Neuro Endocrinol Lett.](#) 2005 Oct;26(5):439-46.

Mercury and autism: accelerating evidence?

[Mutter J](#), [Naumann J](#), [Schneider R](#), [Walach H](#), [Haley B](#).

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### Abstract

The causes of autism and neurodevelopmental disorders are unknown. Genetic and environmental risk factors seem to be involved. Because of an observed increase in autism in the last decades, which parallels cumulative mercury exposure, it was proposed that autism may be in part caused by mercury. We review the evidence for this proposal. Several epidemiological studies failed to find a correlation between mercury exposure through thimerosal, a preservative used in vaccines, and the risk of autism. Recently, it was found that autistic children had a higher mercury exposure during pregnancy due to maternal dental amalgam and thimerosal-containing immunoglobulin shots. It was hypothesized that children with autism have a decreased detoxification capacity due to genetic polymorphism. In vitro, mercury and thimerosal in levels found several days after vaccination inhibit methionine synthetase (MS) by 50%. Normal function of MS is crucial in biochemical steps necessary for brain development, attention and production of glutathione, an important antioxidative and detoxifying agent. Repetitive doses of thimerosal leads to neurobehavioral deteriorations in autoimmune susceptible mice, increased oxidative stress and decreased intracellular levels of glutathione in vitro. Subsequently, autistic children have significantly decreased level of reduced glutathione. Promising treatments of autism involve detoxification of mercury, and supplementation of deficient metabolites.

PMID: 16264412 [PubMed - indexed for MEDLINE]

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[Environ Health Perspect.](#) 2005 Aug;113(8):1015-21.

Comparison of blood and brain mercury levels in infant monkeys exposed to methylmercury or vaccines containing thimerosal.

[Burbacher TM](#), [Shen DD](#), [Liberato N](#), [Grant KS](#), [Cernichiari E](#), [Clarkson T](#).

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### **Abstract**

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. PMID: 16079072 [PubMed - indexed for MEDLINE]PMCID: PMC1280342Free PMC Article

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[Neurotoxicology.](#) 2005 Jun;26(3):407-16.

Mitochondrial mediated thimerosal-induced apoptosis in a human neuroblastoma cell line (SK-N-SH).

[Humphrey ML](#), [Cole MP](#), [Pendergrass JC](#), [Kinningham KK](#).

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### **Abstract**

Environmental exposure to mercurials continues to be a public health issue due to their deleterious effects on immune, renal and neurological function. Recently the safety of thimerosal, an ethyl mercury-containing preservative used in vaccines, has been questioned due to exposure of infants during immunization. Mercurials have been reported to cause apoptosis in cultured neurons; however, the signaling pathways resulting in cell death have not been well characterized. Therefore, the objective of this study was to identify the mode of cell death in an in vitro model of thimerosal-induced neurotoxicity, and more specifically, to elucidate signaling pathways which might serve as pharmacological targets. Within 2 h of thimerosal exposure (5 microM) to the human neuroblastoma cell line, SK-N-SH, morphological changes, including membrane alterations and cell shrinkage, were observed. Cell viability, assessed by measurement of lactate dehydrogenase (LDH) activity in the medium, as well as the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assay, showed a time- and concentration-dependent decrease in cell survival upon thimerosal exposure. In cells treated for 24 h with thimerosal, fluorescence microscopy indicated cells undergoing both apoptosis and oncosis/necrosis. To identify the apoptotic pathway associated with thimerosal-mediated cell death, we first evaluated the mitochondrial cascade, as both inorganic and organic mercurials have been reported to accumulate in the organelle. Cytochrome c was shown to leak from the mitochondria, followed by caspase 9 cleavage within 8 h of treatment. In addition, poly(ADP-ribose) polymerase (PARP) was cleaved to form a 85 kDa fragment following maximal caspase 3 activation at 24 h. Taken together these findings suggest deleterious effects on the cytoarchitecture by thimerosal and initiation of mitochondrial-mediated apoptosis.

PMID: 15869795 [PubMed - indexed for MEDLINE]

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[Toxicol Sci](#). 2005 Jul;86(1):132-40. Epub 2005 Apr 20.

Effects of thimerosal on NGF signal transduction and cell death in neuroblastoma cells.

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Virginia-Maryland Regional College of Veterinary Medicine, Laboratory for Neurotoxicity Studies, Virginia Tech, 1 Duckpond Drive, Blacksburg, Virginia 24061-0442, USA.

### Abstract

Signaling through neurotrophic receptors is necessary for differentiation and survival of the developing nervous system. The present study examined the effects of the organic mercury compound thimerosal on nerve growth factor signal transduction and cell death in a human neuroblastoma cell line (SH-SY5Y cells). Following exposure to 100 ng/ml NGF and increasing concentrations of thimerosal (1 nM-10 microM), we measured the activation of TrkA, MAPK, and PKC-delta. In controls, the activation of TrkA MAPK and PKC-delta peaked after 5 min of exposure to NGF and then decreased but was still detectable at 60 min. Concurrent exposure to increasing concentrations of thimerosal and NGF for 5 min resulted in a concentration-dependent decrease in TrkA and MAPK phosphorylation, which was evident at 50 nM for TrkA and 100 nM for MAPK. Cell viability was assessed by the LDH assay. Following 24-h exposure to increasing concentrations of thimerosal, the EC50 for cell death in the presence or absence of NGF was 596 nM and 38.7 nM, respectively. Following 48-h exposure to increasing concentrations of thimerosal, the EC50 for cell death in the presence and absence of NGF was 105 nM and 4.35 nM, respectively. This suggests that NGF provides protection against thimerosal cytotoxicity. To determine if apoptotic versus necrotic cell death was occurring, oligonucleosomal fragmented DNA was quantified by ELISA. Control levels of fragmented DNA were similar in both the presence and absence of NGF. With and without NGF, thimerosal caused elevated levels of fragmented DNA appearing at 0.01 microM (apoptosis) to decrease at concentrations >1 microM (necrosis). These data demonstrate that thimerosal could alter NGF-induced signaling in neurotrophin-treated cells at concentrations lower than those responsible for cell death.

PMID: 15843506 [PubMed - indexed for MEDLINE]Free Article

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[Toxicol In Vitro](#). 2005 Mar;19(2):191-8.

Flow-cytometric analysis on cytotoxic effect of thimerosal, a preservative in vaccines, on lymphocytes dissociated from rat thymic glands.

[Ueha-Ishibashi T](#), [Oyama Y](#), [Nakao H](#), [Umebayashi C](#), [Hirama S](#), [Sakai Y](#), [Ishida S](#), [Okano Y](#).

Laboratory of Cellular Signaling, Faculty of Integrated Arts and Sciences, The University of Tokushima, Minami-Jyosanjima 1-1, Tokushima 770-8502, Japan.

## Abstract

There is a concern on the part of public health community that adverse health consequence by thimerosal, a preservative in vaccines for infants, may occur among infants during immunization schedule. Therefore, the cytotoxic action of thimerosal was examined on lymphocytes dissociated from thymic glands of young rats using a flow cytometer and respective fluorescent probes for monitoring changes in intracellular  $\text{Ca}^{2+}$  concentration ( $[\text{Ca}^{2+}]_i$ ) and membrane potential, and for discriminating intact living cells, apoptotic living cells and dead cells. Incubation with thimerosal at 3  $\mu\text{M}$  or more (up to 30  $\mu\text{M}$ ) for 60 min depolarized the membranes, associated with increasing the  $[\text{Ca}^{2+}]_i$ . Thimerosal at 30  $\mu\text{M}$  induced an apoptotic change in membranes of almost all living cells. Furthermore, the prolonged incubation with 30  $\mu\text{M}$  thimerosal induced a loss of membrane integrity, leading to cell death. Since the blood concentration of thimerosal after receiving vaccines is theoretically submicromolar, it may be unlikely that thimerosal affects lymphocytes of infants.

PMID: 15649632 [PubMed - indexed for MEDLINE]

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[Neurotoxicology](#). 2005 Jan;26(1):1-8.

Thimerosal neurotoxicity is associated with glutathione depletion: protection with glutathione precursors.

[James SJ](#), [Slikker W 3rd](#), [Melnyk S](#), [New E](#), [Pogribna M](#), [Jernigan S](#).

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## Abstract

Thimerosal is an antiseptic containing 49.5% ethyl mercury that has been used for years as a preservative in many infant vaccines and in flu vaccines. Environmental methyl mercury has been shown to be highly neurotoxic, especially to the developing brain. Because mercury has a high affinity for thiol (sulfhydryl (-SH)) groups, the thiol-containing antioxidant, glutathione (GSH), provides the major intracellular defense against mercury-induced neurotoxicity. Cultured neuroblastoma cells were found to have lower levels of GSH and increased sensitivity to thimerosal toxicity compared to glioblastoma cells that have higher basal levels of intracellular GSH. Thimerosal-induced cytotoxicity was associated with depletion of intracellular GSH in both cell lines. Pretreatment with 100  $\mu\text{M}$  glutathione

ethyl ester or N-acetylcysteine (NAC), but not methionine, resulted in a significant increase in intracellular GSH in both cell types. Further, pretreatment of the cells with glutathione ethyl ester or NAC prevented cytotoxicity with exposure to 15 microM Thimerosal. Although Thimerosal has been recently removed from most children's vaccines, it is still present in flu vaccines given to pregnant women, the elderly, and to children in developing countries. The potential protective effect of GSH or NAC against mercury toxicity warrants further research as possible adjunct therapy to individuals still receiving Thimerosal-containing vaccinations.

PMID: 15527868 [PubMed - indexed for MEDLINE]

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[Int J Mol Med.](#) 2005 Dec;16(6):971-7.

Thimerosal induces neuronal cell apoptosis by causing cytochrome c and apoptosis-inducing factor release from mitochondria.

[Yel L](#), [Brown LE](#), [Su K](#), [Gollapudi S](#), [Gupta S](#).

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### **Abstract**

There is a worldwide increasing concern over the neurological risks of thimerosal (ethylmercury thiosalicylate) which is an organic mercury compound that is commonly used as an antimicrobial preservative. **In this study, we show that thimerosal, at nanomolar concentrations, induces neuronal cell death through the mitochondrial pathway.** Thimerosal, in a concentration- and time-dependent manner, decreased cell viability as assessed by calcein-ethidium staining and caused apoptosis detected by Hoechst 33258 dye. Thimerosal-induced apoptosis was associated with depolarization of mitochondrial membrane, generation of reactive oxygen species, and release of cytochrome c and apoptosis-inducing factor (AIF) from mitochondria to cytosol. Although thimerosal did not affect cellular expression of Bax at the protein level, we observed translocation of Bax from cytosol to mitochondria. Finally, caspase-9 and caspase-3 were activated in the absence of caspase-8 activation. **Our data suggest that thimerosal causes apoptosis in neuroblastoma cells by changing the mitochondrial microenvironment.**

PMID: 16273274 [PubMed - indexed for MEDLINE]

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[Toxicol Appl Pharmacol.](#) 2004 Jan 15;194(2):169-79.

Dose-response study of thimerosal-induced murine systemic autoimmunity.

[Havarinasab S](#), [Lambertsson L](#), [Qvarnström J](#), [Hultman P](#).

Molecular and Immunological Pathology (AIR), Department of Molecular and Clinical Medicine, Linköping University, SE-581 85 Linköping, Sweden.

### Abstract

The organic compound ethylmercurithiosalicylate (thimerosal), which is primarily present in the tissues as ethylmercury, has caused illness and several deaths due to erroneous handling when used as a disinfectant or as a preservative in medical preparations. Lately, possible health effects of thimerosal in childhood vaccines have been much discussed. Thimerosal is a well-known sensitizing agent, although usually of no clinical relevance. In rare cases, thimerosal has caused systemic immune reactions including acrodynia. We have studied if thimerosal might induce the systemic autoimmune condition observed in genetically susceptible mice after exposure to inorganic mercury. A.SW mice were exposed to 1.25-40 mg thimerosal/l drinking water for 70 days. Antinucleolar antibodies, targeting the 34-kDa protein fibrillarlin, developed in a dose-related pattern and first appeared after 10 days in the two highest dose groups. The lowest observed adverse effect level (LOAEL) for antifibrillarlin antibodies was 2.5 mg thimerosal/l, corresponding to an absorbed dose of 147 microg Hg/kg bw and a concentration of 21 and 1.9 microg Hg/g in the kidney and lymph nodes, respectively. The same LOAEL was found for tissue immune-complex deposits. The total serum concentration of IgE, IgG1, and IgG2a showed a significant dose-related increase in thimerosal-treated mice, with a LOAEL of 5 mg thimerosal/l for IgG1 and IgE, and 20 mg thimerosal/l for IgG2a. The polyclonal B-cell activation showed a significant dose-response relationship with a LOAEL of 10 mg thimerosal/l. Therefore, thimerosal induces in genetically susceptible mice a systemic autoimmune syndrome very similar to that seen after treatment with inorganic mercury, although a higher absorbed dose of Hg is needed using thimerosal. The autoimmune syndrome induced by thimerosal is different from the weaker and more restricted autoimmune reaction observed after treatment with an equipotent dose of methylmercury.

PMID: 14736497 [PubMed - indexed for MEDLINE]

What is the significance of these findings re: the doses of thimerosal infants and children have received?

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[Mol Psychiatry](#). 2004 Sep;9(9):833-45.

Neurotoxic effects of postnatal thimerosal are mouse strain dependent.

[Hornig M](#), [Chian D](#), [Lipkin WJ](#).

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### **Abstract**

The developing brain is uniquely susceptible to the neurotoxic hazard posed by mercurials. Host differences in maturation, metabolism, nutrition, sex, and autoimmunity influence outcomes. How population-based variability affects the safety of the ethylmercury-containing vaccine preservative, thimerosal, is unknown. Reported increases in the prevalence of autism, a highly heritable neuropsychiatric condition, are intensifying public focus on environmental exposures such as thimerosal. Immune profiles and family history in autism are frequently consistent with autoimmunity. We hypothesized that autoimmune propensity influences outcomes in mice following thimerosal challenges that mimic routine childhood immunizations. Autoimmune disease-sensitive SJL/J mice showed growth delay; reduced locomotion; exaggerated response to novelty; and densely packed, hyperchromic hippocampal neurons with altered glutamate receptors and transporters. Strains resistant to autoimmunity, C57BL/6J and BALB/cJ, were not susceptible. These findings implicate genetic influences and provide a model for investigating thimerosal-related neurotoxicity.

PMID: 15184908 [PubMed - indexed for MEDLINE]

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[Toxicology](#). 2004 Jan 15;195(1):77-84.

Effect of thimerosal, a preservative in vaccines, on intracellular Ca<sup>2+</sup> concentration of rat cerebellar neurons.

[Ueha-Ishibashi T](#), [Oyama Y](#), [Nakao H](#), [Umebayashi C](#), [Nishizaki Y](#), [Tatsuishi T](#), [Iwase K](#), [Murao K](#), [Seo H](#).

Laboratory of Cellular Signaling, Faculty of Integrated Arts and Sciences, The University of Tokushima, Tokushima 770-8502, Japan.



## Abstract

The effect of thimerosal, an organomercurial preservative in vaccines, on cerebellar neurons dissociated from 2-week-old rats was compared with those of methylmercury using a flow cytometer with appropriate fluorescent dyes. Thimerosal and methylmercury at concentrations ranging from 0.3 to 10 microM increased the intracellular concentration of  $\text{Ca}^{2+}$  ( $[\text{Ca}^{2+}]_i$ ) in a concentration-dependent manner. The potency of 10 microM thimerosal to increase the  $[\text{Ca}^{2+}]_i$  was less than that of 10 microM methylmercury. Their effects on the  $[\text{Ca}^{2+}]_i$  were greatly attenuated, but not completely suppressed, under external  $\text{Ca}^{2+}$ -free condition, suggesting a possibility that both agents increase membrane  $\text{Ca}^{2+}$  permeability and release  $\text{Ca}^{2+}$  from intracellular calcium stores. The effect of 10 microM thimerosal was not affected by simultaneous application of 30 microM L-cysteine whereas that of 10 microM methylmercury was significantly suppressed. The potency of thimerosal was similar to that of methylmercury in the presence of L-cysteine. Both agents at 1 microM or more similarly decreased the cellular content of glutathione in a concentration-dependent manner, suggesting an increase in oxidative stress. Results indicate that thimerosal exerts some cytotoxic actions on cerebellar granule neurons dissociated from 2-week-old rats and its potency is almost similar to that of methylmercury.

PMID: 14698570 [PubMed - indexed for MEDLINE]

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[Int J Toxicol.](#) 2004 Nov-Dec;23(6):369-76.

Neurodevelopmental disorders following thimerosal-containing childhood immunizations: a follow-up analysis.

[Geier D](#), [Geier MR](#).

MedCon, Inc., Maryland, USA.

## Abstract

The authors previously published the first epidemiological study from the United States associating thimerosal from childhood vaccines with neurodevelopmental disorders (NDs) based upon assessment of the Vaccine Adverse Event Reporting System (VAERS). A number of years have gone by since their previous analysis of the VAERS. The present study was undertaken to determine whether the previously observed effect between thimerosal-containing childhood vaccines and NDs are still apparent in the VAERS as children have had a chance to further mature and potentially be diagnosed with additional NDs. In the present

study, a cohort of children receiving thimerosal-containing diphtheria-tetanus-acellular pertussis (DTaP) vaccines in comparison to a cohort of children receiving thimerosal-free DTaP vaccines administered from 1997 through 2000 based upon an assessment of adverse events reported to the VAERS were evaluated. It was determined that there were significantly increased odds ratios (ORs) for autism (OR = 1.8,  $p < .05$ ), mental retardation (OR = 2.6,  $p < .002$ ), speech disorder (OR = 2.1,  $p < .02$ ), personality disorders (OR = 2.6,  $p < .01$ ), and thinking abnormality (OR = 8.2,  $p < .01$ ) adverse events reported to the VAERS following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines. Potential confounders and reporting biases were found to be minimal in this assessment of the VAERS. It was observed, even though the media has reported a potential association between autism and thimerosal exposure, that the other NDs analyzed in this assessment of the VAERS had significantly higher ORs than autism following thimerosal-containing DTaP vaccines in comparison to thimerosal-free DTaP vaccines. **The present study provides additional epidemiological evidence supporting previous epidemiological, clinical and experimental evidence that administration of thimerosal-containing vaccines in the United States resulted in a significant number of children developing NDs.**

PMID: 15764492 [PubMed - indexed for MEDLINE]

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[Med Sci Monit.](#) 2004 Mar;10(3):PI33-9. Epub 2004 Mar 1.

A comparative evaluation of the effects of MMR immunization and mercury doses from thimerosal-containing childhood vaccines on the population prevalence of autism.

[Geier DA](#), [Geier MR](#).

President, MedCon, Inc, Silver Spring, MD, USA.

Comment in:

- [Med Sci Monit. 2005 Oct;11\(10\):LE13-4.](#)

### **Abstract**

**BACKGROUND:** The purpose of the study was to evaluate the effects of MMR immunization and mercury from thimerosal-containing childhood vaccines on the prevalence of autism.

**MATERIAL/METHODS:** Evaluations of the Biological Surveillance Summaries of the Centers for Disease Control and Prevention (CDC), the U.S. Department of Education datasets, and the CDC's yearly live birth estimates were undertaken

**RESULTS:** It was determined that there was a close correlation between mercury doses from thimerosal--containing childhood vaccines and the prevalence of autism from the late 1980s through the mid-1990s. In contrast, there was a potential correlation between the number of primary pediatric measles-containing vaccines administered and the prevalence of autism during the 1980s. In addition, it was found that there were statistically significant odds ratios for the development of autism following increasing doses of mercury from thimerosal-containing vaccines (birth cohorts: 1985 and 1990-1995) in comparison to a baseline measurement (birth cohort: 1984). The contribution of thimerosal from childhood vaccines (>50% effect) was greater than MMR vaccine on the prevalence of autism observed in this study.

**CONCLUSIONS:** The results of this study agree with a number of previously published studies. These studies have shown that there is biological plausibility and epidemiological evidence showing a direct relationship between increasing doses of mercury from thimerosal-containing vaccines and neurodevelopmental disorders, and measles-containing vaccines and serious neurological disorders. It is recommended that thimerosal be removed from all vaccines, and additional research be undertaken to produce a MMR vaccine with an improved safety profile.

PMID: 14976450 [PubMed - indexed for MEDLINE]

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[Int J Immunopathol Pharmacol.](#) 2003 Sep-Dec;16(3):189-99.

Infections, toxic chemicals and dietary peptides binding to lymphocyte receptors and tissue enzymes are major instigators of autoimmunity in autism.

[Vojdani A](#), [Pangborn JB](#), [Vojdani E](#), [Cooper EL](#).

Lab. Comparative Immunology, Dept. Neurobiology, UCLA Medical Center, Los Angeles, CA, USA. DrAri@msn.com

### **Abstract**

Similar to many complex autoimmune diseases, genetic and environmental factors including diet, infection and xenobiotics play a critical role in the development of autism. In this study, we postulated that infectious agent antigens such as streptokinase, dietary peptides (gliadin and casein) and ethyl mercury (xenobiotic) bind to different lymphocyte receptors and tissue enzyme (DPP IV or CD26). We assessed this hypothesis first by measuring IgG, IgM and IgA antibodies against CD26, CD69, streptokinase (SK), gliadin and casein peptides and against

ethyl mercury bound to human serum albumin in patients with autism. A significant percentage of children with autism developed anti-SK, anti-gliadin and casein peptides and anti-ethyl mercury antibodies, concomitant with the appearance of anti-CD26 and anti-CD69 autoantibodies. These antibodies are synthesized as a result of SK, gliadin, casein and ethyl mercury binding to CD26 and CD69, indicating that they are specific. Immune absorption demonstrated that only specific antigens, like CD26, were capable of significantly reducing serum anti-CD26 levels. However, for direct demonstration of SK, gliadin, casein and ethyl mercury to CD26 or CD69, microtiter wells were coated with CD26 or CD69 alone or in combination with SK, gliadin, casein or ethyl mercury and then reacted with enzyme labeled rabbit anti-CD26 or anti-CD69. Adding these molecules to CD26 or CD69 resulted in 28-86% inhibition of CD26 or CD69 binding to anti-CD26 or anti-CD69 antibodies. The highest % binding of these antigens or peptides to CD26 or CD69 was attributed to SK and the lowest to casein peptides. We, therefore, propose that bacterial antigens (SK), dietary peptides (gliadin, casein) and Thimerosal (ethyl mercury) in individuals with pre-disposing HLA molecules, bind to CD26 or CD69 and induce antibodies against these molecules. In conclusion, this study is apparently the first to demonstrate that dietary peptides, bacterial toxins and xenobiotics bind to lymphocyte receptors and/or tissue enzymes, resulting in autoimmune reaction in children with autism.

PMID: 14611720 [PubMed - indexed for MEDLINE]

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[Anal Chem.](#) 2003 Aug 15;75(16):4120-4.

Determination of methylmercury, ethylmercury, and inorganic mercury in mouse tissues, following administration of thimerosal, by species-specific isotope dilution GC-inductively coupled plasma-MS.

[Qvarnström J](#), [Lambertsson L](#), [Havarinasab S](#), [Hultman P](#), [Frech W](#).

Analytical Chemistry, Department of Chemistry, Umeå University, S-901 87 Umeå, Sweden.  
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### **Abstract**

Isotopically enriched HgO standards were used to synthesize CH<sub>3</sub>(<sup>200</sup>Hg)<sup>+</sup> and C<sub>2</sub>H<sub>5</sub>(<sup>199</sup>Hg)<sup>+</sup> using Grignard reagents. These species were employed for isotope dilution GC-ICPMS to study uptake and biotransformation of ethylmercury in mice treated with thimerosal, (sodium ethylmercurithiosalicylate) 10 mg L<sup>-1</sup> in drinking water ad libitum for 1, 2.5, 6, or 14 days. Prior to analysis, samples were spiked with aqueous solutions of

CH<sub>3</sub>(200)Hg<sup>+</sup>, C<sub>2</sub>H<sub>5</sub>(199)Hg<sup>+</sup>, and <sup>201</sup>Hg<sup>2+</sup> and then digested in 20% tetramethylammonium hydroxide and extracted at pH 9 with DDTC/toluene. Extracted mercury species were reacted with butylmagnesium chloride to form butylated derivatives. Absolute detection limits for CH<sub>3</sub>Hg<sup>+</sup>, C<sub>2</sub>H<sub>5</sub>Hg<sup>+</sup>, and Hg<sup>2+</sup> were 0.4, 0.2, and 0.6 pg on the basis of 3sigma of five separate blanks. Up to 9% of the C<sub>2</sub>H<sub>5</sub>Hg<sup>+</sup> was decomposed to Hg<sup>2+</sup> during sample preparation, and it is therefore crucial to use a species-specific internal standard when determining ethylmercury. No demethylation, methylation, or ethylation during sample preparation was detected. The ethylmercury component of thimerosal was rapidly taken up in the organs of the mice (kidney, liver, and mesenteric lymph nodes), and concentrations of C<sub>2</sub>H<sub>5</sub>Hg<sup>+</sup> as well as Hg<sup>2+</sup> increased over the 14 days of thimerosal treatment. This shows that C<sub>2</sub>H<sub>5</sub>Hg<sup>+</sup> in mice to a large degree is degraded to Hg<sup>2+</sup>. Increased concentrations of CH<sub>3</sub>Hg<sup>+</sup> were also observed, which was found to be due to impurities in the thimerosal.

PMID: 14632125 [PubMed - indexed for MEDLINE]

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[Pediatr Rehabil.](#) 2003 Apr-Jun;6(2):97-102.

An assessment of the impact of thimerosal on childhood neurodevelopmental disorders.

[Geier DA](#), [Geier MR](#).

The Genetic Centers of America, 14 Redgate Court, Silver Spring, MD 20905, USA.

### **Abstract**

The prevalence of autism in the US has risen from 1 in approximately 2500 in the mid-1980s to 1 in approximately 300 children in the mid-1990s. The purpose of this study was to evaluate whether mercury from thimerosal in childhood vaccines contributed to neurodevelopmental disorders. Neurodevelopmental disorder dose-response curves for increasing mercury doses of thimerosal in childhood vaccines were determined based upon examination of the Vaccine Adverse Events Reporting System (VAERS) database and the 2001 US' Department of Education Report. The instantaneous dosage of mercury children received in comparison to the Food and Drug Administration (FDA)'s maximum permissible dose for the oral ingestion of methylmercury was also determined. The dose-response curves showed increases in odds ratios of neurodevelopmental disorders from both the VAERS and US Department of Education data closely linearly correlated with increasing doses of mercury from thimerosal-containing childhood vaccines and that for overall odds

ratios statistical significance was achieved. Similar slopes and linear regression coefficients for autism odds ratios in VAERS and the US Department of Education data help to mutually validate each other. Controls employed in the VAERS and US Department of Education data showed minimal biases. **The evidence presented here shows that the occurrence of neurodevelopmental disorders following thimerosal-containing childhood vaccines does not appear to be coincidental.**

PMID: 14534046 [PubMed - indexed for MEDLINE]

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[Int J Toxicol.](#) 2003 Jul-Aug;22(4):277-85.

Reduced levels of mercury in first baby haircuts of autistic children.

[Holmes AS](#), [Blaxill ME](#), [Haley BE](#).

SafeMinds, Cambridge, Massachusetts, USA.

### **Abstract**

Reported rates of autism have increased sharply in the United States and the United Kingdom. One possible factor underlying these increases is increased exposure to mercury through thimerosal-containing vaccines, but vaccine exposures need to be evaluated in the context of cumulative exposures during gestation and early infancy. Differential rates of postnatal mercury elimination may explain why similar gestational and infant exposures produce variable neurological effects. First baby haircut samples were obtained from 94 children diagnosed with autism using Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV) criteria and 45 age- and gender-matched controls. Information on diet, dental amalgam fillings, vaccine history, Rho D immunoglobulin administration, and autism symptom severity was collected through a maternal survey questionnaire and clinical observation. Hair mercury levels in the autistic group were 0.47 ppm versus 3.63 ppm in controls, a significant difference. The mothers in the autistic group had significantly higher levels of mercury exposure through Rho D immunoglobulin injections and amalgam fillings than control mothers. Within the autistic group, hair mercury levels varied significantly across mildly, moderately, and severely autistic children, with mean group levels of 0.79, 0.46, and 0.21 ppm, respectively. Hair mercury levels among controls were significantly correlated with the number of the mothers' amalgam fillings and their fish consumption as well as exposure to mercury through childhood vaccines, correlations that were absent in the autistic group. Hair excretion patterns among autistic infants were significantly reduced

relative to control. These data cast doubt on the efficacy of traditional hair analysis as a measure of total mercury exposure in a subset of the population. In light of the biological plausibility of mercury's role in neurodevelopmental disorders, the present study provides further insight into one possible mechanism by which early mercury exposures could increase the risk of autism.

PMID: 12933322 [PubMed - indexed for MEDLINE]

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[Exp Biol Med \(Maywood\)](#). 2003 Jun;228(6):660-4.

Neurodevelopmental disorders after thimerosal-containing vaccines: a brief communication.

[Geier MR](#), [Geier DA](#).

The Genetic Centers of America, Silver Spring, Maryland 20905, USA. mgeier@erols.com

Comment in:

- [Exp Biol Med \(Maywood\)](#). 2003 Oct;228(9):991-2; discussion 993-4.

### **Abstract**

We were initially highly skeptical that differences in the concentrations of thimerosal in vaccines would have any effect on the incidence rate of neurodevelopmental disorders after childhood immunization. This study presents the first epidemiologic evidence, based upon tens of millions of doses of vaccine administered in the United States, that associates increasing thimerosal from vaccines with neurodevelopmental disorders. Specifically, an analysis of the Vaccine Adverse Events Reporting System (VAERS) database showed statistical increases in the incidence rate of autism (relative risk [RR] = 6.0), mental retardation (RR = 6.1), and speech disorders (RR = 2.2) after thimerosal-containing diphtheria, tetanus, and acellular pertussis (DTaP) vaccines in comparison with thimerosal-free DTaP vaccines. The male/female ratio indicated that autism (1.7) and speech disorders (2.3) were reported more in males than females after thimerosal-containing DTaP vaccines, whereas mental retardation (1.2) was more evenly reported among male and female vaccine recipients. Controls were employed to determine if biases were present in the data, but none were found. It was determined that overall adverse reactions were reported in similar-aged populations after thimerosal-containing DTaP (2.4 +/- 3.2 years old) and thimerosal-free DTaP (2.1 +/- 2.8 years old) vaccinations. Acute control adverse reactions such as deaths (RR = 1.0), vasculitis (RR = 1.2), seizures (RR = 1.6), ED visits (RR = 1.4), total adverse reactions (RR = 1.4), and gastroenteritis (RR = 1.1) were reported similarly after thimerosal-

containing and thimerosal-free DTaP vaccines. **An association between neurodevelopmental disorders and thimerosal-containing DTaP vaccines was found, but additional studies should be conducted to confirm and extend this study.**

PMID: 12773696 [PubMed - indexed for MEDLINE]Free Article

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[Mutat Res.](#) 2003 Jun 6;537(2):151-68.

Characterization of cytotoxic and genotoxic effects of different compounds in CHO K5 cells with the comet assay (single-cell gel electrophoresis assay).

[Kiffe M](#), [Christen P](#), [Arni P](#).

Syngenta Crop Protection AG, CH-4002 Basel, Switzerland.

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### **Abstract**

Different variants of the comet assay were used to study the genotoxic and cytotoxic properties of the following eight compounds: chloral hydrate, colchicine, hydroquinone, DL-menthol, mitomycin C, sodium iodoacetate, thimerosal and valinomycin. **Colchicine, mitomycin C, sodium iodoacetate and thimerosal induced genotoxic effects.** The other compounds were found to be inactive. The compounds were tested in the standard comet assay as well as in the all cell comet assay (recovery of floating cells after treatment), designed in our laboratory for adherently-growing cells. This latter procedure proved to be more adequate for the assessment of the cytotoxicity for some of the compounds tested (hydroquinone, DL-menthol, thimerosal, valinomycin). Colchicine was positive in the standard comet assay (3h treatment) and in the all cell comet assay (24h treatment). Sodium iodoacetate and thimerosal were positive in the standard and/or the all cell comet assay. Chloral hydrate, hydroquinone, sodium iodoacetate, mitomycin C and thimerosal were also tested in the modified comet assay using lysed cells. Mitomycin C and thimerosal showed effects in this assay, whereas sodium iodoacetate was inactive. This indicates that it does not induce direct DNA damage. Compounds that are known or suspected to form DNA-DNA cross-links or DNA-protein cross-links (chloral hydrate, hydroquinone, mitomycin C and thimerosal) were checked for their ability to reduce ethyl methanesulfonate (EMS)-induced DNA damage. This mode of action could be demonstrated for mitomycin C only.

PMID: 12787820 [PubMed - indexed for MEDLINE]

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[Toxicol Sci.](#) 2003 Aug;74(2):361-8. Epub 2003 May 28.

Thimerosal induces DNA breaks, caspase-3 activation, membrane damage, and cell death in cultured human neurons and fibroblasts.

[Baskin DS](#), [Ngo H](#), [Didenko VV](#).

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### **Abstract**

Thimerosal is an organic mercurial compound used as a preservative in biomedical preparations. Little is known about the reactions of human neuronal and skin cells to its micro- and nanomolar concentrations, which can occur after using thimerosal-containing products. A useful combination of fluorescent techniques for the assessment of thimerosal toxicity is introduced. Short-term thimerosal toxicity was investigated in cultured human cerebral cortical neurons and in normal human fibroblasts. Cells were incubated with 125-nM to 250-microM concentrations of thimerosal for 45 min to 24 h. A 4', 6-diamidino-2-phenylindole dihydrochloride (DAPI) dye exclusion test was used to identify nonviable cells and terminal transferase-based nick-end labeling (TUNEL) to label DNA damage. Detection of active caspase-3 was performed in live cell cultures using a cell-permeable fluorescent caspase inhibitor. The morphology of fluorescently labeled nuclei was analyzed. After 6 h of incubation, the thimerosal toxicity was observed at 2 microM based on the manual detection of the fluorescent attached cells and at a 1-microM level with the more sensitive GENios Plus Multi-Detection Microplate Reader with Enhanced Fluorescence. The lower limit did not change after 24 h of incubation. Cortical neurons demonstrated higher sensitivity to thimerosal compared to fibroblasts. The first sign of toxicity was an increase in membrane permeability to DAPI after 2 h of incubation with 250 microM thimerosal. A 6-h incubation resulted in failure to exclude DAPI, generation of DNA breaks, caspase-3 activation, and development of morphological signs of apoptosis. We demonstrate that thimerosal in micromolar concentrations rapidly induce membrane and DNA damage and initiate caspase-3-dependent apoptosis in human neurons and fibroblasts. We conclude that a proposed combination of fluorescent techniques can be useful in analyzing the toxicity of thimerosal. PMID: 12773768 [PubMed - indexed for MEDLINE]PMCID: PMC1892749Free PMC Article

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[Arch Toxicol.](#) 2003 Jan;77(1):50-5. Epub 2002 Nov 6.

Thimerosal induces micronuclei in the cytochalasin B block micronucleus test with human lymphocytes.

[Westphal GA](#), [Asgari S](#), [Schulz TG](#), [Bünger J](#), [Müller M](#), [Hallier E](#).

Department of Occupational Health, Georg-August-University Göttingen, Waldweg 37, 37073 Göttingen, Germany. [gwestph@gwdg.de](mailto:gwestph@gwdg.de)

### Abstract

Thimerosal is a widely used preservative in health care products, especially in vaccines. Due to possible adverse health effects, investigations on its metabolism and toxicity are urgently needed. An in vivo study on chronic toxicity of thimerosal in rats was inconclusive and reports on genotoxic effects in various in vitro systems were contradictory. Therefore, we reinvestigated thimerosal in the cytochalasin B block micronucleus test. Glutathione S-transferases were proposed to be involved in the detoxification of thimerosal or its decomposition products. Since the outcome of genotoxicity studies can be dependent on the metabolic competence of the cells used, we were additionally interested whether polymorphisms of glutathione S-transferases (GSTM1, GSTT1, or GSTP1) may influence the results of the micronucleus test with primary human lymphocytes. Blood samples of six healthy donors of different glutathione S-transferase genotypes were included in the study. At least two independent experiments were performed for each blood donor. Significant induction of micronuclei was seen at concentrations between 0.05-0.5 micro g/ml in 14 out of 16 experiments. Thus, genotoxic effects were seen even at concentrations which can occur at the injection site. Toxicity and toxicity-related elevation of micronuclei was seen at and above 0.6 micro g/ml thimerosal. Marked individual and intraindividual variations in the in vitro response to thimerosal among the different blood donors occurred. However, there was no association observed with any of the glutathione S-transferase polymorphism investigated. In conclusion, thimerosal is genotoxic in the cytochalasin B block micronucleus test with human lymphocytes. These data raise some concern on the widespread use of thimerosal.

PMID: 12491041 [PubMed - indexed for MEDLINE]

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The UCI Undergraduate Research Journal (2003)

Thimerosal Induces Programmed Cell Death of Neuronal Cells via

## Changes in the Mitochondrial Environment

Brown L

### Abstract

Thimerosal, a preservative and anti-microbial agent used in vaccines, ophthalmic solutions, and cosmetics, is a mercury-containing compound that has raised public concern due to its potentially harmful effects. While past studies have implicated mercurial compounds in apoptosis, or programmed cell death, in human T-cells and cells of the central nervous system, no studies have examined the specific effect of thimerosal on neuronal cells, despite evidence that mercurial compounds readily cross the bloodbrain barrier. This study examines whether thimerosal induces apoptosis in neuronal cells, and, if so, via which mechanism. To this end, neuronal cells were incubated in the absence and presence of thimerosal at various concentrations for various exposure times and then examined for cell viability, specific morphological changes associated with apoptosis, and changes in the mitochondrial environment. Thimerosal decreased neuronal cell viability in time- and dose-dependent trials, with 90% viability at 2 hr, decreasing to 60% viability at 24 hr (1  $\mu$ M); at 5  $\mu$ M thimerosal, viability decreased below 20% at 24 and 48 hr. Thimerosal caused depolarization of the mitochondrial membrane and enhanced superoxide generation. At 5  $\mu$ M thimerosal, cytochrome c was released from mitochondria to the cytosol in 30% of cells at 1 hr and 85% of cells at 3

hr. Apoptosis-Inducing Factor was released in 40% and 90% of cells at 30 min and 1 hr, respectively. **The results suggest that thimerosal causes apoptosis via the mitochondrial pathway and warrant continued efforts to find a replacement compound.**

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[Exp Biol Med \(Maywood\)](#). 2003 Oct;228(9):991-2; discussion 993-4.

Questions about thimerosal remain.

[Mann JR](#).

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USA. [joshua.mann@palmettohealth.org](mailto:joshua.mann@palmettohealth.org)

From the article: **"All these issues aside, the authors' findings are interesting and potentially very important, as they do give some support to what the authors note is generally a skeptically-viewed theory about the possible connection between thimerosal-containing vaccines and neurodevelopmental disorders. Perhaps future research can build on their work. In the meantime, it seems prudent for clinicians to use thimerosal-free vaccines when possible."**

Comment on:

- [Exp Biol Med \(Maywood\)](#). 2003 Jun;228(6):660-4.

PMID: 14530505 [PubMed - indexed for MEDLINE]Free

Article <http://ebm.rsmjournals.com/cgi/content/full/228/9/991>

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[Genes Immun.](#) 2002 Aug;3(5):270-8.

Biochemical and molecular basis of thimerosal-induced apoptosis in T cells: a major role of mitochondrial pathway.

[Makani S](#), [Gollapudi S](#), [Yel L](#), [Chiplunkar S](#), [Gupta S](#).

Cellular and Molecular Immunology Laboratories, Division of Basic and Clinical Immunology, University of California, Irvine 92697, USA.

### **Abstract**

The major source of thimerosal (ethyl mercury thiosalicylate) exposure is childhood vaccines. It is believed that the children are exposed to significant accumulative dosage of thimerosal during the first 2 years of life via immunization. Because of health-related concerns for exposure to mercury, we examined the effects of thimerosal on the biochemical and molecular steps of mitochondrial pathway of apoptosis in Jurkat T cells. Thimerosal and not thiosalicylic acid (non-mercury component of thimerosal), in a concentration-dependent manner, induced apoptosis in T cells as determined by TUNEL and propidium iodide assays, suggesting a role of mercury in T cell apoptosis. Apoptosis was associated with depolarization of mitochondrial membrane, release of cytochrome c and apoptosis inducing factor (AIF) from the mitochondria, and activation of caspase-9 and caspase-3, but not of caspase-8. In addition, thimerosal in a concentration-dependent manner inhibited the expression of XIAP, cIAP-1 but did not influence cIAP-2 expression. Furthermore, thimerosal enhanced intracellular reactive oxygen species and reduced intracellular glutathione (GSH). Finally, exogenous glutathione protected T cells from thimerosal-induced apoptosis by upregulation of XIAP and cIAP1 and by inhibiting activation of both caspase-9 and caspase-3. These data suggest that thimerosal induces apoptosis in T cells via mitochondrial pathway by inducing oxidative stress and depletion of GSH.

PMID: 12140745 [PubMed - indexed for MEDLINE]Free Article

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[Altern Med Rev.](#) 2002 Aug;7(4):292-316.

Autism, an extreme challenge to integrative medicine. Part: 1: The knowledge base.

[Kidd PM.](#)

## Abstract

Autism, archetype of the autistic spectrum disorders (ASD), is a neurodevelopmental disorder characterized by socially aloof behavior and impairment of language and social interaction. Its prevalence has surged in recent years. Advanced functional brain imaging has confirmed pervasive neurologic involvement. Parent involvement in autism management has accelerated understanding and treatment. Often accompanied by epilepsy, cognitive deficits, or other neurologic impairment, autism manifests in the first three years of life and persists into adulthood. Its etiopathology is poorly defined but likely multifactorial with heritability playing a major role. Prenatal toxic exposures (teratogens) are consistent with autism spectrum symptomatology. Frequent vaccinations with live virus and toxic mercurial content (thimerosal) are a plausible etiologic factor. Autistic children frequently have abnormalities of sulfoxidation and sulfation that compromise liver detoxification, which may contribute to the high body burden of xenobiotics frequently found. Frequent copper-zinc imbalance implies metallothionein impairment that could compound the negative impact of sulfur metabolism impairments on detoxification and on intestinal lining integrity. Intestinal hyperpermeability manifests in autistic children as dysbiosis, food intolerances, and exorphin (opioid) intoxication, most frequently from casein and gluten. Immune system abnormalities encompass derangement of antibody production, skewing of T cell subsets, aberrant cytokine profiles, and other impairments consistent with chronic inflammation and autoimmunity. Coagulation abnormalities have been reported. Part 2 of this review will attempt to consolidate progress in integrative management of autism, aimed at improving independence and lifespan for people with the disorder.

PMID: 12197782 [PubMed - indexed for MEDLINE]Free Article

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[Med Hypotheses](#). 2001 Apr;56(4):462-71.

Autism: a novel form of mercury poisoning.

[Bernard S](#), [Enayati A](#), [Redwood L](#), [Roger H](#), [Binstock T](#).

ARC Research, Cranford, New Jersey 07901, USA.

## Abstract

Autism is a syndrome characterized by impairments in social relatedness and communication, repetitive behaviors, abnormal movements, and sensory dysfunction. Recent epidemiological studies suggest that autism may affect 1 in 150 US children.

Exposure to mercury can cause immune, sensory, neurological, motor, and behavioral dysfunctions similar to traits defining or associated with autism, and the similarities extend to neuroanatomy, neurotransmitters, and biochemistry. Thimerosal, a preservative added to many vaccines, has become a major source of mercury in children who, within their first two years, may have received a quantity of mercury that exceeds safety guidelines. A review of medical literature and US government data suggests that: (i) many cases of idiopathic autism are induced by early mercury exposure from thimerosal; (ii) this type of autism represents an unrecognized mercurial syndrome; and (iii) genetic and non-genetic factors establish a predisposition whereby thimerosal's adverse effects occur only in some children.

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PMID: 11339848 [PubMed - indexed for MEDLINE]

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[Drugs](#). 2001;61(5):565-72.

Vaccines without thiomersal: why so necessary, why so long coming?

[van't Veen AJ](#).

Department of Dermatology and Venereology, Erasmus University Hospital Rotterdam-Dijkzigt, Rotterdam, The Netherlands.

### **Abstract**

The inorganic mercurial thiomersal (merthiolate) has been used as an effective preservative in numerous medical and non-medical products since the early 1930s. Both the potential toxicity of thiomersal and sensitisation to thiomersal in relation to the application of thiomersal-containing vaccines and immunoglobulins, especially in children, have been debated in the literature. The very low thiomersal concentrations in pharmacological and biological products are relatively non-toxic, but probably not in utero and during the first 6 months of life. The developing brain of the fetus is most susceptible to thiomersal and, therefore, women of childbearing age, in particular, should not receive thiomersal-containing products. Definitive data of doses at which developmental effects occur are not available. Moreover, revelation of subtle effects of toxicity needs long term observation of children. The ethylmercury radical of the thiomersal molecule appears to be the prominent sensitiser. The prevalence of thiomersal hypersensitivity in mostly selected populations varies up to 18%, but higher figures have been reported. The overall exposure to thiomersal

differs considerably between countries. In many cases a positive routine patch test to thiomersal should be considered an accidental finding without or, probably more accurately, with low clinical relevance. In practice, some preventive measures can be taken with respect to thiomersal hypersensitivity. However, with regard to the debate on primary sensitisation during childhood and renewed attention for a reduction of children's exposure to mercury from all sources, the use of thiomersal should preferably be eliminated or at least be reduced. In 1999 the manufacturers of vaccines and immunoglobulins in the US and Europe were approached with this in mind. The potential toxicity in children seems to be of much more concern to them than the hidden sensitising properties of thiomersal. In The Netherlands, unlike many other countries, the exposure to thiomersal from pharmaceutical sources has already been reduced. **Replacement of thiomersal in all products should have a high priority in all countries.**

PMID: 11368282 [PubMed - indexed for MEDLINE]

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[Neurotoxicology](#). 2001 Oct;22(5):691-7.

Predicted mercury concentrations in hair from infant immunizations: cause for concern.

[Redwood L](#), [Bernard S](#), [Brown D](#).

Coalition for Safe Minds, Cranford, NJ 07016, USA. [tlredwood@mindspring.com](mailto:tlredwood@mindspring.com)

### **Abstract**

Mercury (Hg) is considered one of the worlds most toxic metals. Current thinking suggests that exposure to mercury occurs primarily from seafood contamination and rare catastrophic events. Recently, another common source of exposure has been identified. Thimerosal (TMS), a preservative found in many infant vaccines, contains 49.6% ethyl mercury (EtHg) by weight and typically contributes 25 microg of EtHg per dose of infant vaccine. As part of an ongoing review, the Food and Drug Administration (FDA) announced in 1999 that infants who received multiple TMS-preserved vaccines may have been exposed to cumulative Hg in excess of Federal safety guidelines. According to the centers for disease control (CDC) recommended immunization schedule, infants may have been exposed to 12.5 microg Hg at birth, 62.5 microg EtHg at 2 months, 50 microg EtHg at 4 months, 62.5 microg EtHg at 6 months, and 50 microg EtHg at approximately 18 months, for a total of 237.5 microg EtHg during the first 18 months of life, if all TMS-containing vaccines were administered. Neurobehavioral alterations, especially to the more susceptible fetus and

infant, are known to occur after relatively low dose exposures to organic mercury compounds. In effort, to further elucidate the levels of ethyl mercury resulting from exposure to vaccinal TMS, we estimated hair Hg concentrations expected to result from the recommended CDC schedule utilizing a one compartment pharmacokinetic model. This model was developed to predict hair concentrations from acute exposure to methylmercury (MeHg) in fish. Modeled hair Hg concentrations in infants exposed to vaccinal TMS are in excess of the Environmental Protection Agency (EPA) safety guidelines of 1 ppm for up to 365 days, with several peak concentrations within this period. More sensitive individuals and those with additional sources of exposure would have higher Hg concentrations. Given that exposure to low levels of mercury during critical stages of development has been associated with neurological disorders in children, including ADD, learning difficulties, and speech delays, the predicted hair Hg concentration resulting from childhood immunizations is cause for concern. Based on these findings, the impact which vaccinal mercury has had on the health of American children warrants further investigation.

PMID: 11770890 [PubMed - indexed for MEDLINE]

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[Int Arch Allergy Immunol.](#) 1994 Jul;104(3):296-301.

Thimerosal induces toxic reaction in non-sensitized animals.

[Uchida T](#), [Naito S](#), [Kato H](#), [Hatano I](#), [Harashima A](#), [Terada Y](#), [Ohkawa T](#), [Chino F](#), [Eto K](#).

Department of Safety Research on Biologics, National Institute of Health, Tokyo, Japan.

Comment in:

- [Int Arch Allergy Immunol.](#) 1994 Dec;105(4):408.

### **Abstract**

The effects of injection of thimerosal solution on nonsensitized animals was investigated. Intrafootpad injection of thimerosal solution in nonsensitized mice resulted in a swelling response which peaked 1 h after injection and lasted for more than 24 h. Histopathological examination showed that there were severe edema and infiltration of polymorphonuclear neutrophils at the site of injection. An increased vascular permeability was observed after cutaneous injection of thimerosal solution on the back of nonsensitized rats. Since mercuric chloride and methyl mercury induced severer reactions, and thiosalicylic acid had no effect, mercury contained in thimerosal would have caused the reactions observed in this study. These results suggest that part of these hypersensitivity reactions against thimerosal



observed among patients were possibly induced by the toxic effect of thimerosal. Therefore, thimerosal contained as a preservative in vaccine may augment the side-effects of the vaccination.

PMID: 7518269 [PubMed - indexed for MEDLINE]

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[Mutat Res.](#) 1993 May;287(1):57-70.

C-mitosis and numerical chromosome aberration analyses in human lymphocytes: 10 known or suspected spindle poisons.

[Sbrana I](#), [Di Sibio A](#), [Lomi A](#), [Scarcelli V](#).

Dipartimento di Scienze dell'Ambiente e del Territorio, Università di Pisa, Italy.

### Abstract

As a part of a coordinated EEC project to validate suitable assays for chemically induced genomic mutations, numerical chromosomal aberrations and spindle effects were studied in human lymphocyte cultures exposed to cadmium chloride, chloral hydrate, colchicine, diazepam, econazole, hydroquinone, pyrimethamine, thiabendazole, thimerosal and vinblastine. Chromosome number analysis was carried out after treatment for 48 and 72 h; spindle effects, i.e., increases in the mitotic indices and c-mitoses, were analyzed in cultures treated 5 h before fixation. Dose-related numerical chromosomal aberrations are induced by colchicine and vinblastine, the only chemicals that also induce c-mitotic effects in a wide range of doses. Hyperdiploidy is induced by chloral hydrate, cadmium chloride and thimerosal without dose-effect relationship; chloral hydrate and thimerosal affect spindle functions while only a weak spindle effect is produced by cadmium chloride. Tetraploid and/or endoreduplicated cells are induced without dose-effect relationship by hydroquinone, thiabendazole and thimerosal, all of them able to produce c-mitotic effects. Diazepam and econazole induce only hypodiploidy; pyrimethamine does not induce numerical chromosomal aberrations.

PMID: 7683385 [PubMed - indexed for MEDLINE]

C-mitosis is abnormal [mitosis](#).

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[Mutat Res.](#) 1993 May;287(1):47-56.

Induction of mitotic aneuploidy using Chinese hamster primary embryonic cells. Test results of 10 chemicals.

[Natarajan AT](#), [Duivenvoorden WC](#), [Meijers M](#), [Zwanenburg TS](#).

MGC Department of Radiation Genetics and Chemical Mutagenesis, State University of Leiden, The Netherlands.

### **Abstract**

Using primary Chinese hamster embryonic cells, 10 known or suspected aneugens supplied as a part of the EC 4th Environmental Research and Development Programme were evaluated by the technique described by Dulout and Natarajan (1987). The chemicals included cadmium chloride, chloral hydrate, colchicine, diazepam, econazole, hydroquinone, pyrimethamine, thiabendazole, thimerosal and vincristine. **All chemicals except pyrimethamine gave clearly positive effect at most of the doses tested.** The ease with which the assay is performed and reproducible results that are obtained with the suspected compounds indicate that this in vitro test using primary embryonic fibroblasts is a promising one for routine screening.

PMID: 7683384 [PubMed - indexed for MEDLINE]

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[Dermatol Clin.](#) 1990 Jan;8(1):161-4.

Reactions to thimerosal in hepatitis B vaccines.

[Rietschel RL](#), [Adams RM](#).

Department of Dermatology, Ochsner Clinic, New Orleans, Louisiana.

### **Abstract**

**Hypersensitivity to thimerosal in vaccines has been reported to induce persistent local reactions, urticarial and generalized exanthematic eruptions, and, in the case of the hepatitis B vaccine, urticaria with asthma. The authors describe two cases of extensive reactions, one in a patient who did not form antibodies to the principal vaccine antigen. Although not all thimerosal-sensitive patients develop adverse reactions to vaccines containing this material, there is a potential risk, and the reactions can be very long lasting.**

PMID: 2137393 [PubMed - indexed for MEDLINE]

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[Ann Dermatol Venereol.](#) 1988;115(8):793-6.

[Multicenter survey related to the frequency of positive patch tests with mercury and thiomersal].

[Article in French]

[Lachapelle JM](#), [Chabeau G](#), [Ducombs G](#), [Lacroix M](#), [Martin P](#), [Reuter G](#), [Marot L](#).

Unité de Dermatologie Professionnelle et de l'Environnement, Université Catholique de Louvain, Bruxelles, Belgium.

### **Abstract**

A multicentric study concerning the frequency of positive allergic patch test reactions to mercury and to thiomersal has been conducted in France and in Belgium among 2,000 adult patients submitted to routine patch testing. 73 (3.6 p. 100) patients had a positive patch test to mercury and 47 (2.3 p. 100) to thiomersal, 22 (1.1 p. 100) reacted positively to both mercurials. These high figures are most probably in relation with a broad use of mercurials in both countries, as antiseptics as well as preservative agents in topical drugs. They lead to a careful use of mercurials, which have to be avoided when they can be advantageously replaced by other antiseptics or preservative agents. As far as cosmetics are concerned, the use of mercurials (chemical nature and concentration) is restricted by a Recommendation of the European Council.

PMID: 2974266 [PubMed - indexed for MEDLINE]

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[Am J Optom Physiol Opt.](#) 1988 Nov;65(11):867-73.

Toxic effects of ophthalmic preservatives on cultured rabbit corneal epithelium.

[Simmons PA](#), [Clough SR](#), [Teagle RH](#), [Jaanus SD](#).

Department of Basic and Visual Sciences, Southern California College of Optometry, Fullerton.

### **Abstract**

We investigated the effects of the ophthalmic preservatives thimerosal and sorbic acid on the proliferation and survival of rabbit corneal epithelial cells in tissue culture. Normally, explants of corneal epithelium grow vigorously during the first 7 days in culture. With 0.004% thimerosal present in the culture medium, the normal proliferation of corneal cells is suppressed completely. When 0.1% sorbic acid is present, proliferation is delayed and the lifespan of the corneal cells is reduced. After a 1-h exposure to concentrations of thimerosal of 0.0005% or greater, virtually all corneal cells present in established cultures are killed. These results suggest that use of ophthalmic preparations containing these chemicals may affect the metabolic and proliferative capacity of the corneal epithelium adversely.

PMID: 3252733 [PubMed - indexed for MEDLINE]

But okay to inject?

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[Contact Dermatitis](#). 1988 Apr;18(4):229-33.

Thiomersal allergy and vaccination reactions.

[Cox NH](#), [Forsyth A](#).

Department of Dermatology, Royal Victoria Infirmary, Newcastle-upon-Tyne, UK.

### Abstract

Thiomersal is the preservative in all toxoid vaccines routinely administered to children in the UK, but exposure from other sources is uncommon. Delayed hypersensitivity to thiomersal was demonstrated in 1% of individuals attending the Contact Dermatitis Investigation Unit, and 50 of these patients with positive patch tests to thiomersal were studied. Cross-reaction with other mercurials occurred in 17 of 29 patients tested (59%). 31 of the patients replied to a questionnaire regarding vaccination reactions, and were compared with case-controls matched for age, sex, and site of dermatitis. 4 patients in each group reported reactions to vaccines which contained thiomersal, suggesting that thiomersal hypersensitivity was not associated with an increased risk of vaccination reactions. However, individual cases of severe reactions to thiomersal demonstrate a need for vaccines with an alternative preservative.

PMID: 3378430 [PubMed - indexed for MEDLINE]

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[Presse Med](#). 1988 Apr 30;17(16):795-6.

[Allergy to mercuriothiolate in an infant during heparinization of an intracaval catheter].

[Article in French]

[Chastagner P](#), [Morali A](#), [Trechot JP](#), [May I](#), [Vidailhet M](#).

Service de Médecine infantile 3, CHRU de Brabois, Vandoevre.

### Abstract

A 4-month old infant developed an immediate and proven systemic allergic reaction to mercuriothiolate. The acute accident occurred while an intracaval catheter was being treated with a dry-frozen heparin which excipient contains mercuriothiolate. This conservative agent is present in numerous pharmaceutical preparations for topical and systemic use.

PMID: 2968567 [PubMed - indexed for MEDLINE]

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[Contact Dermatitis](#). 1988 May;18(5):268-73.

Thimerosal: a hidden allergen in ophthalmology.

[Tosti A](#), [Tosti G](#).

Department of Dermatology, University of Bologna, Italy.

### **Abstract**

We report 36 patients with thimerosal-induced follicular allergic contact conjunctivitis. 18 patients had follicular conjunctivitis without eyelid involvement, while 5 patients had follicular conjunctivitis associated with an allergic contact dermatitis of the eyelids; all these patients had been using thimerosal-containing eye drops. A further 13 patients were soft contact lens wearers who became sensitized to their own thimerosal-containing lens solutions. All 36 patients showed a positive patch test reaction to thimerosal, while only 1 of them reacted to an ophthalmic solution. **Thimerosal sensitization appears to be clinically relevant in ophthalmic patients.**

PMID: 3416589 [PubMed - indexed for MEDLINE]

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[Arch Toxicol](#). 1985 Sep;57(4):260-7.

The comparative toxicology of ethyl- and methylmercury.

[Magos L](#), [Brown AW](#), [Sparrow S](#), [Bailey E](#), [Snowden RT](#), [Skipp WR](#).

### **Abstract**

Neurotoxicity and renotoxicity were compared in rats given by gastric gavage five daily doses of 8.0 mg Hg/kg methyl- or ethylmercuric chloride or 9.6 mg Hg/kg ethylmercuric chloride. Three or 10 days after the last treatment day rats treated with either 8.0 or 9.6 mg Hg/kg ethylmercury had higher total or organic mercury concentrations in blood and lower concentrations in kidneys and brain than methylmercury-treated rats. In each of these tissues the inorganic mercury concentration was higher after ethyl- than after methylmercury. Weight loss relative to the expected body weight and renal damage was higher in ethylmercury-treated rats than in rats given equimolar doses of methylmercury. These effects became more severe when the dose of ethylmercury was increased by 20%. Thus in renotoxicity the renal concentration of inorganic mercury seems to be more

important than the concentration of organic or total mercury. In methylmercury-treated rats damage and inorganic mercury deposits were restricted to the P2 region of the proximal tubules, while in ethylmercury-treated rats the distribution of mercury and damage was more widespread. There was little difference in the neurotoxicities of methylmercury and ethylmercury when effects on the dorsal root ganglia or coordination disorders were compared. **Based on both criteria, an equimolar dose of ethylmercury was less neurotoxic than methylmercury, but a 20% increase in the dose of ethylmercury was enough to raise the sum of coordination disorder scores slightly and ganglion damage significantly above those in methylmercury-treated rats.** (ABSTRACT TRUNCATED AT 250 WORDS)

PMID: 4091651 [PubMed - indexed for MEDLINE]

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[Hautarzt.](#) 1984 Apr;35(4):192-6.

[Reactions to vaccinations against tetanus and tick-borne encephalitis caused by merthiolate (thiomersal)].

[Article in German]

[Lindemayr H](#), [Drobil M](#), [Ebner H](#).

#### **Abstract**

Thirty patients with suspected adverse reactions to tetanus- or tick-borne encephalitis-vaccines were subjected to allergy tests. In 8 of 30 patients epicutaneous and/or intracutaneous tests with merthiolate were positive. Testing anorganic mercury, formaldehyde, aluminium hydroxide, gentamycin and egg white (i.c. and RAST), no positive reactions were found. **After vaccination - prior to testing - merthiolate - positive patients had suffered from local inflammatory reactions at the injection site, fever and lymphadenopathy (four patients), urticarial (three patients) or lichenoid exanthemas (one patient). Reviewing the literature it is suggested that alternatively merthiolate-free vaccines be provided for sensitized individuals.**

PMID: 6724907 [PubMed - indexed for MEDLINE]

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[Am J Optom Physiol Opt.](#) 1983 Sep;60(9):759-61.

Reactions induced by the concurrent use of thimerosal and tetracycline.

[Crook TG](#), [Freeman JJ](#).

#### **Abstract**

We examined the reaction to thimerosal which occurred when patients were prescribed tetracyclines simultaneously. Nine patients were identified who had been using a 0.004% thimerosal-containing contact lens solution for over 6 months. All had developed varying degrees of ocular reaction (red eye, irritation, blepharitis) apparently as a result of taking tetracyclines concurrently. The reaction disappeared upon discontinuance of either the thimerosal or the tetracyclines. The hypothesis that the reaction was due to an interaction between thimerosal and tetracyclines was confirmed in rabbits.

PMID: 6681469 [PubMed - indexed for MEDLINE]

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[Transfusion](#). 1982 May-Jun;22(3):241-3.

Thimerosal dependent agglutination, a newly described blood bank problem.

[Shulman IA](#), [Hasz LA](#), [Simpson RB](#).

#### **Abstract**

A number of ABO grouping, Rh typing, antibody screening, and antibody identification problems are associated with chemicals in blood bank reagents. We describe a newly discovered agglutination phenomenon due to a thimerosal (Merthiolate)-dependent agglutinin found in the serum of a normal blood donor. Thimerosal is used as a preservative in several low-ionic strength reagents. This agglutination phenomenon is detected only in test systems (low-ionic-strength, albumin, saline, ficin treated test cells) in which test cells are incubated in the presence of thimerosal. Agglutination does not occur in the absence of thimerosal. The thimerosal-dependent agglutinin behaves like an IgG IgG autoantibody. There is no evidence that the thimerosal-dependent agglutinin is responsible for increased red cell destruction.

PMID: 7090037 [PubMed - indexed for MEDLINE]

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[Contact Dermatitis](#). 1980 Jun;6(4):241-5.

Merthiolate hypersensitivity and vaccination.

[Förström L](#), [Hannuksela M](#), [Kousa M](#), [Lehmuskallio E](#).

#### **Abstract**

Epicutaneous tests with 0.1% merthiolate in petrolatum showed hypersensitivity in 96 of 4647 eczema patients (2.0%) and in seven of 105 healthy recruits (7%). There was a marked

preponderance of young age classes in the eczema group. Twelve of 41 merthiolate-positive patients tested reacted to mercury alone, three to thiosalicylic acid alone and one to both. The remaining 25 patients reacted to neither of the individual components although the merthiolate complex as a whole gave a positive test result. Forty-five of the merthiolate-positive patients were tested subcutaneously with 0.5 ml of a 0.01% merthiolate solution, i.e. a dose equal to that contained in one shot of tetanus toxoid, for example. Nine patients developed a local reaction at the site of the injection, and the area became eczematous in four cases. In one of the patients the eczema spread over the body, causing fever. Since merthiolate-sensitive patients also react to merthiolate administered intracutaneously, the vaccinator should avoid the use of a needle whose outer surface has been contaminated when the vaccine was aspirated from the bottle. However, even when this precautionary measure is taken, local reactions can be expected in such a high percentage of merthiolate-sensitive persons that merthiolate in vaccines should be replaced by another antibacterial agent.

PMID: 6447032 [PubMed - indexed for MEDLINE]

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[J Neurol Neurosurg Psychiatry](#). 1980 Feb;43(2):143-9.

Accidental ethyl mercury poisoning with nervous system, skeletal muscle, and myocardium injury.

[Cinca I](#), [Dumitrescu I](#), [Onaca P](#), [Serbănescu A](#), [Nestorescu B](#).

#### **Abstract**

Four case reports are presented of patients who ate the meat of a hog inadvertently fed seed treated with fungicides containing ethyl mercury chloride. The clinical, electrophysiological, and toxicological, and in two of the patients the pathological data, showed that this organic mercury compound has a very high toxicity not only for the brain, but also for the spinal motoneurons, peripheral nerves, skeletal muscles, and myocardium.

PMID: 7359151 [PubMed - indexed for MEDLINE]PMCID: PMC490489Free PMC Article

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[Toxicology](#). 1979 Mar-Apr;12(3):325-33.

Problems associated with the use of merthiolate as a preservative in anti-lymphocytic globulin.

[Heyworth MF](#), [Truelove SC](#).



## Abstract

The cytotoxic properties of 2 anti-lymphocytic globulin (ALG) preparations were investigated in vitro by measuring the release of <sup>51</sup>Cr from labelled human peripheral blood mononuclear cells, tonsil lymphocytes and Chang cells, incubated with different concentrations of ALG. One of the ALG preparations showed non-selective cytotoxicity in the absence of complement. Evidence was obtained to suggest that this effect was due to merthiolate (sodium ethylmercurithiosalicylate) which had been added to the ALG as a preservative during manufacture. The mercury concentration in the ALG was found to be greater than that stated by the manufacturers. **It is conceivable that the clinical use of such as ALG preparation might lead to mercury accumulation in the tissues, with resulting toxic effects.** The whole question of the use of merthiolate in the preparation of sera for administration to human subjects needs to be reconsidered.

PMID: 494313 [PubMed - indexed for MEDLINE]

**But okay to inject?**

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[Arch Dis Child.](#) 1977 Dec;52(12):962-4.

Organ mercury levels in infants with omphaloceles treated with organic mercurial antiseptic.

[Fagan DG](#), [Pritchard JS](#), [Clarkson TW](#), [Greenwood MR](#).

## Abstract

Samples of fresh and fixed tissues from infants with exomphalos treated by thiomersal application were analysed for mercury content. **The results showed that thiomersal can induce blood and organ levels of organic mercury which are well in excess of the minimum toxic level in adults and fetuses.** The analysis of fresh and fixed tissues must be carefully controlled against normal tissues in order to interpret mercury levels accurately.

PMID: 606172 [PubMed - indexed for MEDLINE]PMCID: PMC1545035Free PMC Article

**This appears to mean that even topical application can result in toxic internal levels.**

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[Invest Ophthalmol Vis Sci.](#) 1977 Apr;16(4):273-80.

Effect of the ophthalmic preservative thimerosal on rabbit and human corneal endothelium.

[Van Horn DL](#), [Edelhauser HF](#), [Prodanovich G](#), [Eiferman R](#), [Pederson HF](#).

## Abstract

Widespread use of the mercurial-containing preservative thimerosal as an antibacterial agent in ophthalmic drugs and solutions warranted an investigation into its possible cytotoxic effects on the functional and ultrastructural integrity of the corneal endothelium. No changes in corneal thickness were observed during 5 hours' perfusion of the endothelium of rabbit and human corneas with 0.0001 and 0.0005 percent thimerosal in glutathione bicarbonate Ringer's solution (GBR). Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) of the endothelium of the 0.0001 percent group revealed normal ultrastructure. SEM and TEM of the endothelium of corneas perfused with 0.0005 percent thimerosal for 5 hours revealed condensed mitochondria, cytoplasmic vacuoles, and cytoplasmic flaps at the apical end of the cellular junctions. Perfusion of higher concentrations (0.001 and 0.005 percent) of thimerosal in GBR resulted in increases in corneal thickness after 2 hours and irreversible ultrastructural damage to the endothelial cells by 5 hours. Corneas perfused with 0.01 and 0.1 percent thimerosal in GBR showed a rapid and immediate increase in corneal thickness and endothelial cell death and necrosis within 1 hour. It is postulated that the mercury in thimerosal becomes bound to the cell membrane protein sulfhydryl groups, causing an increase in cellular permeability; **These results suggest that the prolonged exposure of the corneal endothelium to thimerosal in the accepted antimicrobial dosage of 0.005 to 0.001 percent may result in functional and structural damage to the endothelium.**

PMID: 844986 [PubMed - indexed for MEDLINE]Free Article

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[Poult Sci.](#) 1976 Sep;55(5):1913-7.

Preliminary study of the effects of feeding ethyl mercury chloride on four breeds of chickens.

[Al-Soudi KA](#), [Al Fayadh HA](#), [Al-Khazrje AK](#), [Mehdi AW](#), [Al-Jiboori A](#), [Al Muraib S](#).

### **Abstract**

Different breeds of chickens namely Single Comb White Leghorn (S.C.W.L.), New Hampshire (N.H.), Iraqi (IRQ) and a cross (CRS.) S.C.W.L. X N.H. X IRQ. were housed in small pens (20 females and 2 males each) and given, in the diet, 40% wheat treated with ethyl mercury chloride, for 88 days. Throughout the whole experiment all birds remained active and showed no symptoms of toxicity. The Iraqi breed was significantly higher than the other breeds with respect to egg production. The results also indicated that mercury in egg white is almost three times as much as that in the yolk, although there was no significant

difference between the breeds. The liver and kidney of the four breeds tended to accumulate the highest amount of mercury. Significant differences appeared between sexes according to liver and kidney. White Leghorn and local breeds behaved the same, but N.H. had the highest concentration of mercury in most tissues.

PMID: 792857 [PubMed - indexed for MEDLINE]

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[Poult Sci.](#) 1976 Mar;55(2):772-9.

Effects of feeding ethyl mercury chloride to chickens.

[Al-Fayadh H](#), [Mehdi AW](#), [Al-Soudi K](#), [Al-Khazraji AK](#), [Al-Jiboori NA](#), [Al-Muraib S](#).

### **Abstract**

Four groups, 0, 5, 10 and 20%, of Single Comb White Leghorn chickens (30 males plus 30 females each) were fed a diet which contained either 0, 5, 10 or 20% ethyl mercury chloride dressed wheat for a period of 88 days. The wheat was dressed with the organic mercury compound at the rate of 500 gm. ethyl mercury chloride per metric ton of wheat. Therefore, the diets contained respectively 0, 25, 50 and 100 mg. organic mercury compound/kg. With average daily feed consumption of 101, 102, 101 and 98 gm. by the individual birds of the respective groups, the birds did not show any symptoms of disease during the course of the study. Egg production, egg quality and mortality of the treatment groups were comparable with those of the control group. The amount of residual mercury in egg white and yolk was determined at intervals. The residual mercury of egg white of the treatment groups was about three times as much as that of egg yolk, and made its significant appearance in the 20% group on the third day of the trial. The concentration was increasing with time in both white and yolk and was parallel to the concentration of the organic mercury in the diet. The liver followed by the kidney of both sexes accumulated the highest amounts of mercury. Tissues of female birds accumulated less mercury than tissues of male birds did probably due to the passage of some of the ingested mercury with the egg white and yolk. The results were discussed on the basis that the kind of mercury compound, daily intake and duration of treatment play major roles in the determination of induced effects.

PMID: 778821 [PubMed - indexed for MEDLINE]

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[Toxicology.](#) 1975;3(2):171-6.

Tissue concentrations of mercury after chronic dosing of squirrel monkeys with thiomersal.

[Blair AMJN](#), [Clark B](#), [Clarke AJ](#), [Wood P](#).

### **Abstract**

Squirrel monkeys were dosed intranasally with saline or thiomersal (sodium ethylmercurithiosalicylate, 0.002 percent w/v) daily for six months. The total amounts of thiomersal given during the six months period were 418 mug (low dose group) and 2280 mug (high dose group). This was equivalent to 207 and 1125 mug mercury. The dose differential was achieved by more frequent administration to the high dose group. Mercury concentrations were significantly raised over control values in brain (high dose group only), liver, muscle and kidney, but not in blood. Concentrations were highest in the kidney, moderate in liver and lowest in brain and muscle. Much of the mercury was present in the inorganic form (37-91 percent). No evidence of toxicity due to thiomersal was seen in any animal. Nevertheless accumulation of mercury from chronic use of thiomersal-preserved medicines is viewed as a potential health hazard for man.

PMID: 804725 [PubMed - indexed for MEDLINE]

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[Arch Ophthalmol](#). 1975 Jan;93(1):52-55.

Teratogenicities of ophthalmic drugs. II. Teratogenicities and tissue accumulation of thimerosal.

[Gasset AR](#), [Itoi M](#), [Ishii Y](#), [Ramer RM](#).

### **Abstract**

Under the conditions of this study, systemically or topically applied thimerosal was found to have no teratogenic effect even when given in concentrations approaching the 50% lethal dose of these compounds. A comparison of topical and subcutaneous administration of thimerosal to rabbits shows that a substantial concentration of mercury was present in blood and tissues of the treated animals and their offspring. Thimerosal was found to cross the blood-brain and placenta barriers.

PMID: 1111489 [PubMed - indexed for MEDLINE]

Topical as well as subcutaneous...

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[Contact Dermatitis](#). 1975 Aug;1(4):221-2.

Acute laryngeal obstruction presumed secondary to thiomersal (merthiolate) delayed hypersensitivity.

[Maibach H.](#)

#### **Abstract**

A patient treated his slight sore-throat with a thiomersal first aid spray. The next day, because of continued discomfort, he repeated its use. Laryngeal obstruction followed within hours. Emergency tracheostomy produced prompt improvement. Patch testing revealed an extreme spreading reaction to thiomersal. It is our interpretation that the acute laryngeal obstruction was delayed hypersensitivity to this first aid spray.

PMID: 1235252 [PubMed - indexed for MEDLINE]

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Science. 1972 Jan 21;175(19):328-31.

**Ethyl mercury p-toluene sulfonilide: lethal and reproductive effects on pheasants.**

[Spann JW](#), [Heath RG](#), [Kreitzer JF](#), [Locke LN](#).

#### **Abstract**

Ethyl mercury p-toluene sulfonilide (active ingredient of Ceresan M) at a dietary concentration of 30 parts per million (12.5 parts of mercury per million) was lethal to adult ring-necked pheasants. Egg production and survival of third-week embryos were sharply reduced when breeders were maintained on feed containing 10 parts of this compound per million (4.2 parts of mercury per million).

PMID: 5008162 [PubMed - indexed for MEDLINE]

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#### **Aneugen**

Genetics. Any agent that affects cell division and the mitotic spindle apparatus resulting in the loss or gain of whole chromosomes, thereby inducing an aneuploidy.

#### **Aneuploidie**

Genetics. A genetically unbalanced condition in which a cell or an organism has a number of chromosomes that is not an exact multiple of the haploid number for that species. E.g., trisomy 21 is a form of aneuploidy.

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Quelle: <http://www.vaccinationnews.org/evidence-thimerosal-risk>

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