



NATIONAL TOXICOLOGY PROGRAM

U.S. Department of Health and Human Services

NATIONAL INSTITUTE OF
ENVIRONMENTAL HEALTH SCIENCES
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Via email: tlredwood@mindspring.com

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Executive Director
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254 Trickum Creek Rd.
Tyrone, GA 30290

Dear Lyn:

Thank you for your letter of March 1 requesting that the National Toxicology Program (NTP) return the thimerosal nomination to active status. The NTP has carefully considered this request, and in consultation with the U.S. Food and Drug Administration (FDA), has decided to maintain the nomination in a deferred status.

The FDA nominated thimerosal to the NTP in 2002 to assess gaps in knowledge regarding toxicokinetics and the potential for neurodevelopmental toxicity¹. These gaps included comparative toxicity of ethyl- and methylmercury, metabolism and elimination of ethylmercury compared with methylmercury, the effect of intermittent intramuscular doses of thimerosal from vaccines compared with chronic low dose oral exposure to methylmercury, and the susceptibility of the infant compared with the fetus to adverse effects from organic mercurials. The NTP nomination of thimerosal was reviewed by the Interagency Committee for Chemical Evaluation and Coordination (ICCEC) in April 2002. At that time, the nomination was discussed within the framework of ongoing toxicology studies supported by the NIEHS, the National Institute of Allergy and Infectious Diseases, and the Agency for Toxic Substances and Disease Registry. The ICCEC endorsed a program of research to address those knowledge gaps identified in the nomination, but to coordinate the program with ongoing federally-sponsored research efforts. In September 2002, the NTP Board of Scientific Counselors reviewed the thimerosal nomination and endorsed recommendations of the ICCEC to review data from ongoing studies before proceeding with study design efforts for new studies. This effectively placed the nomination in a deferred status until ongoing studies of thimerosal and methylmercury kinetics in non-human primates and rodents were completed. These studies have since been published². Also during this time, several epidemiological studies were initiated to examine whether there was any association of vaccines containing thimerosal with neurodevelopmental disorders, as well as research evaluating blood mercury pharmacokinetics in children receiving thimerosal-containing vaccines. In April 2006, an interagency workshop was convened to assess federal efforts relating to thimerosal and identify outstanding data needs. The outcome of this meeting was a recommendation that the FDA thimerosal nomination should remain deferred and that a safety assessment of ethylmercury be conducted to inform the development of safe exposure guidelines for ethylmercury. No toxicology data needs were identified at that time.

¹ NTP, Nominations in Review 2002, <http://ntp.niehs.nih.gov/go/199>.

² Harry *et al.*, 2004, Mercury concentrations in brain and kidney following ethylmercury, methylmercury and Thimerosal administration to neonatal mice, *Toxicol Lett.* 154(3): 183-9; Burbacher *et al.*, 2005, Comparison of blood and brain mercury levels in infant monkeys exposed to methylmercury or vaccines containing thimerosal, *Environ Health Perspect.* 113(8): 1015-1021; Zareba *et al.*, 2007, Thimerosal distribution and metabolism in neonatal mice: comparison with methyl mercury, *J Appl Toxicol.* 27(5): 511-8; Berman *et al.*, 2008, Low-level neonatal thimerosal exposure: Further evaluation of altered neurotoxic potential in SJL mice. *Toxicol. Sci.* 101(2), 294-309.

The decision to maintain the deferred status of the thimerosal nomination is grounded in our evaluation that the knowledge gaps originally identified in the nomination have largely been filled, and that the accumulated human epidemiological studies and experimental animal studies provide a sufficient basis on which to guide decisions regarding safety of thimerosal. Also factoring into this decision are the conclusions on vaccine safety by the National Academy of Sciences' Institute of Medicine Immunization Safety Review Committee, the results of Centers for Disease Control and Prevention (CDC) funded research demonstrating lack of any consistent association between thimerosal containing vaccines and adverse neurologic outcomes³, and the substantial progress that has been made towards eliminating thimerosal from all vaccines⁴.

Published research on the effects of thimerosal on neurologic and neurodevelopmental outcomes in animal models are generally consistent with the known effects of methylmercury. Even with qualitative similarities in the toxicity profile of ethylmercury and methylmercury, there are quantitative differences. The basis for the quantitative differences appears to be largely due to altered pharmacokinetics, with faster elimination and more efficient conversion to inorganic mercury for ethylmercury relative to methylmercury.

While the NTP does not develop guidelines for safe human exposure limits, the NTP, and more broadly the NIEHS, supports much of the scientific research underpinning public health decisions regarding adverse health impacts of environmental exposures to hazardous substances. A nomination to the NTP to conduct toxicology studies may be deferred or the NTP may decide not to conduct studies for a particular nomination for several reasons. Most importantly, such decisions do not at all reflect an opinion or a conclusion by the NTP that a particular substance is safe or without potential hazard.

In closing, the NTP will continue to monitor research on thimerosal and engage in cooperative efforts with the FDA, CDC and other federal partners regarding safety concerns for thimerosal or other organomercurial compounds that could be addressed by new toxicology studies.

Sincerely,

/Scott A. Masten/
Scott A. Masten, PhD, DABT
Director, Office of Nomination and Selection
National Toxicology Program
National Institute of Environmental Health Sciences

Cc:
Dr. Linda Birnbaum
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NTP Central Files

³ CDC, 2010, Immunization Safety and Autism - Thimerosal and Autism Research chart, http://www.cdc.gov/vaccinesafety/00_pdf/VSD_Chart_of_Autism_Studies-Updated_Sep_27_2010.pdf.

⁴ FDA, 2010, Thimerosal in Vaccines, <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/UCM096228>.