ACIP 2025

Thimerosal as a Vaccine Preservative

Prepared for the Advisory Committee for Immunization Practices

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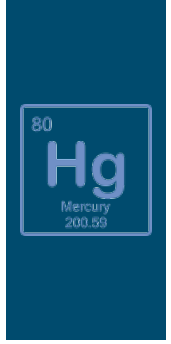
Disclosures

- No financial conflicts or relationships to disclose



The Food and Drug Administration Modernization Act of 1997

- Compiled list of drugs and foods that contained intentionally introduced mercury compounds
- Provided quantitative and qualitative analysis of mercury compounds
- Report included 219 products which included 11 biologics and immunoglobulin therapies

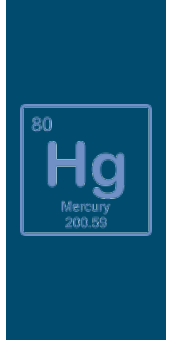
Ref: U.S. Congress. (1997, November 21). Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296.

1999 Joint Statement by US Public Health Service (PHS) and American Academy of Pediatrics (AAP)

- On July 7th, 1999, a joint statement issued by PHS and AAP called for the immediate reduction and elimination of the mercury based preservative thimerosal from infant vaccines based on the findings that infants and children who received vaccines preserved with thimerosal **could be exposed to mercury in excess of federal safety guidelines.**

- "because any potential risk is of concern, the Public Health Service (PHS), the American Academy of Pediatrics (AAP), and vaccine manufacturers agree that thimerosal-containing vaccines should be removed as soon as possible."

Centers for Disease Control and Prevention (CDC). Recommendations regarding the use of vaccines that contain thimerosal as a preservative. MMWR Morb Mortal Wkly Rep. 1999 Nov 5;48(43):996-8. PMID: 10577494.

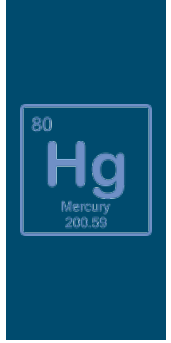


Institute of Medicine
Immunization Safety Review of Thimerosal Containing Vaccines and Neurodevelopmental Disorders (October 2001)

- The committee "supported prior decisions made by the ACIP and the American Academy of Pediatrics to call for the removal of thimerosal from vaccines that are part of the recommended childhood immunization schedule."

- But they noted that "vaccines that are not part of the recommended childhood immunization schedule still contain thimerosal as a preservative and may be given to some children" and a lingering concern that there remains "on the shelf" an unknown quantity of thimerosal-containing Hib, hepatitis B, and DTaP vaccines.

Institute of Medicine (US) Immunization Safety Review Committee; Stratton K, Gable A, McCormick MC, editors. Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders. Washington (DC): National Academies Press (US); 2001. Immunization Safety Review, Thimerosal-Containing Vaccines and Neurodevelopmental Disorders. Available from: https://www.ncbi.nlm.nih.gov/books/NBK223724/

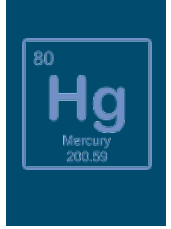


Institute of Medicine
Immunization Safety Review of Thimerosal Containing Vaccines and Neurodevelopmental Disorders (October 2001)

- Recommended: “the use of thimerosal free DTaP, HiB and Hepatitis B vaccines despite the fact that there might be remaining supplies of thimerosal-containing vaccines available.”

- “full consideration be given by appropriate professional societies and government agencies to removing thimerosal from vaccines administered to infants, children or pregnant women in the united States.”

Institute of Medicine (US) Immunization Safety Review Committee; Stratton K, Gable A, McCormick MC, editors. Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders. Washington (DC): National Academies Press (US); 2001. Immunization Safety Review, Thimerosal-Containing Vaccines and Neurodevelopmental Disorders. Available from: https://www.ncbi.nlm.nih.gov/books/NBK223724/



Safety Studies
Prior to Marketing Thimerosal as Vaccine Preservative

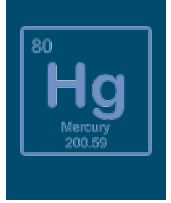
- In 1997, FDA Modernization Act prompted assessment of thimerosal use in vaccines.

- FDA was unable to find any clinical studies formally evaluating the use of thimerosal before its initial marketing in 1930's. (1)

- Single study published in 1931 where thimerosal administered to individuals suffering from meningitis. (2)
  - Not designed to specifically examine toxicity and no clinical assessments or laboratory studies reported.

- FDA grandfathered in the use of thimerosal and did not require the typical animal safety data for finished biological products, including active and inactive ingredients. (3)

(1) Ball LK, Ball R, Pratt RD. An assessment of thimerosal use in childhood vaccines Pediatrics. 2001;(107)5:1147-1153.
(2) Powell HM, Jamieson WA. Merthiolate as a germicide. Am J. Hyg. 1931;(13):296-310.
(3) Department of Health and Human Services. 21 Code of Federal Regulations: 601.25. 1985



Thimerosal use in vaccines

- Thimerosal was first introduced as a preservative in vaccines in the 1930's after being developed and patented by Morris Kharasch in 1927 and subsequently marketed by Eli Lilly under the trade name "Merthiolate" in 1928.

- Thimerosal was used during the manufacturing process and when packaged in multi-dose vials to prevent bacterial and fungal contamination. By the 1930's thimerosal became widely used as a preservative in vaccines and other medical products.

- After a deadly incident of bacterial contamination of vaccines in Australia where 12 children dies from staphylococcal-contaminated diphtheria vaccine, the FDA began enforcing safety standards which led to regulations requiring that all multidose vaccines contain a preservative to prevent contamination.

Ref: 1. Ball LK, Ball R, Pratt RD. An assessment of thimerosal use in childhood vaccines Pediatrics. 2001;(107)5:1147-1153.
2. Powell HM, Jamieson WA. Merthiolate as a germicide. Am J. Hyg. 1931;(13):296-310.
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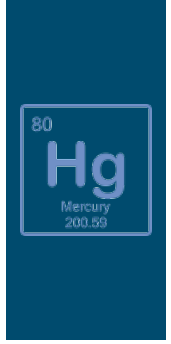
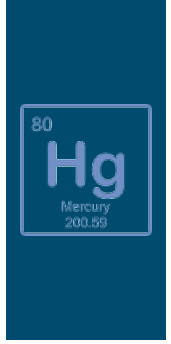


Thimerosal Track Record
Effectiveness as a Preservative

- Morton et al. (1948) JAMA study titled “The bacteriostatic and bactericidal actions of some mercurial compounds on hemolytic streptococci”
- Authors argued that thimerosal was ineffective as a “disinfectant, germicide and antiseptic.”
- Cited eight additional studies which all drew similar conclusions.

Morton HE, North LL, and Engley FB. The bacteriostatic and bactericidal actions of some mercurial compounds on hemolytic streptococci. JAMA. 1948;136(1):37-41

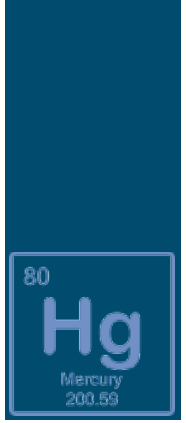


Thimerosal Effectiveness

Track Record as a Preservative

- In 1975, FDA convened panel of experts to evaluate mercury-containing over-the-counter (OTC) products.
- The panel issued report as part of an advance notice for proposed rulemaking that would classify OTC mercury containing drug products as not recognized as safe and effective and being misbranded. (1)
- With respect to thimerosal, the panel found evidence which concluded that “thimerosal was no better than water in protecting mice from potential fatal streptococcal infections.” (2-3)

1. Federal Register, Department of Health and Human Services, Food and Drug Administration. Mercury-Containing Drug Products for Topical Antimicrobial Over-the-Counter Human Use; Establishment of a Monograph. (January 5, 1982);47(2):436-442. 47 FR 436 [Docket No. 75N-0183].
2. Engley FB. Evaluation of mercurial compounds as antiseptics. Annals of the New York Academy of Sciences. 1950;53:197-206. Citing a 1935 study, the panel reported that thimerosal was “35.3 times more toxic for embryonic chick heart tissue than for Staphylococcus aureus.”
3. Salle AJ and Lazarus AS. A comparison of the resistance of bacteria and embryonic tissue to germicidal substances. I. Merthiolate. Proceedings of the Society for Experimental Biology and Medicine. 1935;32:665-667.

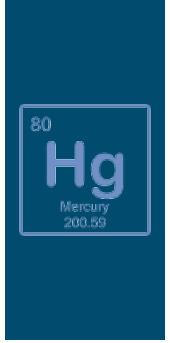


Thimerosal Effectiveness
Track Record as a Preservative Documents Toxicity and Ineffectiveness

- The FDA issued a report of the panel's findings in the Federal Register in 1982 which concluded that "thimerosal was not safe for OTC topical use because of its potential for cell damage if applied to broken skin and its allergy potential.

- It is not effective as a topical antimicrobial because its bacteriostatic action can be reversed. "a topical antimicrobial because its bacteriostatic action can be reversed."

Ref: Federal Register, Department of Health and Human Services, Food and Drug Administration. *Mercury-Containing Drug Products for Topical Antimicrobial Over-the-Counter Human Use; Establishment of a Monograph.* (January 5, 1982);47(2):436-442. 47 FR 436 [Docket No. 75N-0183].



Thimerosal Not Generally Recognized as Safe and Effective (GRASE) in OTC Drugs

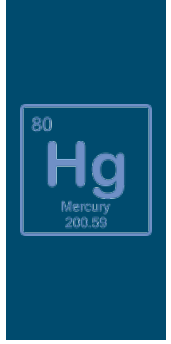
- In response to the reports from the FDA expert panel tasked with reviewing thimerosal in over-the-counter products in the 1980's, the FDA published in the April 22, 1998, Federal Register a conclusion that the use of thimerosal in over the counter products is not "generally recognized as safe or effective" (GRASE).

- In the Final Rulemaking FDA states that "safety and effectiveness have not been established for the ingredients (mercury-based preservatives) included in this current final rule and **manufacturers have not submitted the necessary data in response to earlier opportunities.**

- **The agency's experience has been that under these circumstances companies have not submitted data in response to yet another opportunity.**

Consumers will benefit from the early removal from the marketplace of products containing ingredients for which safety and effectiveness has not been established."

(1) Federal Register, Department of Health and Human Services, Food and Drug Administration. Status of Certain Additional Over-the-Counter Drug Category II and III Active Ingredients. (April 22, 1998);63(77):19799-19802. 21 CFR Part 310 [Docket No. 75N-183F, 75N-183D, and 80N-0280.

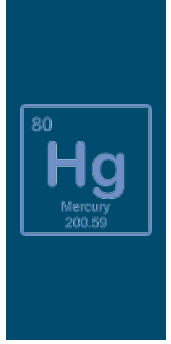


Evidence of Thimerosal Ineffectiveness as a Preservative

- In 1982, clusters of disease from Group A streptococcus infections were traced back to multi-dose vials of diphtheria toxoid, pertussis, and tetanus toxoid (DPT) vaccine which were contaminated after being opened. Thimerosal was present in acceptable limits in unopen vials of vaccine from the same lot. Challenge studies indicated that the strain of streptococcus from one of the patients can survive for up to 15 days at 4 degrees centigrade environment.

- The authors concluded that “Preservatives in multidose vials do not prevent short term bacterial contamination” and the “only feasible and cost-effective preventative measure now available is careful attention to sterile technique when administering vaccines from multidose vials.”

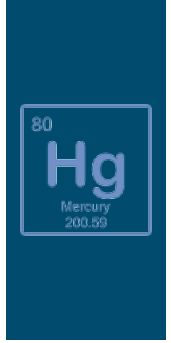
Stetler HC, Garbe PL, Dwyer DM, Facklam RR, Orenstein WA, West GR, Dudley KJ, Bloch AB. Outbreaks of group A streptococcal abscesses following diphtheria-tetanus toxoid-pertussis vaccination. Pediatrics. 1985 Feb;75(2):299-303. PMID: 3881728. Stetler HC, Garbe PL, Dwyer DM, Facklam RR, Orenstein WA, West GR, Dudley KJ, Bloch AB. Outbreaks of group A streptococcal abscesses following diphtheria-tetanus toxoid-pertussis vaccination. Pediatrics. 1985 Feb;75(2):299-303. PMID: 3881728.



Evidence of Thimerosal Ineffectiveness as a Preservative

- In 2004, a Chiron plant that manufactured Fluvirin vaccine preserved with thimerosal was forced to close because its vaccine was contaminated with Serratia marcescens.
- The closure created shortages in the vaccine supply and caused concern among providers and patients. In this case and others, thimerosal failed to prevent bacterial growth.

Smith S. Safety fears cut vaccine for flu. Priority urged for the aged, frail. *Boston Globe*. (October 6, 2004). http://www.boston.com/news/globe/health_science/articles/2004/10/06/safety_fears_cut_vaccine_for_flu?mode=PF

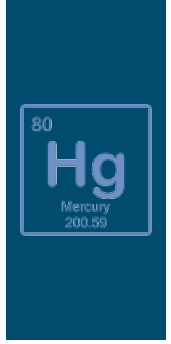


Current Research
Thimerosal safety and effectiveness

- A more current in vitro investigation into the cytotoxic effects and antimicrobial activity of thimerosal was published in 2023. The authors reported that thimerosal **should be present in culture media at 100 µg/ml** concentration to achieve effective antimicrobial activity. **But all tested cell lines lost viability completely at 4.6 µg/mL.**

- "Overall, our study revealed **Thimerosal was 333-fold more cytotoxic to human and animal cells as compared to bacterial and fungal cells**. Our results promote more study on Thimerosal toxicity and its antimicrobial effectiveness to obtain more safe concentrations in biopharmaceuticals."

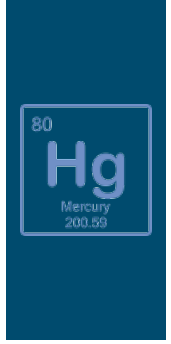
Ref: Rahimian A, Lakzaei M, Askari H, Dostdari S, Khafri A, Aminian M. In vitro assessment of Thimerosal cytotoxicity and antimicrobial activity. J Trace Elem Med Biol. 2023 May;77:127129. doi: 10.1016/j.jtemb.2023.127129. Epub 2023 Jan 4. PMID: 36630761.



Evidence of Thimerosal
Developmental Neurotoxicity

- In 1987 the Commission of the European Communities initiated a research project on 10 known or suspected spindle poisons. Thimerosal was found to cause causing significant interference with microtubule polymerization destabilizing the spindle machinery that ensures accurate chromosome separation during cell division.
- This mechanistic disruption suggests direct mutagenic potential via structural chromosomal abnormalities, which is a known pathway to carcinogenesis or congenital defects.
- By affecting fundamental cellular structures at the molecular level, thimerosal revealed “strong mechanistic evidence for mutagenicity and developmental toxicity, even before in vivo confirmation.”

Wallin, M. (1993). Effects of potential aneuploidy-inducing agents on microtubule assembly in vitro.
Mutation Research. Fundamental and Molecular Mechanisms of Mutagenesis, 287(1), 17–22. https://doi.org/10.1016/0027-5107(93)90141-2



Evidence of Thimerosal

Developmental Neurotoxicity cont.

- A similar study was published in 1990 which documented that Thimerosal significantly increased the frequency of chromosome malsegregation at concentrations of 10 µg/mL.
- The observed effect suggests thimerosal interferes with the mitotic spindle apparatus, leading to chromosome loss or nondisjunction, consistent with a spindle poison profile, confirming the findings of Wallin.
- A typical 0.5 ml influenza vaccine contains 50 µg. of thimerosal.

Albertini S. Analysis of nine known or suspected spindle poisons for mitotic chromosome malsegregation using Saccharomyces cerevisiae D61.M. Mutagenesis. 1990 Sep;5(5):453-9. doi: 10.1093/mutage/5.5.453. PMID: 2263203.

CALIFORNIA EPA

Proposition -65

Californias Proposition 65, formerly known as the Safe Drinking Water and Toxic Enforcement Act of 1986, is a state law that requires California to identify chemicals known to cause cancer, birth defects or other reproductive harm, and to ensure public warnings when people might be exposed to them.

Thimerosal has been recognized as a Prop 65 chemical since 1990.

Bayer Petition to Remove Thimerosal from CA Prop-65

In 2003, a petition was filed on behalf of the Bayer Corporation **“for reconsideration of the determination that “Mercury and mercury compounds as reproductive toxins”**

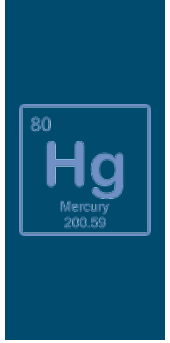
THE PETITION

The Petition specifically seeks "to discern whether OEHHA interprets the 'mercury and mercury compounds' listing to encompass thimerosal and PMA [phenylmercuric acetate]." Bayer requests that if OEHHA interprets the "mercury and mercury compounds" listing under Proposition 65 to encompass thimerosal or PMA, the listing should be reconsidered.

Bayer Petition to Remove Thimerosal from CA Prop-65

The CA EPA responded that "The scientific evidence that thimerosal cause reproductive toxicity is clear and voluminous. Thimerosal dissociates in the body to ethyl mercury. The evidence for its reproductive toxicity includes severe mental retardation or malformations in human offspring who were poisoned when their mothers were exposed to ethyl mercury or thimerosal while pregnant, studies in animals demonstrating developmental toxicity after exposure to either ethyl mercury or thimerosal, and data showing interconversion to other forms of mercury that also clearly cause reproductive toxicity."

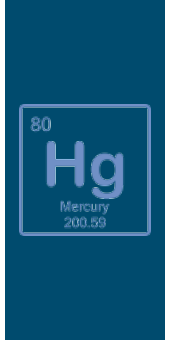
Based upon the review, OEHHA found that neither of the reconsideration criteria is met for thimerosal or PMA to be removed from the list.



Evidence From Animal Research

- **Berman RF, et al, (2008) Low-level neonatal thimerosal exposure: Long term consequences in the brain**. Newborn rats given ethylmercury doses equivalent to the vaccine schedule showed persistent microglial activation, particularly in the cerebellum and hippocampus. Suggests long-tern neuroimmune effects.
- **Olczak M, et al, (2010) Neurodevelopmental disorders after neonatal thimerosal vaccination: Roles of glial activation and oxidative stress**. Thimerosal exposure in neonatal rats induced persistent glial activation and oxidative damage in regions critical for motor and cognitive development.

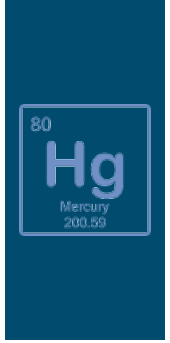
Berman, R. F., Pessah, I. N., Moser, V. C., Harry, G. J., Elinoff, M. C., & Pearson, D. B. (2008).
Low-level neonatal thimerosal exposure: Long-term consequences in the brain. Neurotoxicology, 29(5), 914–922.
Olczak, M., Duszczyk, M., Mierzejewski, P., & Majewska, M. D. (2010). Neurodevelopmental disorders after neonatal thimerosal vaccination: Roles of glial activation and oxidative stress. Brain Research Bulletin, 81(4–5), 447–454.



Evidence From Human Research (1)

- A study published in Pediatrics in 2000 measured blood mercury levels in preterm and term infants after administration of the Hepatitis B vaccine containing 12.5 µg ethyl mercury.
- The investigation documented elevated post-immunization concentrations relative to pre-immunization levels in all neonates studied. Levels of blood mercury after exposure in low-birth-weight infants were 7.36 (± 4.99) µg/L.
- One infant was found to have developed a mercury level of 23.6 µg/L, thus meeting the CDC criteria as a case of chemical poisoning from mercury 10µg /L. The study subjects had measurable blood Hg concentrations prior to immunization, indicating that risk assessment must include background mercury levels from other sources.

Stajich GV, Lopez GP, Harry SW, Sexson WR. Iatrogenic exposure to mercury after Hepatitis B vaccination in preterm infants. J.Pediatrics. 2000;136 (5):679-81.
Centers for Disease Control and Prevention. (2005, January 14). Case Definitions for Chemical Poisoning. MMWR Recommendations and Reports, 54(RR-1), 1–24. Retrieved from https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5401a1.htm

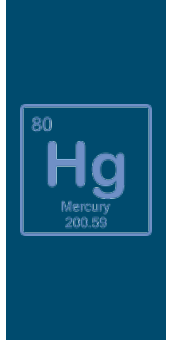


Evidence From Human Research (2)

- Experts contend that there are “windows of vulnerability” which occur during neurological development and that specific types of developmental outcomes may have separate windows of vulnerability. These critical periods of development have not been established and may be relatively short in duration.

- The fact that thimerosal from vaccines has been documented to raise blood mercury levels concentrations over known thresholds where developmental effects have been documented to occur during the first few months of life means that particular "windows of vulnerability" may have been breached. Even minor neurological impairment can have profound societal effects when amortized across the entire population and life span.

Rice D, Barone S Jr. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ Health Perspect. 2000;108 Suppl 3:511-33.

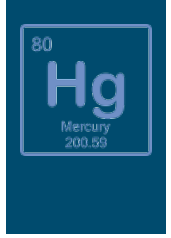


Exposure To Vaccine Level Thimerosal

Crosses the Blood Brain Barrier and Results in Significant Deposition of Mercury in the Brain

- A 2005 study funded by NIH compared brain mercury levels in infant Macaca fascicularis primates exposed to: 1) injected ethyl mercury (thimerosal) and 2) equal amounts of ingested methylmercury.
- Ethyl mercury more rapidly converted to inorganic mercury in the brains of the primates which resulted in increasing levels of inorganic mercury.
- Primates exposed to ethyl mercury retained much higher levels of inorganic mercury in their brains, up to 71% vs. 10% compared to primates exposed to methyl mercury.
- Once organic mercury compounds reach the brain tissue and dealkylate, Hg2+ (toxic inorganic mercury) the mercury cannot cross the blood brain barrier and becomes trapped, resulting in neuroinflammation.

Burbacher TM, Shen DD, Liberato N, Grant KS, Cernichiari E, and Clarkson T. Comparison of blood and brain mercury levels I infant monkeys exposed to methylmercury or vaccines containing thimerosal. Environmental Health Perspectives. 2005;113(8):1015-1021.



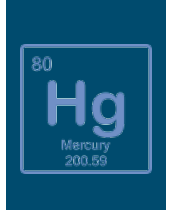
Inorganic Mercury and the Developing Brain

- A recent review outlined evidence from human and animal studies which estimating the inorganic mercury half-life in human brains of at least five to 27 years. (1)

- The impact of mercury exposure to the developing brain interferes with neuronal proliferation, migration, differentiation, synaptogenesis, tightly regulated apoptosis, and other processes vital to the formation and functioning of the nervous system which can result in lifelong neurodevelopmental impacts.

- Exposure during the first trimester of pregnancy may result in deficits or defects very different from those developed by someone who is exposed during the third trimester of pregnancy. “There may never be a safe level of mercury exposure, especially for an unborn child.” (2)

1.Rooney JP. The retention time of inorganic mercury in the brain--a systematic review of the evidence. Toxicol Appl Pharmacol. 2014 Feb 1;274(3):425-35.
2. Pletz J, Sánchez-Bayo F, Tennekes HA. Dose-response analysis indicating time-dependent neurotoxicity caused by organic and inorganic mercury-Implications for toxic effects in the developing brain. Toxicology. 2016 Mar 10;347-349:1-5. doi: 10.1016/j.tox.2016.02.006. Epub 2016 Mar 2. PMID: 26945727.



Mercury Content In Thimerosal-containing Flu Vaccines

- Thimerosal is ~49.6% mercury by weight with a concentration of 0.01% thimerosal in vaccines. This equates to 100 µg/mL of thimerosal and 50 µg/mL of ethyl mercury per ml.
- The EPA's Toxicity Characteristic Leaching Procedure (TCLP) determines whether a substance is considered hazardous waste based on its potential to leach toxic chemicals into groundwater.
- According to EPA TCLP Mercury Threshold (40 CFR § 261.24) the regulatory threshold for mercury (D009) under TCLP is: 0.2 mg/L (200 parts per billion, or 200 µg/L).
- Flu vaccine mercury concentration (~50,000 µg/L) is 250 times greater than the TCLP limit. **Therefore, thimerosal-containing vaccines exceed the TCLP threshold by orders of magnitude and are classified as D009 Hazardous Waste (characteristic waste due to mercury toxicity**)

Vaccine Mercury: Disposal Guidelines

PHARMECOLOGY® WM

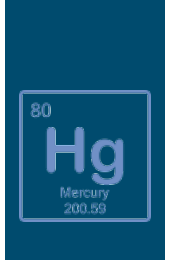
PharmEcology® Provides Disposal Guidelines for the 2024-2025 Flu Season

PharmEcology Services, a division of WM Sustainability Services, is pleased to publish a summary of the proper flu vaccine disposal guidelines for the 2024-2025 flu season as a public service to the healthcare community. Please also see additional information regarding this year's vaccines following the table below.

Flu vaccine summary table:

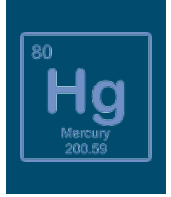
The table below summarizes the waste categorizations of the specific products available this season. Applying EPA's federal regulations to the flu vaccines, the vaccines meet the toxicity characteristic when the concentration of mercury is equal to or greater than 0.2mg/liter as a result of performing a test known as the toxicity characteristic leaching procedure (TCLP).

While we do not have results for such tests for vaccines, a calculation of the concentration of mercury in vaccines in which thimerosal is present as a preservative would cause the waste vaccine to fail the TCLP. Unless a manufacturer provides actual TCLP data indicating the mercury level to be below 0.2mg/liter or a healthcare facility has the test performed and the waste does not fail the TCLP, any vaccine waste containing thimerosal as a preservative should be managed as a toxic hazardous waste. As a result, all full or partially used multi-dose vials of the seasonal flu vaccine should be disposed of as federally hazardous waste, waste code D009 for mercury.



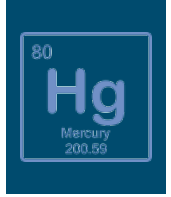
Susceptible Populations

Population	Susceptibility Factors
Fetus / Developing Infant	Rapid neurodevelopment, immature blood-brain barrier, low glutathione, high brain accumulation
Pregnant Women	Placental transfer, fetal susceptibility, breast milk transfer
Young Children	Higher exposure per kg, immature detoxification systems
Older Adults	Reduced renal clearance, pre-existing neurodegenerative conditions
Genetically Susceptible	Impaired detox (e.g., GST, MTHFR, APOE4), mitochondrial dysfunction
High Fish Consumers	Bioaccumulation through predatory fish, dietary exposure
Occupationally Exposed Workers	Inhalation exposure, chronic accumulation (e.g., dentists, miners)



Summary (1)

- Mercury is the third most toxic element on earth, behind polonium and plutonium, and has no physiological role in the human body.
- Thimerosal was grandfathered for use without adequate safety testing by the FDA.
- Thimerosal is not “generally recognized as safe or effective” (GRASE) by the FDA OTC Division since 1998.
- There is evidence that thimerosal is not an effective preservative at vaccine levels.
- Thimerosal can cross the placenta and blood brain barriers and converts to inorganic mercury in the brain at higher levels that methyl mercury.
- Studies have identified infants with blood levels after exposure to thimerosal that breach EPA safety guidelines.



Summary (2)

- Thimerosal is recognized as a developmental and reproductive toxicant and is listed as a chemical on the California Proposition 65 list since 1990.
- Unused doses of thimerosal preserved flu shots must be disposed of as hazardous waste.
- Tremendous progress has been made in removing thimerosal, but more than 60,000 pregnant mothers receiving Medicaid in the 2019-2020 flu season received TCVs.
- We currently have enough thimerosal free flu vaccines to recommend that all pregnant women, infants and children receive only thimerosal free vaccines.
- After a critical appraisal of this issue almost 25 years ago, the prestigious Institute of Medicine made this same recommendation.
- Removing a known neurotoxin from being injected into our most vulnerable populations is a good place to start with Making America Healthy Again.