

NIAID Studies on Thimerosal

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NIH, DHHS**

NIAID Studies on Thimerosal

Scientific Questions

- Are the guidelines developed for methyl mercury (MeHg) appropriate for assessing the safety of thimerosal (sodium ethyl mercury thiosalicylate)?
- How are the distribution, metabolism, and excretion of thimerosal and MeHg related?

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Possibilities

- Thimerosal and MeHg are equivalent
- Thimerosal and MeHg are similar; MeHg guidelines offer additional/less margin of safety
- Thimerosal and MeHg are significantly different in distribution, metabolism, and excretion

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Thimerosal Exposure

Ethyl mercury thiosalicylate

IM injection

Spaced intermittent exposure

Infant exposure

Risk to infant

Measure levels directly

MeHg Exposure/Guidelines

Methyl mercury in food

Oral intake – food

Continuing exposure to reach steady state distribution

Maternal and fetal exposure

Risk from fetal exposure – most sensitive to damage

Extrapolate from maternal hair levels to fetal exposure and effects

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- **Pilot clinical study and data –**
University of Rochester
- **Follow-up clinical study –**
University of Rochester, and Center for Toxicological Research (Argentina) and Children's Hospital of Buenos Aires (Argentina)
- **Primate Studies –** University of Washington
and University of Rochester

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Evaluation of mercury in infants after thimerosal-containing vaccines

(Univ. Rochester; The Lancet Vol 360 Nov 30, 2002)

- **The blood half life of mercury from thimerosal-containing vaccines in infants appears to be shorter than the half life of methyl mercury in adults, possibly as short as 6 - 8 days.**
- **Infants excrete significant amounts of mercury in stool, unlike what is seen in rodent animal models of MeHg. This possibly accounts for the relatively short apparent half-life of ethyl mercury in this study.**

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Comparative Toxicokinetics of Methyl mercury (MeHg) and Thimerosal in Infant *Macca fascicularis*

Tom Burbacher and Danny Shen

University of Washington

Tom Clarkson

University of Rochester

Funded by NIAID and NIEHS

Comparative Toxicokinetics of Methyl mercury (MeHg) and Thimerosal in Infant *Macca fascicularis*

Objective: Compare relative levels of mercury in blood and brain after exposure to mercury in the form of thimerosal or methyl mercury

Mercury Exposure from Thimerosal in Typical Immunization Schedules

(The Lancet Vol. 355 April 8, 2000)

Age	Vaccines	Hepatitis B (HB)		Mercury Dose (μg)	
		Scheme A	Scheme B	Scheme A	Scheme B
Birth	BCG, OPV0	HB1		12.5	
6 wks	DTP1, OPV1, Hib1	HB2	HB1	62.5	62.5
10 wks	DTP2, OPV2, Hib2		HB2	50.0	62.5
14 wks	DTP3, OPV3, Hib3	HB3	HB3	62.5	62.5
Total				187.5	187.5

BCG = bacille Calmette-Guerin

Hib = *Haemophilus influenzae* type b

OPV = oral poliovirus

DTP = diphtheria-tetanus-pertussis

Vaccine with Thimerosal and oral MeHg Dosing for Infant *M. fascicularis*

Age	Vaccines	Hepatitis B (HB) Scheme A	Mercury Dose Thimerosal or MeHg ($\mu\text{g Hg/kg}$)
Birth	OPV0	HB1	20
1 wk	DTP1, OPV1, Hib1	HB2	20
2 wks	DTP2, OPV2, Hib2		20
3 wks	DTP3, OPV3, Hib3	HB3	20
Total			80 $\mu\text{g/kg}$

OPV = oral poliovirus

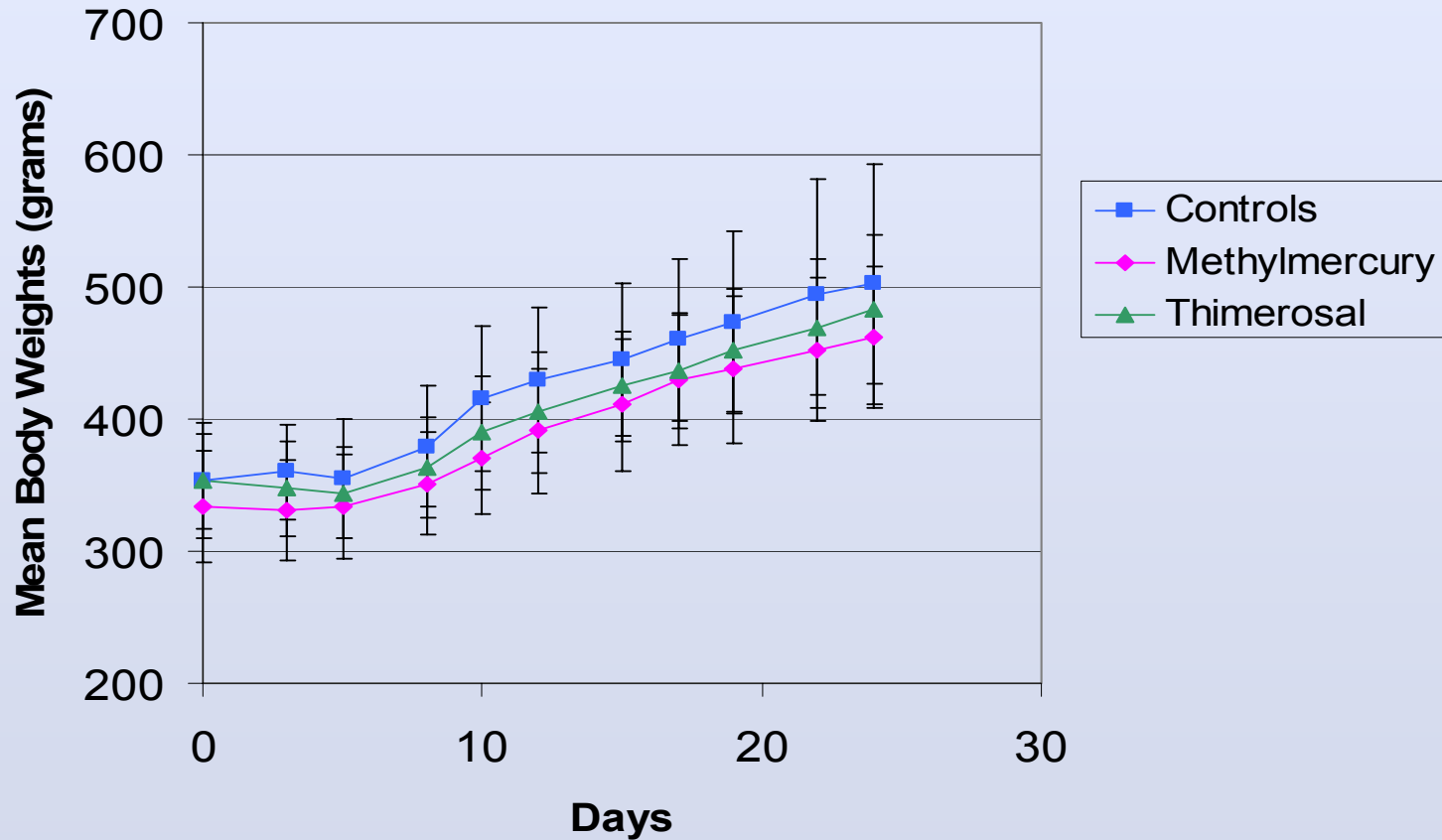
Hib = *Haemophilus influenzae* type b

BCG = bacille Calmette-Guerin

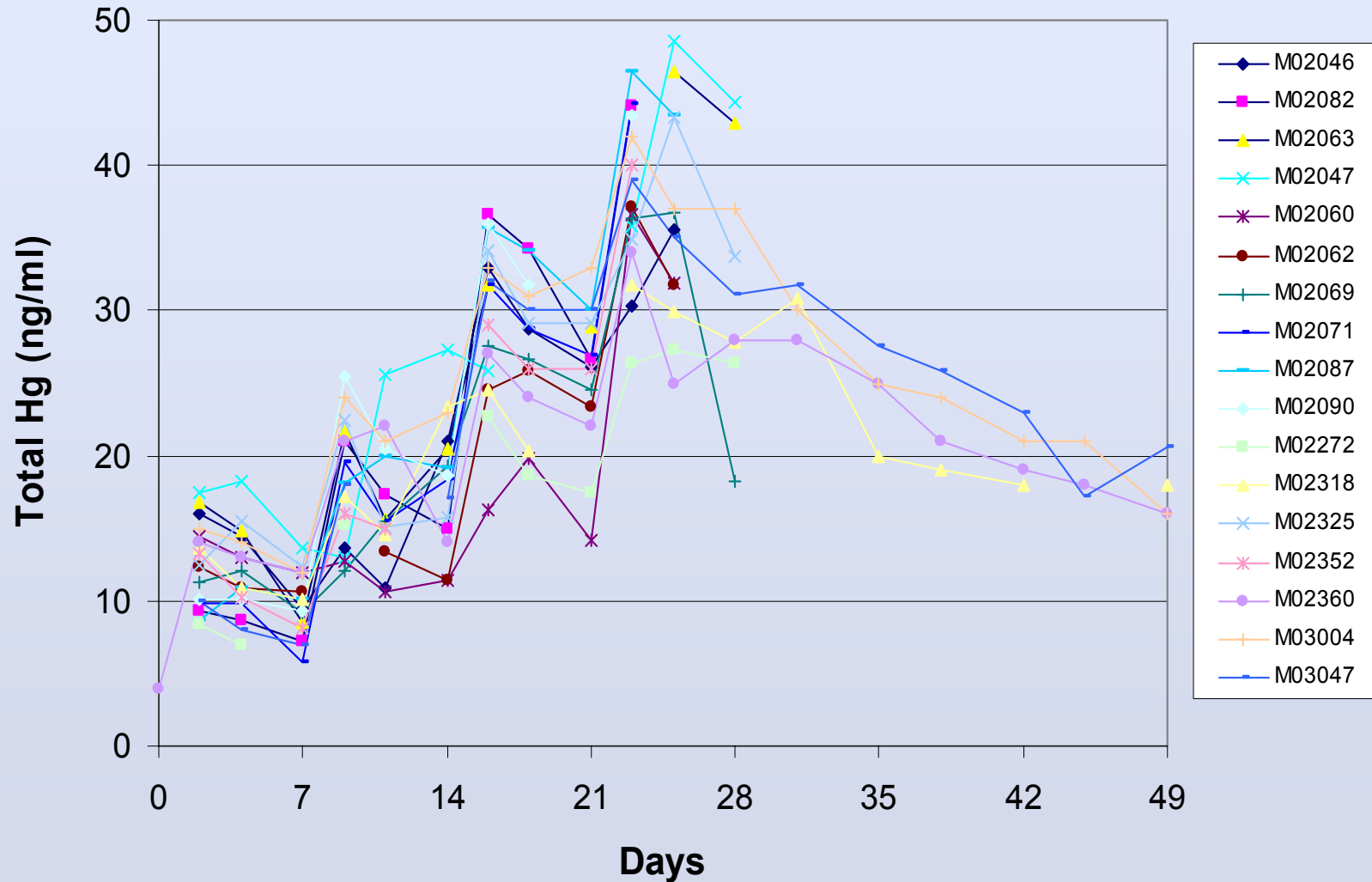
DTP = diphtheria-tetanus-pertussis

Thimerosal was added to vaccines; MeHg given by oral gavage
Animals sacrificed 2, 4, 7 or 29 days after last exposure

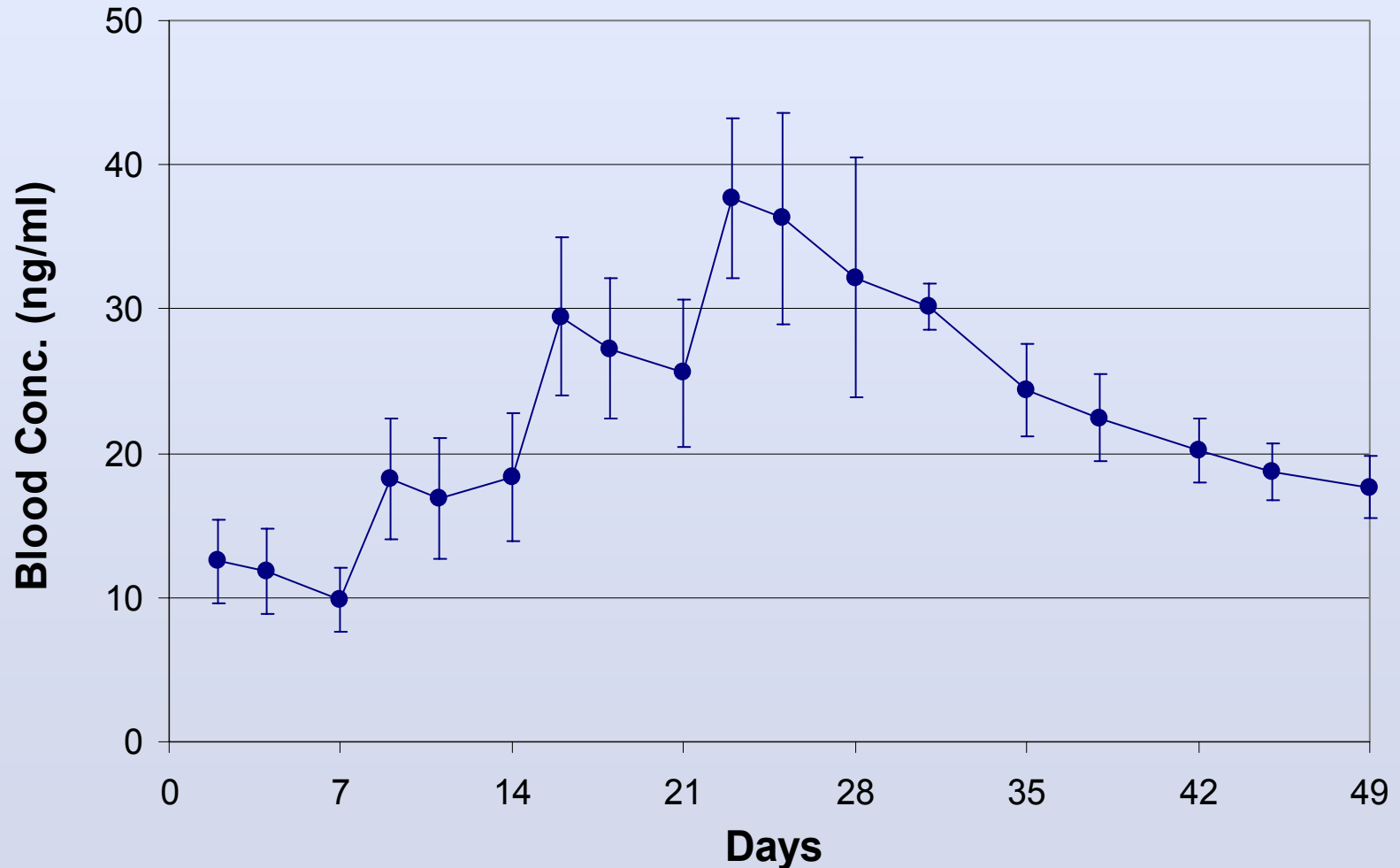
Body Weight (grams) at Dosing



Blood Total Hg in Infant Monkeys During/Post Four Weekly Oral Doses of Methylmercury (20 μg Hg/kg)



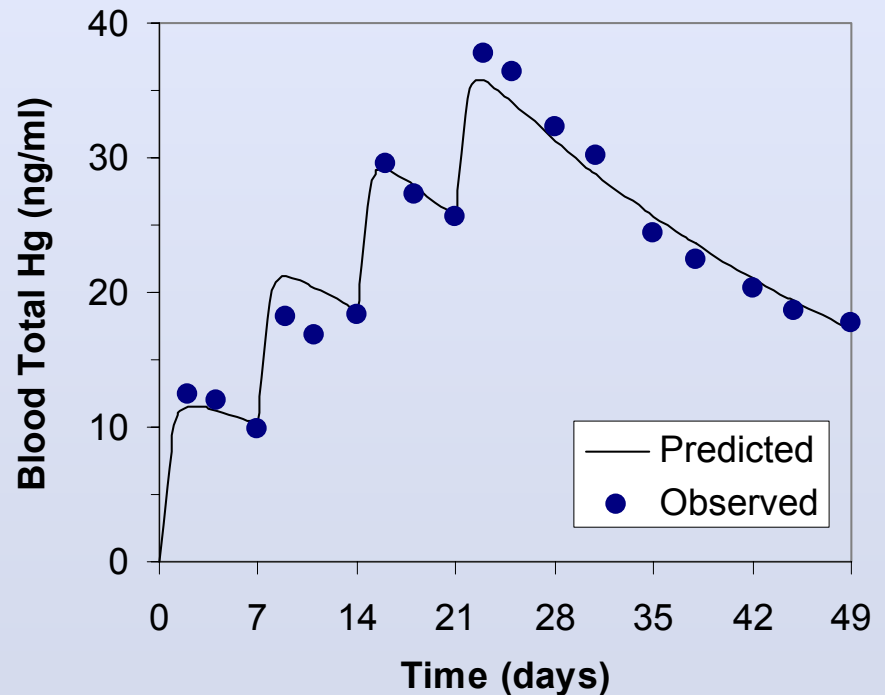
Mean Blood Total Hg in Infant Monkeys During/Post Four Weekly Oral Doses of Methylmercury (20 μg Hg/kg)



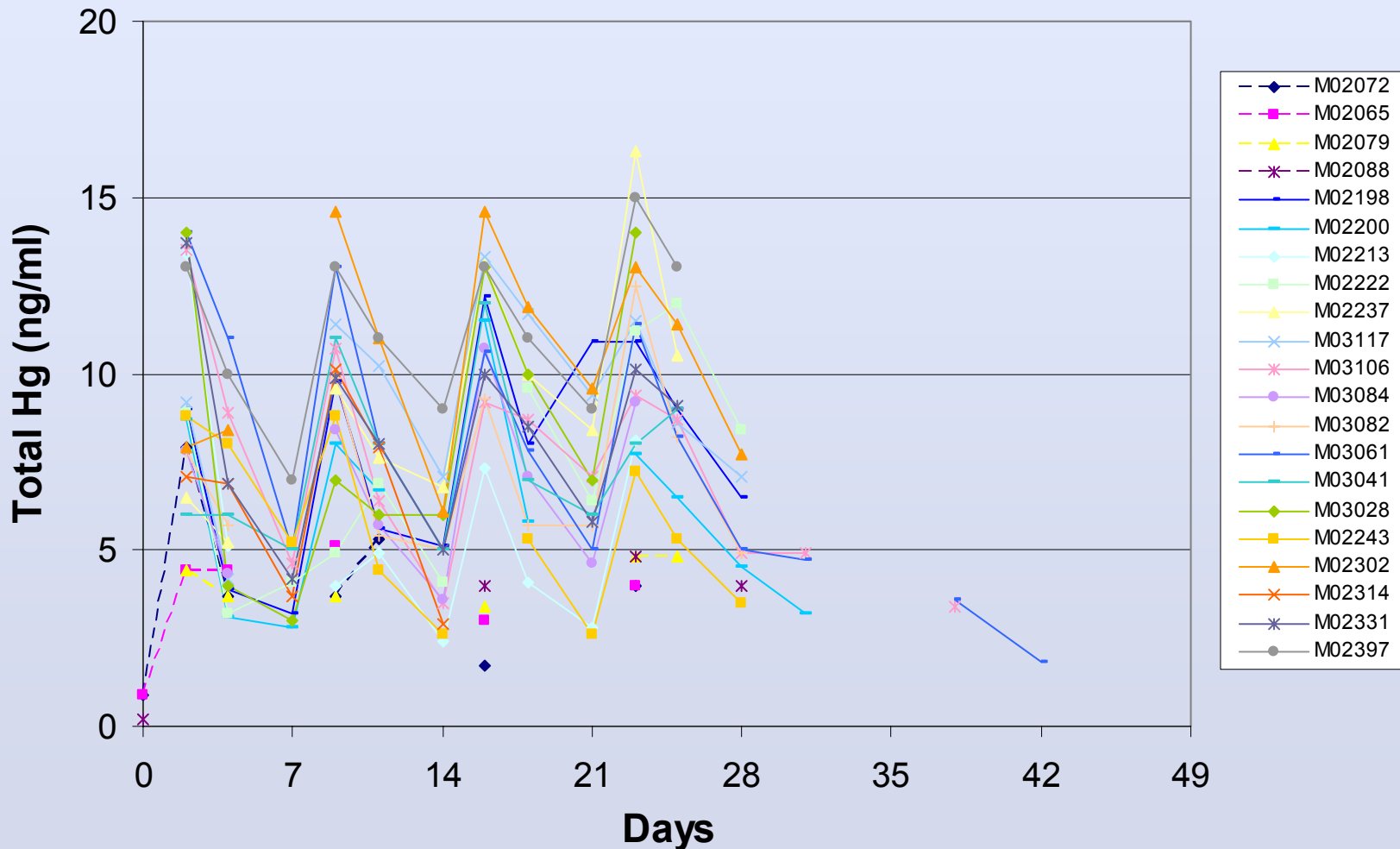
One-Compartment Model Analysis of Mean Blood Total Hg Data from MeHg-Exposed Infant Monkeys (n = 17)

Parameters	Mean \pm SD
V/F (L/kg)	1.62 \pm 0.04
k_a (day ⁻¹)	1.87 \pm 1.14
K (day ⁻¹)	0.0283 \pm 0.0014
$T_{1/2}$ (days)	24.5
Cl/F (ml/day/kg)	45.8

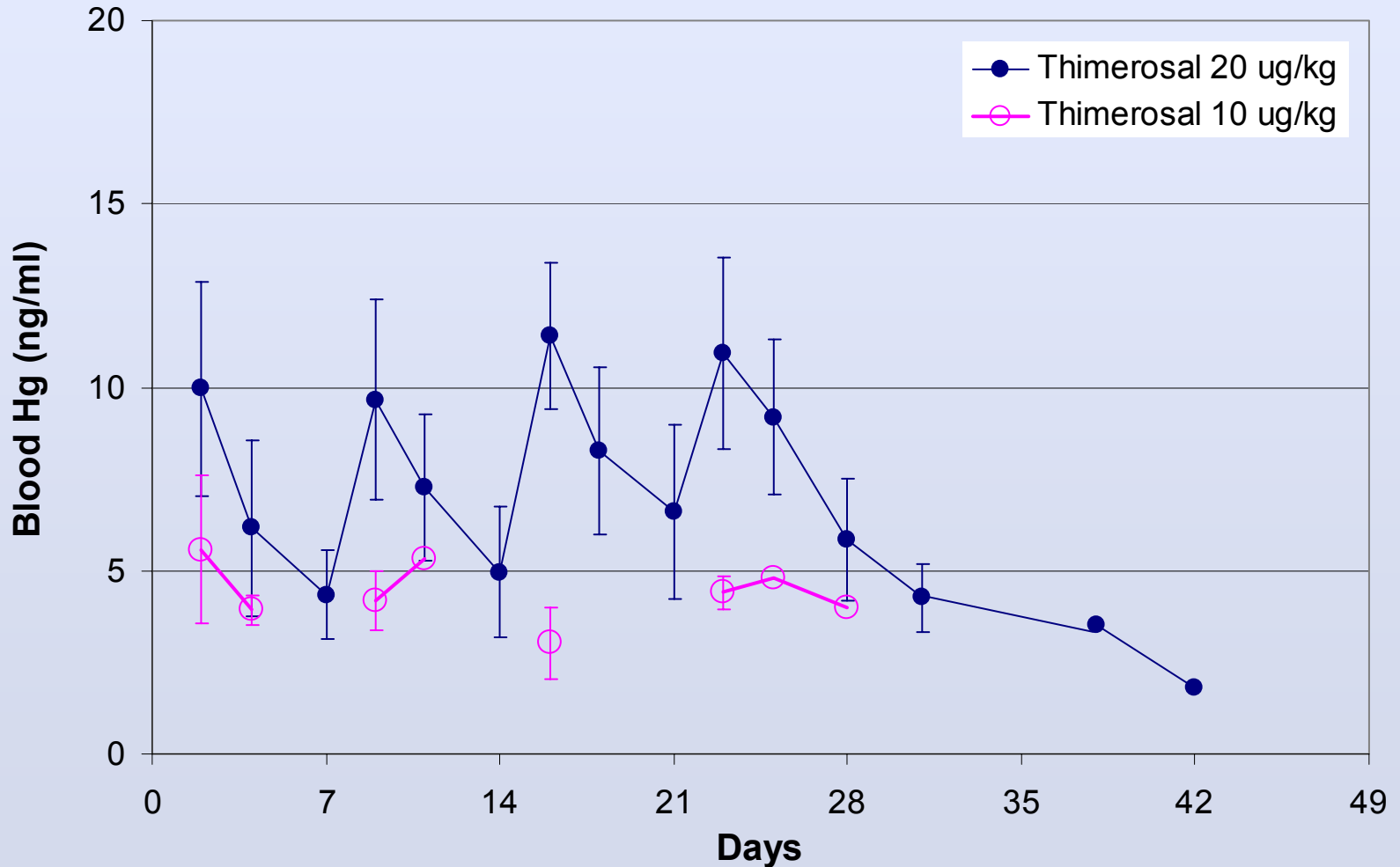
Analysis performed with SAAM II



Blood Total Hg in Infant Monkeys During and Post Four Weekly IM Injections of Vaccine Thimerosal at 10 μg Hg/kg (N=4) and 20 μg Hg/kg (N=17)



Mean Blood Total Hg in Infant Monkeys During/Post Four Weekly IM Injections of Vaccine Thimerosal

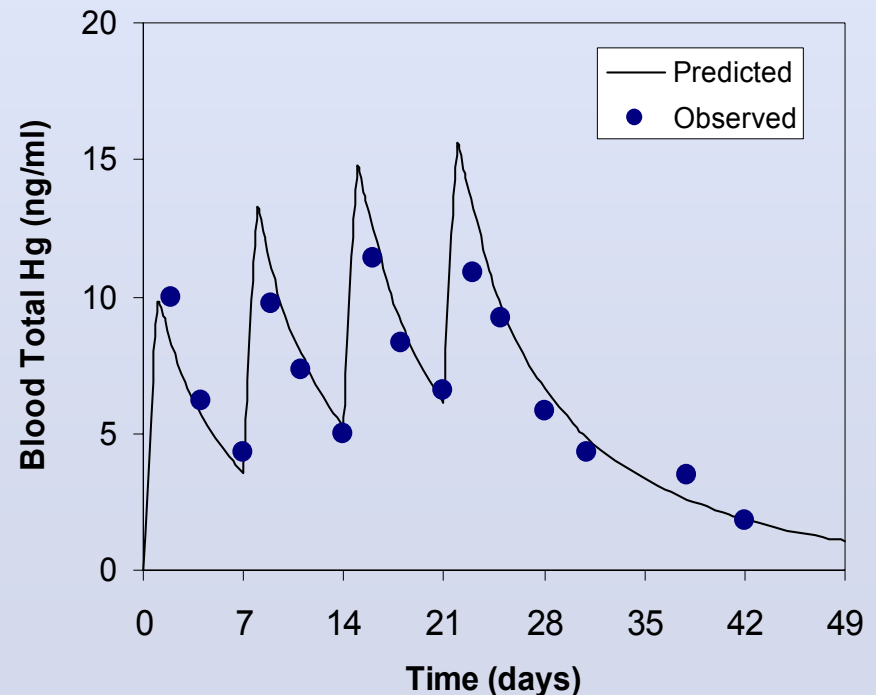
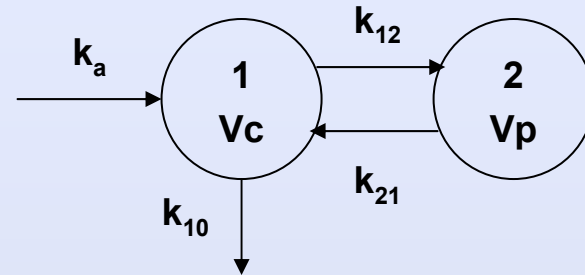


Two-Compartment Model Analysis of Mean Blood Total Hg from Thimerosal-Exposed Infant Monkeys (n = 17)

Parameters	Mean \pm SD
k_a (day ⁻¹)	3.24 \pm 3.00
k_{12} (day ⁻¹)	0.081 \pm 0.076
k_{21} (day ⁻¹)	0.177 \pm 0.138
k_{10} (day ⁻¹)	0.148 \pm 0.024
$T_{1/2,\alpha}$ (day)	2.13
$T_{1/2,\beta}$ (day)	8.62
V_c/F (L/kg)	1.68 \pm 0.30
V_{ss}/F (L/kg)	2.45
V_p (L/kg)	0.77
Cl/F (ml/day/kg)	248

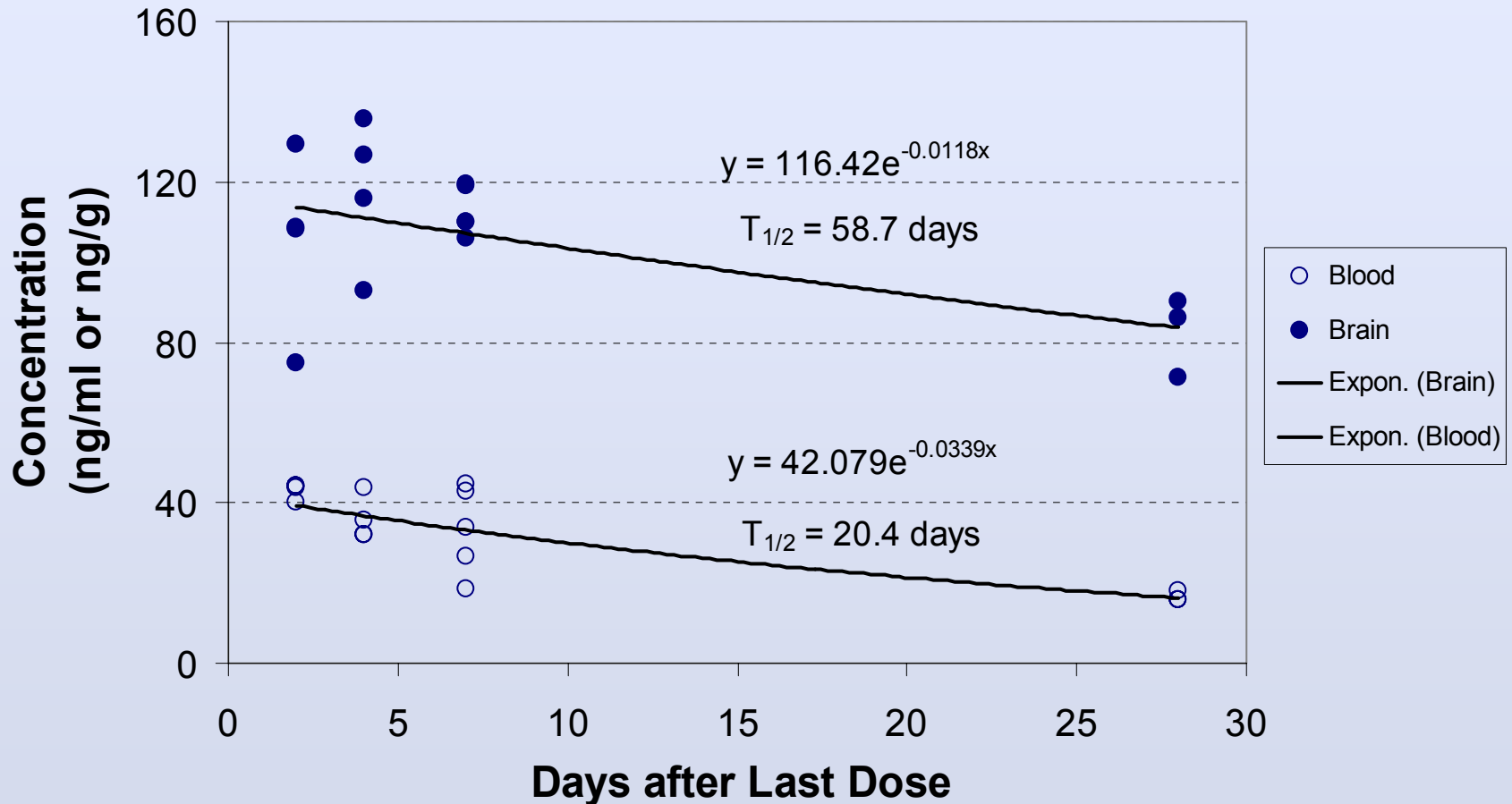
Analysis performed with SAAM II

NIAID, NIH, DHHS



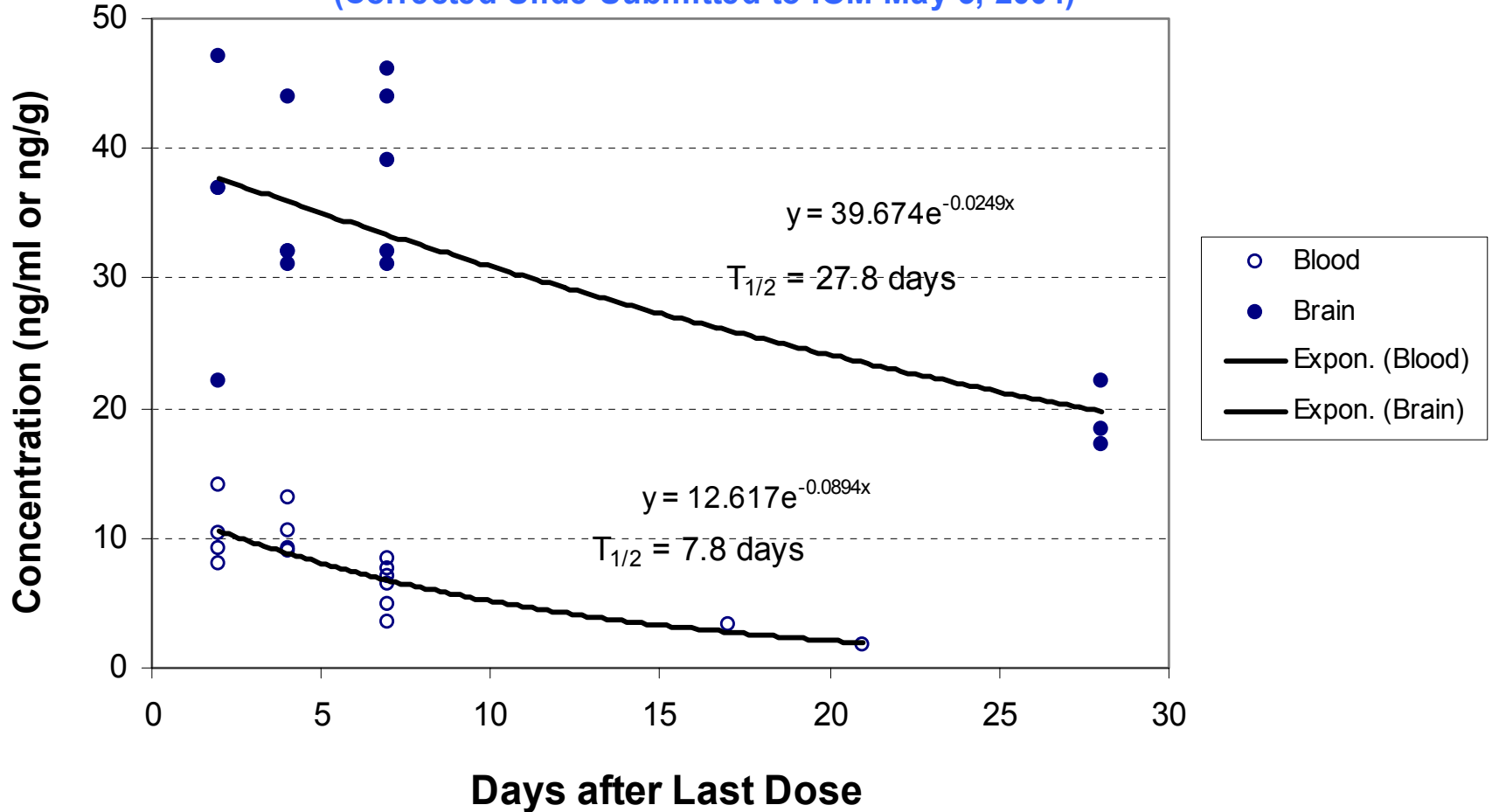
IOM Feb 9, 2004

Washout of Total Hg in Blood and Brain after Four Weekly Oral Doses of Methyl mercury (20 μg Hg/kg)



Average Brain:Blood = 3.6 ± 1.3

**Washout of Total Hg in Blood and Brain after Four Weekly IM
Injections of Vaccine Thimerosal (20 mg/kg)**
(Corrected Slide Submitted to IOM May 3, 2004)



Average Brain:Blood Ratio = 4.5 ± 1.5

Data Summary

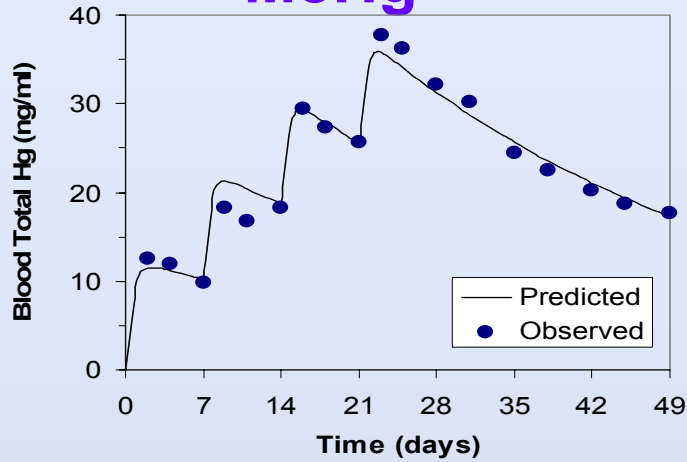
(Corrected Slide Submitted to IOM May 3, 2004)

	MeHg	Thimerosal
T1/2 Blood – Model	24.5 days	T_{1/2α} 2.13 days T_{1/2β} 8.62 days
T1/2 Blood – Washout	20.4 days	7.8 days
T1/2 Brain - Washout	58.7 days	27.8 days
Brain: Blood	3.6 ± 1.3	4.5 ± 1.5

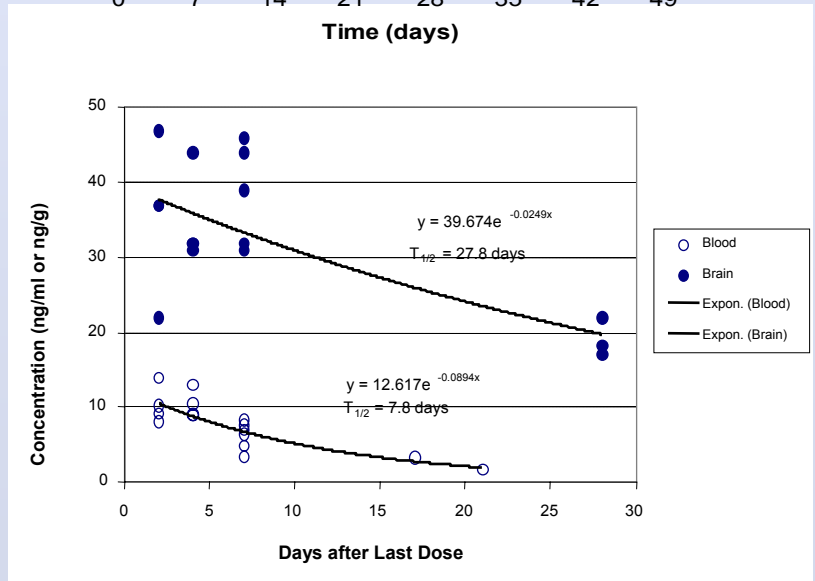
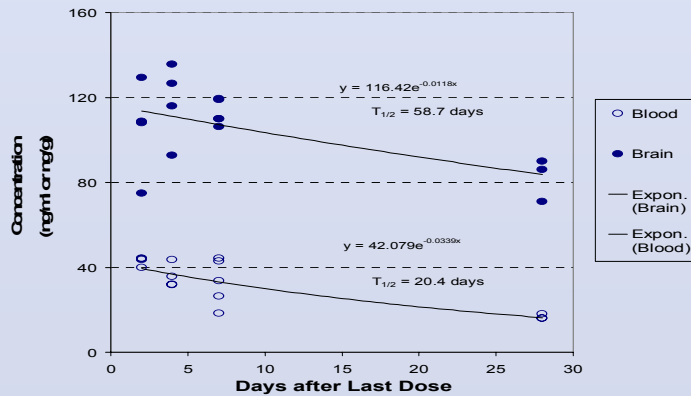
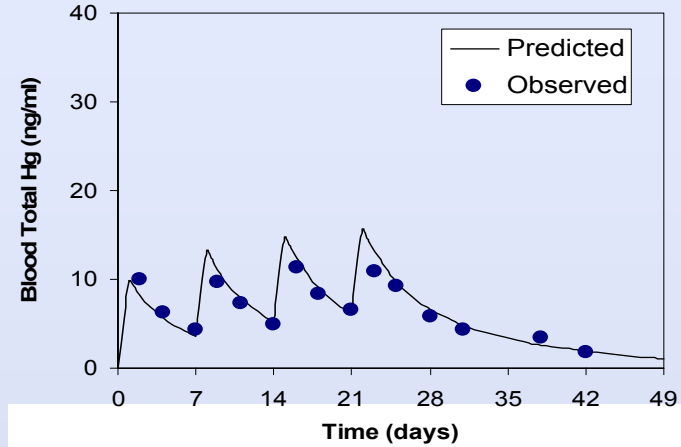
Data Summary

(Corrected Slide Submitted to IOM May 3, 2004)

MeHg



Thimerosal



Conclusions-Monkey Study

(Corrected Slide Submitted to IOM May 3, 2004)

- **Initial absorption and distribution of oral MeHg and Hg derived from i.m. thimerosal (in a vaccine vehicle) are similar.**
- **Blood Hg derived from thimerosal has a shorter terminal elimination half-life compared to MeHg in both blood (9 days vs 25 days) and the brain (28 days vs 59 days).**
- **Minimal accumulation of blood total Hg during weekly i.m. injections of thimerosal; continued accumulation of blood Hg occurred during weekly oral doses of MeHg.**
- **Although the brain-to-blood partition ratio of total Hg after thimerosal exposure (5.1) is higher than that for MeHg (3.4), it does not make up for the shorter half-life and much greater clearance of thimerosal-derived Hg from systemic circulation.**

Thank you

- **Tom Burbacher and Danny Shen – University of Washington**
- **Tom Clarkson and Elsa Cernichiari – University of Rochester**
- **Annette Kirshner and Cindy Lawler - NIEHS**

