

**Theoretical estimation of blood mercury levels from Thimerosal injections
using a one compartment biokinetic model.
(An analysis to “bound” potential mercury tissue levels)**

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Introduction:

This is a biokinetic analysis of the distribution of mercury in the blood and hair of children after injection of Thimerosal containing vaccines. It is a probe study to assess whether there is a plausible basis of concern for accumulation of potentially significant levels of mercury in infants during the first two years of life.

The neurotoxicity of mercury is widely recognized. Mercury has been found to induce immune, sensory, motor and cognitive nervous system dysfunction after accidental exposures. A well documented series of accidental exposures have occurred sporadically for the last 5 decades. Recent studies based on fish and grain exposures have shown that hair levels of mercury are associated with the appearance of certain specific brain lesions in children. Findings from these studies formed the basis for development of a biokinetic model of distribution of mercury overtime in the blood and the hair.

A bio-accumulative toxin, mercury is very slowly released from the body after ingestion and thus has been found to accumulate in blood, brain and hair with repeat exposures. It is also present in several different forms in different media including food, air, cosmetics and drugs. Therefore, it was decided to assess whether patterns of exposure to Thimerosal containing mercury could potentially produce significant tissue levels of mercury in children.

Methodology:

Rationale and model considerations

The biokinetic model designed by Ginsberg and Toal (Risk Analysis, 1999) was adapted for a preliminary assessment of pharmacokinetic behavior of Thimerosal mercury in infants up to two years of age. The Ginsberg and Toal model was designed to evaluate the effect of uptake of methyl mercury from an oral exposure to mercury containing fish. The model is based on findings in children and adults that had been poisoned by organic forms of mercury in grain or fish. Hair levels collected from different groups were shown to vary with the magnitude of exposures. Also deposition of mercury into the hair continued as hair grew after an acute exposure. These parameters were used to develop a predictive model of blood and hair levels of mercury. The model was validated against blood concentrations from 3 data sets in which human subjects ingested methyl mercury in fish, either as single or multiple meals.

Like methyl mercury, ethyl mercury from Thimerosal is an organic form of mercury which would have similar but not the exact same properties as methyl mercury with respect to uptake and

distribution in the body. Methyl mercury is rapidly and nearly completely absorbed into the blood stream after ingestion. In contrast ethyl mercury is injected and can be assumed to be completely absorbed. The model uses a 95% absorption rate for methyl mercury. When a similar 95% rate was used for Thimerosal mercury it would tend to underestimate the uptake rate.

Methyl mercury has a half life for elimination of about 50 days in adult male and females. The half-life of elimination of ethyl mercury is not known but it is probably somewhat shorter than methyl mercury because methylated metals are generally more slowly released than ethylated metals. This places a strong limitation on the assessment in adults. However, infants have poor elimination of organic and inorganic heavy metals in the first 6 months prior to development of metal transport systems. It is possible that mercury is eliminated much more slowly in the child. In order to account for this limitation it was decided to assess the biokinetics under two conditions: one in which adult elimination rate is assumed for the infant and one in which the infant rate of elimination was assumed to be absent up to 6 months of age. Thus an "adult excretion scenario" and a "no excretion scenario" were used.

Elimination and uptake are both dependent on body weight. Therefore the model was modified to account for the child's body weight changes and blood volumes over the two year period from birth. Although there are sources of mercury in food and commercial products and mercury can be taken up by the fetus from the mother's mercury burden, it was assumed that the Thimerosal is the only source of mercury. If that is not the case the half-life for elimination will be prolonged, and maximums higher.

Given the preceding limitations, the findings should be placed in context. This analysis can only assess whether Thimerosal could produce blood and hair mercury in children at levels that could plausibly raise a concern about neurological damage. Such a finding would indicate the need for further study. Therefore the action levels identified for mercury in fish by states are presented as comparison.

Exposure considerations:

According to the Centers for Disease Control (CDC) recommended immunization schedule, infants may have been exposed to 12.5 µg Hg at birth, 62.5 µg/Hg at 2 months, 50 µg Hg at 4 months, 62.5 µg Hg at 6 months, and 50 µg Hg at approximately 18 months, for a total of 237.5 µg Hg during the first year and a half of life. These doses were used in the model at the appropriate time periods.

Child weights and blood volumes.

The following body weight and blood volume assumptions were used.: For the average child, 50th percentile 3.2, 5.0, 6.1, 7.3, 9.5, & 11.1 kilograms body weight and 0.2, 0.3, 0.4, 0.5, 0.6 & 0.7 liters of blood at birth, 2, 4, 6, 12, & 18 months respectively. For the low weight child, 5th percentile 2.5, 3.6, 4.7, 5.6, 8.1, & 9.2 kilograms body weight and 0.26, 0.2, 0.30, 0.36, 0.53, & 0.60 at , at birth, 2, 4, 6, 12, & 18 months respectively. These values were obtained from standard medical texts.

Findings:

In order to obtain an indication of the dispersion of potential blood and hair levels the biokinetic model was used to estimate blood levels under four conditions. An average child having either an "adult excretion scenario" or a "no excretion scenario" and the low body weight, 5th percentile, child using an "adult excretion scenario" and a "no excretion scenario". Thus four sets of charts were developed showing estimates of blood mercury levels and four charts estimating hair mercury levels.

From these charts it is possible to determine the maximum tissue level and the duration of higher levels. It is also possible to determine additive effect of repeated exposures.

FIGURES 1-4

The predicted blood and hair levels of mercury from fish consumption in adults and the levels from Thimerosal are of the same order of magnitude. Moreover the NHANES 90th percentile of blood mercury for women and children 16 to 49 years or 1- 5 years are 6.2 and 1.4 ppb or ug/L respectively. The biokinetic estimates are also in that range. It is interesting that the 90th percentile fish consumers approach the higher levels estimated for Thimerosal. The higher levels modeled here occur prior to 1 year of age, the youngest age measured in NHANES. Because of the long duration of mercury in the body the potential for additivity of exposures from fish and Thimerosal may be a concern.

There is a reasonable amount of data from human accidental exposures that have occurred over the past half century. A summary shown in the following table gives the hair and blood levels at which certain toxic endpoints have been observed..

Studies on Mercury in humans and animals –EPA

<i>Study</i>	<i>Exposure</i>	<i>N</i>	<i>Endpoint</i>	<i>Analysis</i>	<i>PPM Hair</i>	<i>ug/l blood</i>
Iraq	ST seed	81	Developmental	BMD	11	44
			Walking	LOAEL	14	56
New Zealand	LT-fish	237	IQ	Threshold	5-15	19-25
Cree Indians	LT-fish	247	tendon reflex	LOEAL	10-20	40-80
Amazon Natives	LT	29	visual discrimination	LOAEL	20	80
Minamata	LT ?	986	Minamata disease	Threshold	20	80
Peru	LT	131		NOAEL	30	120
Data Review	Animal/human			LOAEL	10-20	40-80

FIGURES 5&6

Mercury toxicity has been predicted at levels as low as 10 to as high as 120 ug/L. The blood levels are derived from the hair levels which range from 10 to 30 ppm. While the estimates of exposure from Thimerosal do not exceed these risk predictions they are in the same range and, with additivity from other sources, may contribute to an elevated mercury approaching these levels.

The National Research Council in 2000 expert panel reviewed the available studies of mercury exposure and toxic outcomes and suggested a BMDL of 58 ppb Hg in cord blood (corresponding to 12 ppm in maternal hair). These levels are also in the same order of magnitude estimated in this probe study. There is a notably relatively low margin of safety for mercury in the current studies and recommendations.

Interpretation and suggestions:

1. Because the estimated levels of mercury in blood and hair after Thimerosal are in the same order of magnitude as those levels which induce toxic actions in humans with accidental exposures, it is important to obtain a more detailed kinetic analysis using more exact transfer factors and a more complete model.
2. Additivity with other mercury exposures such as fish is a serious possibility and requires caution and re-enforcement of state mercury consumption advice to parents of young children.
3. Because the risk to children is believed to be as much as 10 times greater than risk to adults, the fact that estimates are slightly below the toxic levels would not be considered evidence of safety.
4. It is important to determine whether there are other persistent compounds routinely used to protect vaccines or medication from spore growth. It is possible that single doses of Thimerosal would not be hazardous while repeated doses would bioaccumulate and be potentially toxic.
5. More information is needed about the physiological parameters during the first 18 months of life to adequately characterize the biodynamics of potential toxics from birth to 1 year.

References:

1. EPA regulatory guideline to protect public health , In *Mercury Study Report to Congress*. 1997. Office of Air Quality Planning and Standards and Office of Research and Development . WPA-453/R-97-006.
2. Ginsberg G. and Toal B. “ Development of a single meal fish consumption advisory for methyl mercury, Risk Analysis 1999
3. National Academy of Sciences. Toxic effects of methyl mercury. Washington DC: National Research Council, 2000.
4. National Health and Nutrition Examination Survey (NHANES, 1999)
5. Round, M. “Analysis of the Northeast Fish Consumption and Mercury Awareness Survey.” NESCAUM, Boston Massachusetts. (In preparation,2001)

