

Respondent's Exhibit PP

October 3, 2008

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P.O. Box 146
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RE: Dr. Aposhian's Rebuttal Report of July 28, 2008

Dear Mr. Matanoski:

Thank you for asking for my analysis of the rebuttal report written by Dr. Aposhian in the King/Mead cases. I have carefully read Dr. Aposhian's rebuttal report and note that it is replete with incorrect statements, poorly researched science, incorrect calculations, and, hence, invalid conclusions. Virtually every paragraph in the report is scientifically incorrect. However, in the interest of avoiding an extremely tedious exercise for the court, I will restrict my comments to the most important errors in Dr. Aposhian's rebuttal report. If the court prefers a more detailed, point-by-point analysis I would, of course, be willing to comply.

Because of the quantitative nature of both Dr. Aposhian's rebuttal report and this analysis, I will refer sequentially to specific sections and paragraphs in Dr. Aposhian's submission.

My response will be very narrowly restricted only to the issues in Dr. Aposhian's rebuttal. This report offers no new information beyond my specific responses to Dr. Aposhian's rebuttal report. Much of this material has already been covered in my report and live testimony. I have done my best to keep the redundancies to an absolute minimum.

Comments on section II. "Brain Mercury Levels"

The conclusions Dr. Aposhian draws from the data presented in the Burbacher (2005) study (PML 26) are scientifically incorrect. In the third and fourth paragraphs of this section (page 3 of Dr. Aposhian's rebuttal), Dr. Aposhian states that in the study by Burbacher (2005, PML 26) methyl mercury-fed monkeys converted 6-10% of the methyl mercury in their brains to inorganic mercury during the 28-day period after the exposure stopped. This is seen in

the following Figure 4 from the Burbacher publication (with explanatory text boxes inserted by me):

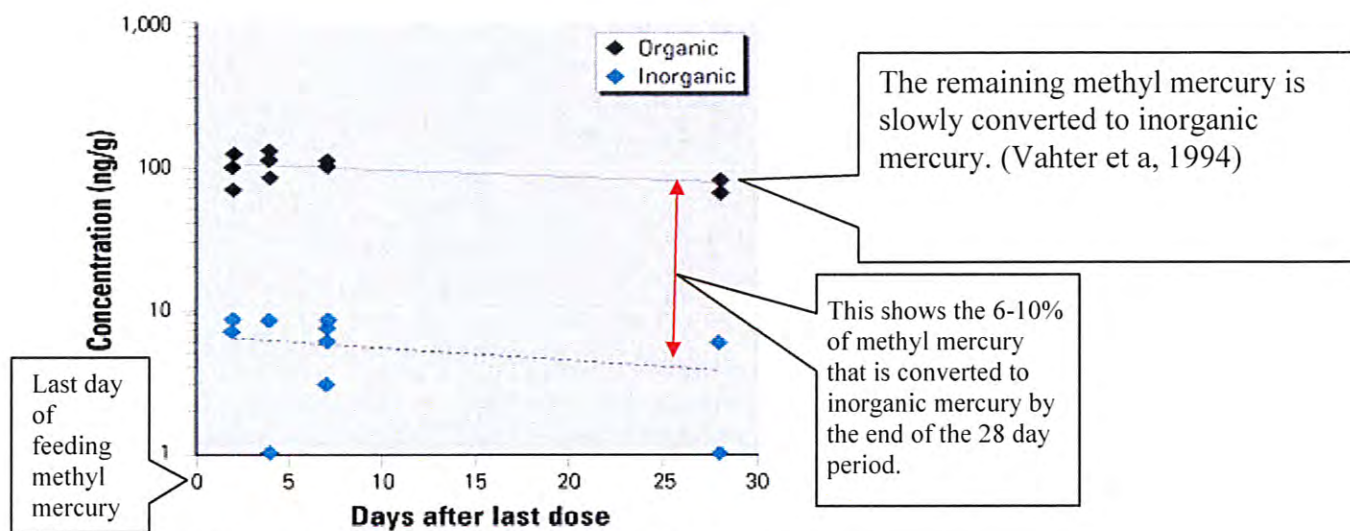


Figure 4. A semilogarithmic plot of the washout of organic and inorganic Hg in the brain after four weekly oral doses (20 $\mu\text{g/kg}$) of MeHg. The data were collected from groups of infant monkeys sacrificed at 2, 4, 7, and 28 days after the last dose. The lines represent nonlinear regression fit of the data to a monoexponential model. The regression estimate (\pm SE) for organic Hg is $T_{1/2} = 58.4 \pm 25.0$ days ($r = 0.57$). The half-life of inorganic Hg is too long (> 120 days) to be accurately estimated from the present data (i.e., r is not significantly different from 0).

The Burbacher experiment was concluded 28 days after the last feeding of methyl mercury or the last administration of a thimerosal-containing vaccine (TCV). The above figure from that paper shows the mercury concentrations in the brain over the 28-day period after the feeding of methyl mercury ceased. At the beginning of this so-called "washout" period, the total methyl mercury (designated as "organic" in the figure) concentration was approximately 100 nanograms of mercury per gram of brain (ng/g). (A ng/g is equivalent to a part per billion (ppb)). At the conclusion of the experiment, 28 days after the last dose of methyl mercury, the concentration of methyl mercury in the brain was very similar to that at the beginning of the washout period. In fact, the data provided in the text of the paper (page 1018, right column, bottom paragraph) makes clear that the methyl mercury concentrations in the brain were not statistically different between the beginning and the end of the 28-day washout period. This point is also made in the last sentence of the legend of this figure,

which notes that the slope of the methyl mercury washout from the brain cannot be shown to be other than zero. A line with a zero slope is flat and horizontal. Methyl mercury has been shown to efflux from the brain to some degree. (Vahter et al, 1994, PML 60). Thus, under the conditions of this experiment, it can be assumed that some of the methyl mercury would have left the brain, but at a very slow rate. The data in the paper shows that the rate was so slow that it could not be detected in this experiment. Thus, it is likely that over time most of the remaining methyl mercury would be slowly converted to inorganic mercury. **Therefore, it can be concluded that in this experiment, the total amount of mercury in the brain after the cessation of methyl mercury feeding is approximately 100 ng/g (or 100 ppb), most likely ultimately in the form of inorganic mercury.** There is no justification for Dr. Aposhian's conclusion that the 6-10% conversion of methyl to inorganic mercury during the brief 28 day washout period means that no further conversion would take place if the monkeys were not sacrificed. All of the data is to the contrary.

In the fifth paragraph of this section, Dr. Aposhian turns his attention to the monkeys treated with the same dose of mercury (20 ug (micrograms)/kg X 4 doses [80 ug/kg]) as the methyl mercury fed ones, but in the form of injected TCVs. The data from that part of the Burbacher experiment is shown in the following Figure 7 from the paper (with an explanatory text box inserted by me):

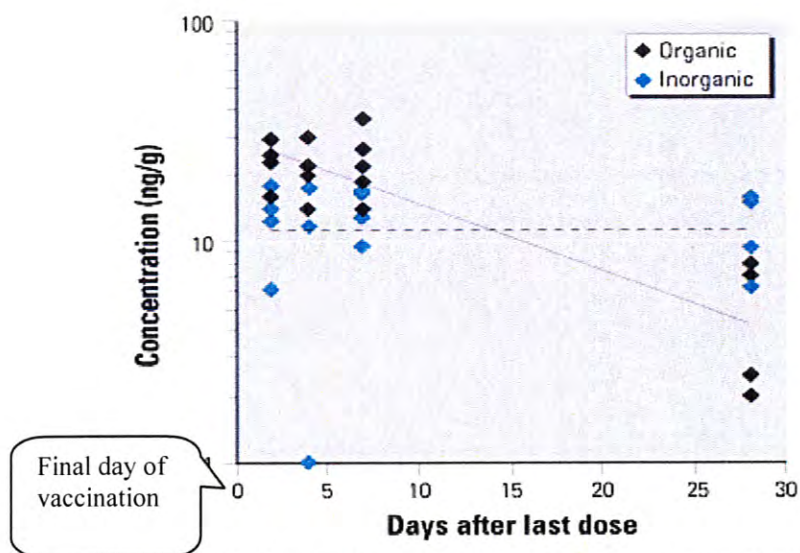


Figure 7. A semilogarithmic plot of washout of organic and inorganic Hg in the brain after four weekly im injection of vaccines containing thimerosal (20 µg/kg Hg). The data were collected from groups of infant monkeys sacrificed at 2, 4, 7, and 28 days after the last dose. The lines represent nonlinear regression fit of the data to a monoexponential model. The regression estimate (\pm SE) of $T_{1/2}$ for organic Hg is $T_{1/2} = 14.2 \pm 5.2$ days ($r = 0.76$). The half-life of inorganic Hg is too long (> 120 days) to be accurately estimated from the present data (i.e., r is not significantly different from 0).

As can be seen from Figure 7, monkeys given the equivalent dose of ethyl mercury as the methyl mercury treated group had at the end of the 28 day washout period a total brain mercury concentration of approximately 20 ng/g, 86% of which was in the form of inorganic mercury. The ethyl mercury was rapidly being converted to inorganic mercury over the washout period. Most of the conversion had taken place by the end of the 28 day period. **Therefore, it can be concluded that the total amount of mercury in the brain after TCVs given at the experimental doses used in this experiment is approximately 20 ng/g (or 20 ppb), ultimately in the form of inorganic mercury.**

The following table compares brain mercury concentrations at the end of the experiment in the 2 groups with the brain mercury concentration if no mercury was administered (the baseline):

Treatment	Brain mercury concentrations in ng/g (ppb)
80 ug/kg methyl mercury*	100
80 ug/kg TCV*	20
Baseline**	16

*Numbers are read from the figures in (Burbacher et al, 2005, PML 26), so they are approximate.

**Data taken from untreated monkeys at the same facility as the Burbacher experiment (Vahter et al, 1994, PML 60).

From these data it is clear that the approximate increment in brain mercury concentrations from the administration of TCVs, at the doses used in the Burbacher experiment, is 20 – 16 or 4 ng/g. Similarly, the increment from methyl mercury feeding is 96 ng/g.

Importantly, Burbacher's experiment on monkeys was designed to study the brain accumulation of mercury in a model of what would occur in the first 6 months of life in a human. However, as Burbacher recognized, the amount of mercury in the monkeys' brains might be too small to measure if the exact doses of thimerosal in TCVs administered to humans were used. Thus, Burbacher increased the doses of thimerosal administered to the monkeys (Sager, 2004, RML 436). As described above, and in his publication, Burbacher administered a total dose of 80 ug/kg. This is considerably in excess of the dose of mercury in TCVs given to humans during the first 6 months of life. A typically immunized human infant by age 6 months may have received up to 187.5 ug of mercury. The 50th percentile of body weight for a 6 month old is 8 kg for a male and 7.3 kg for a female. Thus, by 6 months, a human male would have received 187.5 ug mercury/8 kg or 23 ug/kg. A female would have received 26 ug/kg. This means that the monkeys in the Burbacher experiment received 3.3 X the dose of mercury than a human infant would receive from TCVs. **Therefore, based on the Burbacher data, the amount of mercury retained in the brains following immunization of humans with TCVs would be 4/3.3, or 1.2 ng/g (ppb).**

In the 6th paragraph of this section, Dr. Aposhian cites to data from a paper by Burbacher et al (1990, PMRL 224), which itself quotes a book chapter written in 1987 purporting to show, according to Dr. Aposhian, that the distribution ratio of methyl mercury between the brain and blood is 2.6 for monkeys and 6.0 for humans. Dr. Aposhian then, and without any scientific justification, applies that ratio to ethyl mercury from TCVs in the Burbacher (2005) experiment on monkeys. This is pure speculation by Dr. Aposhian, and the likelihood of

scientific error in so speculating is huge. This is so for several reasons, the most important of which are as follows:

1. Methyl mercury is a very different molecule than is ethyl mercury. One need only to look at, for example, the Burbacher (2005) experiment discussed in this section to realize this is so. Saying that methyl mercury and ethyl mercury behave similarly is pure conjecture, wholly without justification, and has been shown to be incorrect.
2. The danger in relying upon data that someone else quotes from a third paper, as Dr. Aposhian did in this case, is that the initial quote may be wrong. That is exactly what happened here. The ratio of 2.6 for monkeys is found in the 1987 book chapter. However, a close reading of that chapter shows that the ratio of 6.0 for humans is very uncertain, and based on very old studies that did not actually measure the ratios. Rather, the author of the 1987 chapter extracted indirect evidence from these old studies, and acknowledged that the ratio "may be about 6.0." Clearly this is not a reliable number. I have reviewed the 2 papers from which the ratio of 6 was based (Aberg et al, 1969; Meittinen, 1973) in detail. Neither one of these studies would, by contemporary standards, be considered to be reliable for the derivation of the brain/blood ratio. Both base their assessment of "brain" mercury concentrations, determined by feeding human volunteers very small amounts of radioactive methyl mercury, on simply putting a device in the vicinity of the head and counting radioactive emissions. These studies did not account for the major source of error with this technique. The brain has a very large volume blood flow and this technique also counts the mercury in the blood that flows around the brain and then returns to the heart. This creates the possibility of a substantial over-estimation of brain mercury concentrations.
3. The brain-to-blood ratio of 6.0 for humans is not only based on very uncertain data, it is also applicable to adults. The ratio of 2.6 that Dr. Aposhian uses for monkeys is based on his citation of data cited in a book chapter which cited an experiment done over 20 years ago. Dr. Aposhian has completely ignored the clarification that is explicitly stated in the Vahter et al (1994) paper (PML 60), from which he liberally quotes for other premises. That paper indicates that in the monkey model, the brain-to-blood ratio increases from 3.2 at 6 months to 5.1 at 12-18 months. Thus, there is no justification for concluding that the brain-to-blood ratio for methyl mercury distribution is any different in monkeys than in humans.
4. The Burbacher (2005) study clearly showed, as convincingly demonstrated above, that 21 times more mercury gets in the brain of the monkeys from methyl mercury than from an equivalent dose of ethyl mercury from TCVs.

Therefore, applying the methyl mercury ratio to brain accumulation of ethyl mercury is clearly documented to be incorrect.

5. Other data from the Burbacher study also clearly show that this line of scientific logic is seriously flawed. A simple calculation based on the logic articulated by Dr. Aposhian in paragraph 6 of this section of his report is a poignant illustration of its non-validity. He concludes, using the non-validated brain-to-blood ratios of 2.6 for monkeys and 6.0 for humans, that since the human factor is 2.3 times higher than the one for the monkey, then the concentrations in the 2005 Burbacher study should be increased by 2.3 in order to reflect human brain mercury concentrations. If we apply that logic we find that for a feeding of methyl mercury of 80 ug/kg (the dose used by Burbacher) the predicted human brain mercury concentration would be 100 ppb (the amount in the monkey brains) X 2.3, or 230 ppb.

Given that humans consume greater quantities of methyl mercury in their diets, if Dr. Aposhian's model were correct then we would all have brain mercury concentrations of many hundreds, or thousands, of ng/g (or ppb). We know that this is not even close to being the case. Typical Western human brains have been shown to contain well under 50 ng/g (ppb) of mercury (Lapham et al, 1995, PML 609). As described above, the total contribution from TCVs to this amount is extremely small.

In paragraphs 7 and 8 of Dr. Aposhian's rebuttal report, he cites the study by Charleston (Charleston et al, 1994, PML 33) as showing reactive microglia after high dose methyl mercury administration. The questionable significance of this report has been well covered in the live testimony in this case. Note that this study has no relationship to the Burbacher (2005) study discussed above. Dr. Aposhian, however, tries to analogize the two studies in his report.

In the Charleston study, the monkeys received a mercury dose of 50 ug/kg/day, in the form of methyl mercury, for 6 to 18 months. That is a total dose of 9,000 – 27,375 ug/kg. In the Burbacher (2005) study, the monkeys received a total dose of 80 ug/kg (or 3.8 ug/kg/day) over a total of 21 days. Similarly, the animals in the Charleston study had average blood mercury concentrations of 1,100 ug/L. (Vahter et al, 1994, PML 60). In contrast, in the Burbacher (2005) study, the TCV-treated monkeys had a maximum blood concentration of approximately 16 ug/L. The amount of mercury from TCVs in the Burbacher study exceeded those that might be given to a human by a factor of 3.3 (see above). Thus, the blood concentration from TCVs in monkeys receiving what a human would receive when fully immunized would have been approximately 4.8 ug/L, or 229 times less than the monkeys in the study by Charleston. Note that the 4.8 ug/L is very close to the range observed in human infants immunized with TCVs. (Pichichero et al, 2002 PML 223; Pichichero et al, 2008, RML 497)

The experimental data cited by Dr. Aposhian is done so in defense of petitioners' hypothesis that TCVs are in some way related to regressive autism. However, the Burbacher (2005) experiment upon which Dr. Aposhian so heavily relies clearly has no relationship to the percentage of individuals with autism who are regressive. The monkeys in the Burbacher study were normal, and hence are a model of the general population. If Dr. Aposhian's logic were correct, then he would be predicting that TCVs cause autism in the general population, not just in those who suffer a regression. Yet even the petitioners' epidemiologist, Dr. Greenland, has testified that the existing epidemiologic studies have ruled out TCVs as a cause of autism in general.

It should also be pointed out that the studies of Charleston and Vahter, upon which Dr. Aposhian relies, were also done on normal monkeys, and hence would not be a model of the subset of individuals with regressive autism who the petitioners hypothesize are somehow different in the way they handle mercury. Bear in mind also that the Charleston and Vahter studies were done after the administration of methyl mercury, not thimerosal or ethyl mercury. Why then does Dr. Aposhian not implicate methyl mercury as a cause of autism? As described above, there is much more methyl mercury retained in the brain, and converted to inorganic mercury, than there is from ethyl mercury given at an equivalent dose.

Lastly, the fundamental argument that levels of mercury as low 60 ng/g (ppb) in the brain are associated with autism is completely contrary to the scientific evidence. In the heavily fish eating population of the Seychelle Islands, brain mercury concentrations of several hundred ppb are routinely achieved (Lapham et al, 1995, PML 609). Yet, despite the intense scrutiny of the neurological outcome of Seychellese children, no increase in autism has been described. Similarly, in the Faroe islands, where blood, and thus brain, mercury concentrations are similar to those in the Seychelles, the rate of autism is 0.56%, or no higher than in countries like the US or those in Europe (Ellefsen et al, 2007, RML 130).

Comments on section III. "Brain cumulative inorganic mercury levels based on USA children from Pichichero et al, 2002"

In this section of his rebuttal report, Dr. Aposhian formulates a mathematical approach to extrapolate from measured blood mercury concentrations following vaccination to what he believes would be the resulting brain inorganic mercury levels. His approach is purely speculative, not grounded in scientific evidence, and flatly wrong.

To illustrate the unreliability of Dr. Aposhian's calculations, I will first describe his approach and calculations in a step-by-step fashion for clarity, and then provide simple and obvious observations about the errors in the calculations and the implausible conclusions that follow.

Dr. Aposhian's mathematical model uses 6 steps. These are enumerated below.

1. Dr. Aposhian has taken the highest values observed in the study by Pichichero from 2002 (PML 223) following vaccinations at 2 months and 6 months as his starting point.
2. He multiplies the values from #1 above by a factor of 6, which he uses as the ratio of brain-to-blood mercury concentrations. (The problems and speculative nature of his use of this factor are discussed in the prior section of this report.)
3. Dr. Aposhian then takes the values from #2 and multiplies them by 34%, which he takes as the percentage of inorganic mercury derived from total mercury following the administration of TCVs in the Burbacher (2005) study (PML 26). These values, he concludes, are the increments in brain inorganic mercury concentrations from each TCV.
4. He then averages these increments in brain inorganic mercury concentrations, which he believes derive from the 2-month and the 6-month injections. He uses this average value as the increment in brain mercury concentration that would occur with any injection of a TCV.
5. He next observes that it is possible for a child to receive up to 7 TCVs during the first six months of life (not including influenza). He thus takes the value from #4 above for each vaccination and multiplies it by seven.
6. Lastly, he notes that the values used are from Pichichero's 2002 publication from blood drawn 5 days post-vaccination. Dr. Aposhian believes that the blood mercury concentrations were likely higher on days 1 and 2 after vaccination, and thus he made up an arbitrary correction factor of 20%, making the assumption that the peak values were 20% higher.

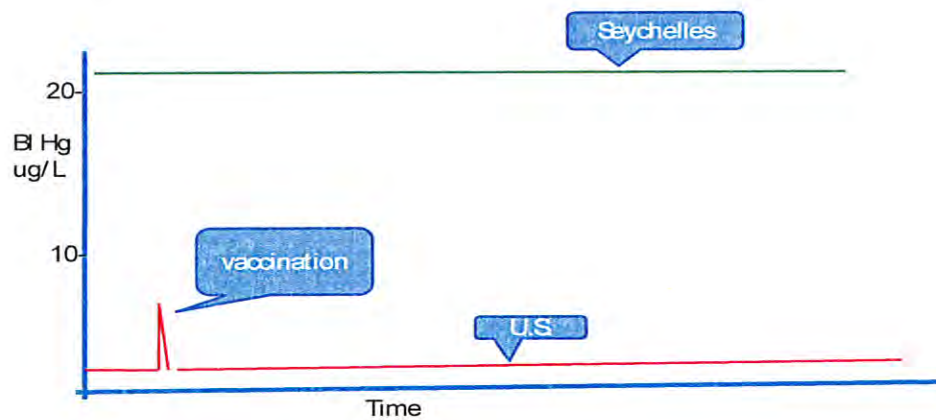
I will next show how, using this methodology, Dr. Aposhian did his calculation.

1. He uses a blood mercury of 4.12 ng/ml for 2 months and 1.4 ng/ml for 6 months.
2. Multiplying each of these by his factor of 6, he comes up with a total brain mercury concentration of 20.7, and 8.4 ng/ml, respectively.
3. He then multiplies each of these values by 34% to get his calculated brain inorganic mercury of 8.4 and 2.0 ng/ml.
4. An average of these values is 5.2 ng/ml.
5. 5.2 ng/ml x 7 TCVs yields 36.4 ng/ml.

6. He then multiplies this number by his correction factor and comes up with a brain mercury concentration of 43.7 ng/ml or ng/g. (A ml of brain can be considered to be equivalent to a gram)

The methodology described above and used by Dr. Aposhian is profoundly flawed. The most erroneous assumption in Dr. Aposhian's calculations is his invocation of the factor of 6 as the brain-to-blood ratio to mercury. A factor such as this, even if it were valid for humans (which, as described above, is questionable), is based on experiments where there is a chronic blood level at a steady state. This is different from a short and episodic increase in blood levels, as would occur following vaccination. Blood mercury concentrations following vaccination return to baseline by approximately day 12 following vaccination. (Pichichero et al., 2008, PML 497). Thus, for infants who were immunized five times in the first six months (birth, 1-,2-,4- and 6-months), 93% of the time there was no elevation in blood mercury concentration from vaccination. In contrast, if we look at populations where children have chronically elevated blood mercury concentrations, a very different story would emerge based on Dr. Aposhian's logic. In the Seychelle Islands, the average blood mercury concentration is 24 ug/L.¹ (Myers et al., 2007). As seen in the figure below, which I made for illustrative purposes, there is a significant difference between a transient elevation in blood mercury concentrations and a constant high level in the blood.

¹ This amount was calculated from maternal hair concentrations, which average 5.7 ppm (parts per million) in the Seychelles population (Myers et al, 2007). This is equivalent to 5.7 ug/g or 5,700 ug/kg (of hair). Since the concentration in blood is 250 times less than that in hair, division by this factor gives a value of 24 ug/kg (of blood), which is equivalent to 24 ug/L.



Comparison between blood mercury concentrations in the Seychelle Islands and the U.S., showing a transient increase for the U.S. population with a single vaccination

This diagram shows that there is a constant concentration of more than 20 ug/L of mercury in the blood in the Seychelle Islands population. In children in the United States, the mean blood mercury concentration is 0.34 ug/L (Schober et al, 2003, PML 226) with small transient increases at the time of vaccination. For simplicity, only one vaccination is shown in the above illustration, although over the first six months of life, children are vaccinated at birth, 1-, 2-, 4-, and 6-months of age. Since mercury moves into the brain from the blood, the amount that will enter the brain depends on the blood concentration at any point in time. Thus, there is a massive difference between transient increases in blood mercury concentrations (as in vaccination of US children) than there is with chronic levels (as in the Faroe and Seychelle Islands).

If we were to accept Dr. Aposhian's logic and apply a factor of 6.0 with each vaccination, then, when applied to the Seychelles' population, we would have to factor in their average blood concentration of 24 ug/L. Since the Seychelles' population maintains that level 100% of the time over the first 6 months of life, we would have to correct for the fact that this is 15 times more than the amount of time children have increases in blood mercury related to vaccination. Therefore, if we multiply the 24 ug/L by Dr. Aposhian's factor of 6.0, we get 144 ug/L. Multiplying that by the factor of 15 for the chronicity of the elevated blood concentration compared to that of vaccinated children gives us a concentration of 2,160 ng/g in the brain. Clearly this cannot be the case. Children in the

Seychelle Islands are known to have brain mercury concentrations, on the average, of under 100 ppb (Lapham et al., 1995 RML 294). This can be seen in Figure 9 of the Lapham paper. Thus, it is clear that Dr. Aposhian's calculations are incorrect.

Comments on Section IV. "Brain cumulative inorganic mercury levels based on USA children from Pichichero et al., 2008"

Here Dr. Aposhian once again uses the same calculations, but in this case, he applies them to the data from Pichichero's 2008 publication (PML 497). Following the same logic, it is clear that these calculations are also incorrect. (Please also note that despite his title of this section, the values obtained are not from U.S. children, but from children in Argentina).

Comments on Section V. "Additional rebuttals of Dr. Brent's testimony"

In this section Dr. Aposhian describes 5 issues that he says are new. These are:

1. The Study of Adams 2008;
2. The study by Windham 2008;
3. His further thoughts on the Bradstreet study;
4. The study by Laurente;
5. His further thoughts on methyl mercury exposures through breast milk.

I will cover each of these in turn.

Adams 2008 (PMRL 667): Dr. Aposhian cites the Adams 2008 study as a verification of the Holmes et al., 2003 study. Only the abstract of the Adams 2008 study was filed. I do not know if Dr. Aposhian has actually read the whole study. The study is difficult to obtain because it appears in an extremely obscure journal that is not even listed by the National Library of Medicine. I have obtained and carefully read the entire version of the study and it in no way supports the data of Holmes et al., 2003 (PML 237). In fact, it is yet another study that shows that Holmes is incorrect. Attempting to use the same methodology (first baby haircut) as the Holmes et al. study, Adams et al. assessed the first baby haircuts in children with autism and neuro-typical controls. That data showed that the median hair mercury concentration in autistics was 0.38 ug/g (I use these units because that is how Adams et al. presented their data), and was 0.72 ug/g in the controls. The difference between the groups is very small and both of these values are in the range found in the general population. These controls are markedly different from the 3.63 ug/g in the controls of the Holmes study. Note that the value of 0.47 ug/g in the autistics in the Holmes study is similar to the results of both autistics and controls in the Adams study.

Adams et al. hypothesized that there is a difference in the mercury concentrations in first baby haircuts between autistics and controls. The logical way to test this hypothesis is to compare the hair mercury concentration of 0.38 in autistics to the 0.72 ug/g in the controls. Tellingly, however, Adams 2008 did not do this (or at least did not report it). Nor did they provide enough information in their paper for a reader to do the calculation. Rather, they took an arbitrary cutoff of 5.5 ug/g and found that children below that line were statistically significantly "more likely to manifest autism." However, they do not tell us more likely than what? One is left to assume that they are making the comparison to children with a hair mercury level greater than 5.5 ug/g. If so, this is a self-fulfilling prophecy, given that the average haircut concentrations in autistics was 0.38 ug/g. Nowhere does the Adams 2008 study tell us how they chose the 5.5 ug/g cutoff. They may simply have done the statistics with a number of cutoffs until they found one that was statistically significant.

There are multiple other problems with the Adams et al. 2008 (PML 667) study. After they say that the autistic children have low hair mercury concentrations, they quickly point out that some of the autistic children have the highest hair mercury levels in their study. They could not find any correlation between the severity of the autism and the hair mercury concentration (if their theory was correct you would certainly expect to see a gradient), and they report no attempt to correlate the amount of mercury the children received through vaccines and their hair mercury concentrations.

In summary, the Adams et al. study, unlike the Holmes study, verifies that children with autism and neuro-typical children have very similar hair concentrations, and both are in the range of the values to the general U.S. population. The very high value of 3.63 ug/g in Holmes' controls, which is essential to her argument that autistics have much lower hair mercury concentrations than controls, once again, as in all of the other published hair studies (Kern et al, 2007, RML 275; Adams et al, 2006, RML 2; Fido et al, 2005, RML 138; Ip et al, 2004, PML 275; Williams et al, 2007) could not be verified.

Windham, 2008 (PMRL 670):

Contrary to what is stated in Dr. Aposhian's rebuttal report, this study did not discuss autism, thimerosal, or mercury in any form.

Bradstreet et al. 2003 (PML 244): The problems with this study have been well covered in prior testimony, and it would be redundant to review them yet again. Dr. Aposhian has adopted Dr. Mumper's explanation that it is difficult to get pre-challenge baseline urine levels in autistic children. Paradoxically, neither Dr. Aposhian or Dr. Mumper has ever said that it is difficult to get post-challenge urines in these children. The study of Soden et al. 2007 (RML 458) has demonstrated that not only can a pre-challenge collection be done in children

with autism, but when it is done, there is no difference between autistic children and neuro-typical controls. This has been very well discussed in my testimony in this case and therefore no other explanation is deemed necessary.

Laurente et al. (PML 668): Dr. Aposhian presents this study as one that replicated the data of Hornig (PML 15). As well covered in my testimony, the Hornig study has been clearly shown to be non-replicable when done by other investigators using more sophisticated techniques (Berman 2007, RML 42). One error in the Hornig study, as pointed out by the data from Berman, is that the half-life of mercury in the blood after ethyl mercury injections in this mouse model was 2.9 days. Since Hornig et al. injected their mice every two days, there would be a progressive accumulation of mercury over time, potentially to extremely high levels. This is markedly different from what happens in humans where immunization injections are given at time periods long after the prior doses have cleared. Laurente et al. make the same mistake by immunizing every two days and not checking blood mercury concentrations. The data is clear that they made their animals, which in this case were hamsters, mercury toxic.

A fundamental principle in toxicological studies on animals is that to assess the adverse effect, if any, of a chemical exposure, it is important not to give doses so high as to make the animal generally sick to the point that they do not eat, become malnourished, and lose weight. Once an animal is made this sick it is impossible to distinguish between effects of malnutrition and weight loss from specific effects of the chemical. This is a concept known as the maximum tolerated dose (MTD). The MTD is the maximum dose that can be given to an animal without having significant weight loss and developing malnutrition. Toxicological studies are only considered valid if they do not exceed the MTD.

The study by Laurente et al clearly exceeded the MTD and, therefore, the effects they observed were non-specific and due to the profound malnutrition in the animals. This is documented by the fact that the treated animals were only 50% of the weight of the untreated ones, and, of course, had significant decreased length and brain weight. The various effects that they describe, only some of which were an attempt to replicate the Hornig study, cannot be distinguished from the fact that they profoundly exceeded the MTD. This was undoubtedly so because of their every 2-day injection schedule. Thus, there is no reasonable way that this study can be interpreted as a verification of the data of Hornig.

The Laurente study appeared in the *Anales de la Facultad de Medicina Universidad Nacional Mayor de San Marcos*, which is a publication from their own University. It is an extremely obscure journal.

Methyl mercury exposures through breast milk:

This has been extensively covered in my testimony. In his rebuttal report Dr. Aposhian provides no new information or analysis regarding this issue.

Yours most sincerely,



Jeffrey Brent, M.D., PH.D.
Clinical Professor of Pediatrics and Internal Medicine
University of Colorado Health Sciences Center

Docs/docs/proj/Hg/doj/thim/rebuttal