Evidence for Thimerosal Risk


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

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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.


Luteolin and thiosalicylate inhibit HgCl2 and thimerosal-induced VEGF release from human mast cells.
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Abstract

HgCl₂ 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 (HgCl₂) 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/10⁶ cells and 335.5±12 pg/10⁶ cells at 10 microM) compared to control cells (242±21 pg/10⁶ cells, n=5, p less than 0.05); this effect is weaker than that induced by HgCl₂ at 10 microM (448±14 pg/10⁶ 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 HgCl₂ (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 HgCl₂ or thimerosal completely blocked their effect. Luteolin and methyl thiosalicylate may be useful in preventing mercury-induced toxicity.

PMID: 21244751 [PubMed - in process]


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

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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.


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

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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.

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In other words, it is not settled….


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]


Mercury toxicokinetics--dependency on strain and gender.

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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 HgCl2 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]
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.

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

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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.

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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.
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 75µg to 187.5µg), 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.
Genotoxicity of thimerosal in cultured human lymphocytes with and without metabolic activation sister chromatid exchange analysis proliferation index and mitotic index.

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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]
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".


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

Park EK, Mak SK, Kültz D, Hammock BD.
Renal inner medullary collecting duct cells (mIMCD3) and human embryonic kidney cells (HEK293) were used for cytoscreening of thimerosal and mercury chloride (HgCl2). Thimerosal and HgCl2 acted in a concentration-dependent manner. In mIMCD3 cells the 24-h LC50 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 LC50 value for HgCl2 in mIMCD3 cells was 40 microM. In HEK293 cells, the 24-h LC50 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]

Thimerosal-induced apoptosis in human SCM1 gastric cancer cells: activation of p38 MAP kinase and caspase-3 pathways without involvement of [Ca2+]i elevation.


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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 [Ca2+]i increases via Ca2+ influx from the extracellular space. However, pretreatment with (bis(o-aminophenoxy)ethane-N,N,N',N'-tetraacetate)AM, a Ca2+ chelator, to prevent thimerosal-induced [Ca2+]i increases did not protect cells from death. The results suggest that in SCM1 cells, thimerosal caused Ca2+-independent apoptosis via phosphorylating p38 MAPK resulting in caspase-3 activation.


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

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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 [HgCl2], methyl mercuric chloride [CH3HgCl], p-chloromercuribenzoate [p-CMB] and thimerosal [TMS; ethylmercurithiosalicylate]) on cell death, microtubules, actin, CD3 receptor expression, protein tyrosine phosphorylation (PTyr-P) and intracellular calcium ([Ca2+]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 microM, with two distinct patterns of effects. Early apoptosis was prolonged for CH3HgCl- and TMS-treated cells, with more than 50% remaining YP+/PI- after 4h. Both CH3HgCl 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. CH3HgCl 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 [Ca2+]i were noted after 1 min exposure. [Ca2+]i increased progressively, reaching levels five- to eight-fold greater than control values. In contrast, dye uptake was delayed with HgCl2 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 HgCl2. HgCl2 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 [Ca2+]i within minutes, though levels remained under twice the baseline concentration after 15 min exposure. With continued exposure, [Ca2+]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]


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

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Abstract

Inorganic mercury (mercuric chloride--HgCl2)) 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 HgCl(2) are present to varying extent. Since these organic Hg species are converted to the autoimmunogen Hg(2+) in the body, their primary autoimmunogen potential is uncertain and the subject of this study. A moderate dose of 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 HgCl(2) inducing AFA was 1.5 mg/L drinking water which corresponded to a renal Hg(2+) concentration of 0.53 micro g/g. Using a dose of 8 mg 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 Hg(2+) concentration of 1.8 micro g/g. The autoimmunogen effect of EtHg might therefore be entirely due to 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 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 HgCl(2) (25 mg/L) caused a balanced Th2-Th1 response already from onset. In conclusion, while metabolically formed 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]


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

Herdman ML, Marcelo A, Huang Y, Niles RM, Dhar S, Kiningham KK.
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.


Mercury and autism: accelerating evidence?

Mutter J, Naumann J, Schneider R, Walach H, Haley B.
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]


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

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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] PMC: PMC1280342 Free PMC Article


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

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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]
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.


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

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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 Ca2+ concentration ([Ca2+]i) and membrane potential, and for discriminating intact living cells, apoptotic living cells and dead cells. Incubation with thimerosal at 3 microM or more (up to 30 microM) for 60 min depolarized the membranes, associated with increasing the [Ca2+]i. Thimerosal at 30 microM induced an apoptotic change in membranes of almost all living cells. Furthermore, the prolonged incubation with 30 microM 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]


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

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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 microM 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]


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

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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 fibrillarin, 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 antifibrillarin 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 finding re: the doses of thimerosal infants and children have received?


Neurotoxic effects of postnatal thimerosal are mouse strain dependent.

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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]

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

Effect of thimerosal, a preservative in vaccines, on intracellular Ca2+ concentration of rat cerebellar neurons.


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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 Ca2+ ([Ca2+]) in a concentration-dependent manner. The potency of 10 microM thimerosal to increase the [Ca2+]i was less than that of 10 microM methylmercury. Their effects on the [Ca2+]i were greatly attenuated, but not completely suppressed, under external Ca(2+)-free condition, suggesting a possibility that both agents increase membrane Ca2+ permeability and release Ca2+ 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]
Characterization of cytotoxic and genotoxic effects of different compounds in CHO K5 cells with the comet assay (single-cell gel electrophoresis assay).

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

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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: PMC1892749 Free PMC Article
Thimerosal induces micronuclei in the cytochalasin B block micronucleus test with human lymphocytes.

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

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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.


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

vant Veen AJ.
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]
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]

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

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

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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.

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

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

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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]

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.