

Answers to Questions on the Toxicity of Ethylmercury
Prepared for the Institute of Medicine Immunization Safety Review Committee

László Magos, M.D., D.C.P., FRCPATH
Independent Consultant

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One of the issues that will be considered during the Immunization Safety Review Committee's upcoming meeting on thimerosal and neurodevelopmental outcomes is the toxicity of ethylmercury. As one of its data gathering activities, the committee asked Dr. László Magos to answer questions regarding the toxicity of ethylmercury. His answers and accompanying reference list are available here. The committee welcomes comments on this material.

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Comments on this material can be emailed to the committee at imsafety@nas.edu. It is most helpful if comments are received by July 9, 2001. **COMMENTS WILL BE PART OF THE PUBLIC ACCESS FILE FOR THIS PROJECT AND PERSONAL IDENTIFIERS WILL BE INCLUDED.**

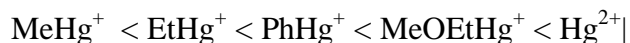
For your information the agenda for the open scientific workshop to be held on July 16 in Cambridge, MA has been posted at www.iom.edu/imsafety. In addition, a list of materials sent to the committee to date will be posted later this week at www.iom.edu/imsafety.

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QUESTION 1. What is the toxicological significance of the decomposition of methyl or ethylmercury?

Answer:

Molecular size is an important property of the organomercurial compounds for two reasons. The size of the radical influences transport through membranes, including the important blood-brain barrier, and it also influences the stability of the compound. The stability of the bond between mercury and the organic radical decreases with the number of carbons in the radical. Thus methylmercury is more stable than ethylmercury, and ethylmercury is more stable than any of the alkoxyalkylmercurials or phenylmercury. The initial mercury uptake by the kidneys after the administration of organomercurials follows the same order as their decomposition rate that is



where PhHg is phenylmercury, MeOEtHg is methoxyethylmercury. The order indicates that ethylmercury is more prone to decomposition than methylmercury, and the initial renal uptake from a single dose is also higher (Magos, 1982). The decomposition rate of ethylmercury exceeds the decomposition rate of methylmercury not only *in vivo*. There was no noticeable decomposition when kidney slices were incubated with methylmercury for 2 hours, but at the same time 6 % of mercury was cleaved from ethylmercury (Fang and Fallin, 1974). In another *in vitro* system, reactive oxygen decomposed ten times more ethyl- than methylmercury (Suda and Takahashi, 1992).

The first step in the metabolism of ethylmercury in the form of thimerosal (ethylmercury-thiosalicylate) is cleavage of the bond between sulfur and mercury with the formation of dithiosalicylic acid. This step is followed by a partial reformation of thimerosal; and a final split to ethylmercuric ion and sulfino- and sulfobenzoic acid. (Parkin, 2000). *In vivo* this reaction must be fast, because there were no differences in the distribution of mercury in mice given either thimerosal or ethylmercuric chloride (Suzuki et al., 1973). The instability of thimerosal and the subsequent adhesion of mercuric ion to the ampule may explain why commercial samples of human plasma contained 62% of the nominal concentration (Suzuki et al., 1973) and some of the 24-36 month-old batches contained even less (Haeney et al., 1979).

Decomposition is a toxicologically important metabolic step because it decreases the body burden of the neurotoxic parent compound and increases the body burden of the renotoxic Hg^{2+} . The consequence of faster decomposition is that, compared with methylmercury, the neurotoxic potential of ethylmercury declines faster.

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QUESTION 2. What are the relative contributions of inorganic and organic mercury to the renotoxicity and neurotoxicity of ethylHg or MethylHg ?

2.a. Answer on renotoxicity:

2.a.a. Differences in animal experiments between methyl- and ethylmercury

As inorganic mercury preferentially accumulates in the kidneys, comparison of renal mercury concentrations after the administration of methyl- or ethylmercury gives an indication on their behavior in the whole body. Decomposition is part of the clearance process for the parent compound, but is also part of the creation of inorganic mercury, which, unlike the parent compound can be attached to biological constituent with two valences. The next table demonstrates the differences between methyl- and ethylmercury in relation to the renal concentration of organic and inorganic mercury after a five day treatment schedule.

TABLE 1 The renal concentration of mercury in rats after five daily oral doses (by gavage) of 8.0 mg Hg/kg b.w., given either as methyl- or ethylmercury. (Data were extracted from Magos et al., 1985)

		µg Hg/g renal tissue (number in bracket is % of inorganic Hg)			
time after last treatment	sex	MeHg		EtHg	
		Total Hg	Inorg Hg	Total Hg	Inorg Hg
3 days	male	88	6.7(7.6 %)	45	12.3(28 %)
	female	107	4.9(4.6 %)	73	19.5(26 %)
10 days	male	69	8.3(12.0 %)	57	13.1(23 %)
	female	113	11.9(10.5 %)	67	16.0(39 %)

Table 1 shows that irrespective of time or sex, the concentration of renal mercury was higher in methylmercury than in ethylmercury treated rats, but the inorganic mercury concentration was higher in ethylmercury treated rats. As decomposition means the loss of neurotoxic potential., it seems justified to conclude that even if the parent compounds were equally neurotoxic, metabolic transformation rendered ethylmercury less neurotoxic and more renotoxic than methylmercury.

As expected, experimental studies have indicated that in rats, ethylmercury is more renotoxic than methylmercury. In the above experiments in which rats were given daily doses of ethylmercury or methylmercury (8 mg Hg/kg) for five days, 12 days after the last dose signs of necrosis and regeneration occupied smaller areas of the proximal tubules in methylmercury than in ethylmercury treated rats. Fibrosis, the sign of severe

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damage, was not seen in any of the animals. The difference between the renotoxicity of ethylmercury and sublimate is substantial. Thus a single parenteral dose of 1 mg Hg/kg given as sublimate necrotised in the first day 80 % of cells in the pars recta and the distal portions of convoluted cells in male rats (Ganote et al., 1978). This dose increased mercury concentration in kidneys to 34 µg/g and killed half of the rats (Magos et al., 1984). The total mercury concentrations in the methyl- and ethylmercury groups (see Table 1) were significantly higher than in the sublimate treated group but inorganic mercury concentration (in male rats) were lower. This indicates that inorganic mercury had a prominent, and the ethylmercury molecule perhaps only a contributory, role in the renal damage of ethylmercury treated rats.

2.a.b. Epidemiological studies and clinical observations

In the Iraqi methylmercury epidemic, renotoxicity was not reported. However, reports from ethylmercury epidemics indicate that the renal system could be affected. In Iraq, two epidemics were caused by the misuse of ethylmercury p-toluene sulfonamide dressed seed. Damluji (1962) observed 21 patients, nine of them had mild toxicity, six had moderately severe toxicity, three had severe intoxication, and 3 patients died. The moribund patients had severe albuminuria, cylindruria and oliguria. These effects were less pronounced in the patients who survived severe intoxication and two of them had polyuria. The report of Jalili and Abbasi (1961) included tabulated data for 26 patients. Neurological signs were dominant, but nineteen patients complained of abdominal or skeletal pain, 13 had polyuria and two oliguria. These two had impaired vision.

2.b. Answer on neurotoxicity:

2.b.a. Differences in animal experiments between methyl- and ethylmercury

Though an ethylmercury molecule is only 6% larger than the molecule of methylmercury, this small difference becomes important through its influence on passage through the blood-brain barrier. Kerper, Ballatori, Clarkson (1992) suggested that because the methylmercury-cysteine complex is structurally similar to L-methionine, methylmercury can use the L (leucine preferring) amino acid transport system through the blood-brain barrier. No such transport facility system is available for ethylmercury with the consequence that after identical dose methylmercury treated rats had twice as much mercury in their brain (1.55 times in males and 2.4 times in females) than ethylmercury treated rats. In addition to the lower brain deposition of mercury, ethylmercury treated rats had 3.4-fold more inorganic mercury in their brain and the contribution to inorganic mercury to total mercury was 5.3 times higher than in their methylmercury counterparts (Magos et al., 1985). These findings exclude the possibility that the cleavage itself or the formed inorganic mercury is responsible for the brain damage. If this were the case, the brain of ethylmercury treated rats would be more affected than the brain of methylmercury treated rats.

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TABLE 2 The brain concentration of mercury in rats after five daily oral doses (by gavage) of 8.0 mg Hg/kg b.w., given either as methyl- or ethylmercury. (Data were extracted from Magos et al., 1985)

		µg Hg/g renal tissue (number in bracket is % of inorganic Hg)			
time after last treatment	sex	MeHg		EtHg	
		Total Hg	Inorg Hg	Total Hg	Inorg Hg
3 days	male	10.1	0.12(1.2 %)	7.1	0.45(6.3 %)
	female	18.7	0.18(1.0 %)	7.8	0.69(8.8%)
10 days	male	8.2	0.18(2.1%)	4.8	0.56(11.7 %)
	female	18.8	0.31(1.6 %)	7.0	0.59(8.4 %)

The difference in the brain uptake of mercury was associated with more extensive damage in the granular layer of the cerebellum of methylmercury treated rats. Methylmercury treated rats also showed a higher degree of co-ordination disorders and their spinal root ganglions were also more affected than in ethylmercury treated rats (Magos et al., 1985). No adverse effects were observed in rats given ethylmercury in daily doses of 2.12 mg Hg/kg for 150 days, but twice this dose produced typical neurological signs in 34 to 84 days (Akitake, 1968). This can be compared with the daily dose of 1.68 mg Hg/kg given as methylmercury which produced ataxia in rats within 4 weeks. Intensive cerebellar granular layer damage was seen in rats killed two weeks later (Magos, Butler, 1972).

In human toxicology, blood is a frequently used indicator media. As increase in the urinary excretion of mercury after exposure to methylmercury is negligible, estimation of mercury in blood has a special importance.

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TABLE 3. The blood concentration of mercury in rats after five daily oral doses (by gavage) of 8.0 mg Hg/kg b.w., given either as methyl- or ethylmercury. (Data were extracted from Magos et al., 1985)

time after last treatment	Sex	µg Hg/ml blood (number in bracket is % of inorganic Hg)			
		MeHg		EtHg	
		Total Hg	Inorg Hg	Total Hg	Inorg Hg
3 days	male	154	0.4(0.3 %)	247	9.3(3.8 %)
	female	209	0.5(0.2 %)	340	7.4(2.2%)
10 days	male	105	0.4(0.4%)	171	5.9(3.3 %)
	female	162	1.1(0.7 %)	264	7.5(3.6 %)

Table 3 shows that the blood concentration of mercury was about 50% higher in ethylmercury than in methylmercury treated rats. The opposite is true for brain mercury: ethylmercury treated rats had 30 to 63% less than the methylmercury counterparts. The different relationship of blood mercury versus brain mercury (or neurotoxicity) makes it impossible to use the same plot to predict brain mercury or response in both alkylmercurials. When the relationship established for methylmercury is used for ethylmercury, the brain mercury concentration and neurotoxicity will be overestimated and vice versa.

When thimerosal was given to squirrel monkeys in daily nasal drops of 5.92 µg Hg/day for six months, brain mercury levels increased from 55 ng/g to 174 ng/g. Judging from their weight range, the monkeys received daily between 2.4 and 5.3 µg Hg/kg. Organ mercury concentrations decreased in the order of kidney, liver, brain, and blood. This order is typical for non-human primates treated with methylmercury. Unfortunately unaccounted exposure of the control rats also increased brain mercury concentration in two monkeys to just below and over the lower range of the dosed animals. The only conclusion drawn from this experiment is that 6 month exposure to daily doses of 2.4 to 5.3 µg Hg/kg as thimerosal and brain mercury concentration between 120 and 245 ng/g were not neurotoxic. From the nares to the nasopharynx, histological examination did not detect abnormality (Blair et al., 1975).

2.b.b. Epidemiological studies and clinical observations

In the Iraq methylmercury epidemic, the frequency of toxic clinical manifestations increased when mercury concentration was over 500 µg/ml and fatal outcome occurred when blood mercury concentration was in the range of 3,000-5,000 µg/ml (Bakir et al., 1973). In two lethal methylmercury intoxication of occupational origin, blood mercury concentration extrapolated to the end of exposure gave 4,600 and

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2,300 $\mu\text{g Hg/ml}$. The third patient, whose disease was linked to mercury exposure shortly after admission to hospital and who also received chelation therapy, had 2000 $\mu\text{g/ml}$ blood mercury concentration. He survived with severely affected coordination, dysarthria and constricted vision (Magos, 1998).

In an ethylmercury epidemic, the frequency of neurological abnormalities in 21 patients decreased in the following order: muscular weakness (20), paraesthesia (19), ataxia and fine tremor (16), dysarthria (15), and constriction of the visual field (5) (Damluji, 1962). In another group of 26 patients, twenty-two had ataxia and/or problems with walking. Twenty-one patients were tested for both vision and speech disorder. Eleven of these 21 had speech disorder and 10 constriction of the visual field. In six patients the two disorders occurred concurrently (Jalili, Abbasi, 1961). Blood mercury concentration was not estimated in these two studies. However, in a separate report of a female and a male victim who died after ingesting daily about 6.7 mg of ethylmercury for three months, their blood mercury concentrations were 15 $\mu\text{g/ml}$ and 15.5 $\mu\text{g/ml}$ respectively (Hilmy et al., 1975). These concentrations were much higher than the 3.0 to 5.0 $\mu\text{g/ml}$ range where death occurred in the methylmercury epidemic (Bakir et al., 1973). Only part of difference can be explained with differences in the kinetics of the two alkylmercurials. An additional factor can be that the consumption of contaminated bread was limited by the onset of intoxication in its severe form. This onset corresponded to a shorter exposure period and a lower blood mercury concentration in the methylmercury than in the ethylmercury epidemic.

In another study of fatal ethylmercury intoxication of occupational origin, no blood mercury was estimated in the patient. Mercury analysis of liver and kidney samples showed higher mercury concentrations (Hay et al., 1963) than the two victims of dietary ethylmercury intoxication in Iraq (Hilmy et al., 1975), and it seems reasonable to assume that the patient also had higher blood mercury concentration.

Somewhat lower blood mercury concentrations were measured in an episode when the onset of the disease of a 15-year-old boy alarmed the family. He died without mercury estimation. His brother had the first mercury estimation just before he died. This was approximately 48 days after the end of their exposure. He had 5 $\mu\text{g/ml}$ blood mercury (Cinca et al., 1979) which corresponded to 10 $\mu\text{g/ml}$ at the end of exposure (assuming 50 days half-life).

Another young boy, who, during an 89 day period, was given 9000 ml human plasma, which included 450 mg Hg as thimerosal (average daily dose of 5.0 mg, or 0.16 mg Hg/kg). He died five days after the last infusion. He had 7 $\mu\text{g/ml}$ mercury in his blood (Suzuki et al., 1973). As the boy suffered from worsening protein-losing enteropathy, the contribution of ethylmercury to his death may have been important but not the sole etiological factor.

One problem with the evaluation of the responsibility of thimerosal for adverse outcomes is that the recipients were not healthy persons. Fagan et al., (1977) report on three infants whose omphaloceles were treated with 1% thimerosal tincture. The report did not give the clinical history, morbid anatomy, or whether the infant had sepsis. The authors wondered whether mercury levels found in necropsy “are acutely toxic or capable of producing chronic neurological damage in the new born infants?” One infant

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had 1.34 $\mu\text{g/ml}$ concentration in blood and 2.36 $\mu\text{g/g}$ in kidney tissue. Applying the blood:kidney ratio given by these values on the renal concentration of two other infants, who had no blood mercury estimation, the extrapolation gave 2.2 and 2.6 $\mu\text{g/g}$ blood mercury. Both the measured and the calculated concentrations are high, but because of the absence of data they can't be compared with methylmercury for this age group. Moreover all the three infants had 6.4, 3.2, and 6.8 hepatic : renal concentration ratios while the ratio in other fatally poisoned patients was 0.2 (see data from Hay et al., 1963), 0.8 and 0.7 (Hilmy et al., 1976), and 0.3 (Cinca et al., 1979). This may indicate that when omphaloceles was treated with thimerosal tincture, thimerosal sipped [sic] through the omphalocele membrane into the abdominal area of liver.

Sepsis was part of the clinical history of an 18-month old girl infant who had purulent otitis media with spontaneous perforations and external otitis. Tympanostomy tubes were inserted and irrigation with aqueous solution of 0.1% thimerosal, and 0.4% sodium borate was prescribed. It was realized only later that the irrigation solution drained through tympanostomy tube and was swallowed and thus the infant was given the total oral dose of 600 mg thimerosal (300 mg Hg) with 840 mg sodium borate. This dose can be compared with the maximum possible dose from vaccines: 187.5 μg in the first six months of life and 237 μg in the first 2 years of life (Ball et al., 2001). After 4 weeks irrigation she had ataxia, opisthotonic posturing, hand tremor, an inability to feed herself, and vomiting. Besides the possible toxic effects of thimerosal and borate, she had sepsis, Epstein-Barr virus, hepatitis, metabolic acidosis, high SGPT level, aminoaciduria, renal failure, hepatic failure, hypertension, and congestive heart failure, she needed tracheal intubation and mechanical ventilation. The first mercury estimation was made shortly after admission, and it gave 1.63 $\mu\text{g/ml}$ plasma (Rohyans et al., 1984). Concentration in whole blood had to be significantly higher. Though after methylmercury exposure red blood cells have about 20 times more mercury than plasma (Kershaw et al., 1980), the ratio was most likely less after exposure to ethylmercury. In a patient who received thimerosal infusion and who subsequently died, plasma contained 1.34 $\mu\text{g/ml}$ mercury and whole blood contained 7.0 $\mu\text{g/ml}$ mercury (Suzuki et al., 1973). The same total mercury to plasma mercury ratio would give 8.9 $\mu\text{g Hg/ml}$ in whole blood of the infant patient who died after a recovery period.

In a family of the two boys who died from ethylmercury intoxication (see above), two female members succumbed to ethylmercury intoxication. The mother had slight bilateral deafness, ataxia, weakness, spastic paraparesis, hypaesthesia, and constricted visual field. She became confused and delirious. Her daughter had staccato speech, ataxia, and spastic quadriparesis. Both recovered, but retained constricted visual field. The first blood mercury estimation gave 1.0 $\mu\text{g/ml}$ for the mother and 3.0 $\mu\text{g/ml}$ for the daughter (Cinca et al., 1979) which corresponds to about 2 and 6 $\mu\text{g Hg/ml}$ at the time of the end of their exposure.

When intervention shortly follows the ingestion of a highly toxic single oral dose, recovery is possible. A patient survived the ingestion of 83 mg/kg thimerosal (41 mg Hg) and 14 $\mu\text{g/ml}$ blood mercury. Signs included renal tubular failure, delirium, coma, polyneuropathy and respiratory failure. Chelation therapy resulted in complete recovery (Pfab et al., 1996). This case demonstrated that the maximum blood mercury

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concentration is less important than the territory under the concentration curve. In animal experiments this rule has been proven for methylmercury (Magos et al., 1978).

In the lower blood mercury range the only neurological sign was hand tremor in three occupationally exposed workers. Their blood mercury concentration was 1.0, 1.51, and .72 $\mu\text{g/ml}$ (Katsunuma et al., 1963). In the Iraqi methylmercury epidemic, 47% of the patients had ataxia, 53% visual disturbances, and 24% dysarthria in the 1-2 $\mu\text{g/ml}$ blood mercury group. These rates even in the 0.5-1.0 group were 11%, 21% and 5%, respectively (Bakir et al., 1973).

When blood mercury concentration was 0.65 $\mu\text{g/ml}$ after occupational exposure (Katsunuma et al., 1963) or 0.55, 0.34, 0.18 or 0.15 $\mu\text{g/ml}$ after thimerosal given in infusion (Suzuki et al., 1973), no sign of intoxication was detected (Suzuki et al., 1973). The patient with 0.15 $\mu\text{g/ml}$ blood mercury concentration received a single dose of ethylmercury corresponding to 72 $\mu\text{g Hg/kg}$ (on the basis of nominal concentration in the infusion) or 46 $\mu\text{g Hg/kg}$ (based on estimated concentration in some batches of human plasma). Thus this adult received 2.8 to 4.5 times higher dose than 16 $\mu\text{g/kg}$ given to preterm infants in hepatitis B vaccine in the first 3 days of life. The blood mercury in preterm infants increased by the vaccine from the average of 0.5 to 7.36 ng/ml and in term infants from 0.04 to 2.24 ng/ml (Ball et al., 2001). Compared with the 0.15 $\mu\text{g/ml}$ in the patient mentioned above, these concentrations were 20 and 67 times lower.

QUESTION 3. What is thought to be currently the best hypothesis (if any) regarding the mechanism of neurotoxic mechanism of neurotoxicity of organic Hg?

Answer:

Unfortunately there is no answer. Chang (1996) suggested four “major thoughts” on the mechanism of actions. These “thoughts” have not reached the level of a hypothesis, and even less the level of “the best hypothesis”.

QUESTION 4. Have there been any studies, including animal studies, which have looked specifically at infant ethylmercury exposure and the effect on neurological development?

Answer:

No, it has not been studied.

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QUESTION 5. Is it an accurate statement that based on current evidence ethyl and methyl Hg are equally toxic?

Answer:

The opposite is true. At equal exposure the risk of neurotoxicity is higher from methylmercury than from ethylmercury, while the opposite is true for renotoxicity. There is no data, which suggest that chronic exposure to methylmercury in human population is renotoxic even in severe intoxication but both are neurotoxic to a different degree. This is true in human populations and in rats. That is why I was surprised to read in the review of Ball et al., (2001) who stated in connection with my experimental study (Magos et al., 1985) that “Neurotoxicity of ethyl and methylmercury was similar.” My report made it clear that the granular layer damage in the cerebellum was widespread only in methylmercury treated rats and ethylmercury was less toxic than the equimolar doses of methylmercury in the dorsal root ganglia or on coordination disorders. However, this difference in effects on the dorsal root ganglia and coordination disorders, but not in the cerebellar granular layer, disappeared when the molar dose of ethylmercury was increased by 1.2. Perhaps one must point out that the dorsal root ganglia do not have a protective barrier like the brain has.

QUESTION 6. Different studies have cited different “normal” mercury levels or levels at which human become symptomatic. Do you think there is enough known about ethyl Hg to predict the blood level at which a person may become symptomatic?

Answer:

There are differences between populations in their background level of blood mercury. You can find references in Table 9 of WHO (1990) . One cause of the variations which influences methylmercury intake and consequently blood mercury levels is fish consumption. Blood mercury level also depends on the number of amalgam surfaces in teeth. For methylmercury there are suggested intakes or blood mercury levels at which a person may become affected. It must be pointed out that these values are not observed values, but extrapolated with mathematical methods (models) from the observed dose-response relationship. No such dose-response relationship has been established for ethylmercury, and therefore a prediction to the lowest toxic exposure is limited to a simple statement: the lowest toxic dose (exposure) for ethylmercury must be higher than the lowest toxic dose for methylmercury.

The advantage in our knowledge for ethylmercury over methylmercury is the study in which measured doses of thimerosal were given intravenously to people to check the tolerance to ethylmercury. No such study has been done on methylmercury. In the thimerosal study no adverse effects were observed when single intravenous doses ranged from 1.6 to 4.8 mg Hg/kg. In the same study multiple doses were given within 3 to 17

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days and the total dose ranged from 3.4 to 15.1 mg Hg/kg. One of the patients, a 2 year-old boy, received four treatments within 17 days, one 1.7 mg Hg/kg, and three doses of 3.6 mg Hg/kg. A seven-year old girl received 5.0 Hg/kg and a second dose of 3.6 mg Hg/kg one week later. None of these patients showed ill effects (Powell and Jamieson, 1931). Though in some cases the observation periods were short, 12 people were observed more than 10 days, 9 were observed over 30 days, and three were observed 50, 53 and 62 days. Thus a seven-year-old girl was observed up to 62 days after the last injection (Powell and Janieson, 1931.)

QUESTION 7. Can you explain in some detail a statement from your 2001 review article in the Journal of Applied Toxicology (Magos, 2001) “Thus both kinetic and toxicological studies indicate that the relationship of dose and blood mercury concentration to the risk of intoxication established for methylmercury overestimates the risk of ethylmercury intoxication”?

Answer:

The summary of the answers to Question 1 and 2 includes the answer to this question, which can be elaborated here. When the two short chain alkylmercurials were given in identical doses, methylmercury treated rats had more mercury in the brain and less in kidneys than in ethylmercury treated rats. As brain and kidneys are the two targets, the finding indicated a difference between the dose response curves of the two alkylmercurials. When instead of dose, response frequencies are plotted against mercury in blood, this difference between the two alkylmercurials becomes even larger because blood retained from the less neurotoxic ethylmercury more than from the more neurotoxic methylmercury and this naturally affects the brain: blood mercury ratio. Ratios are shown on Table 4.

TABLE 4. Brain: blood mercury concentration ratios in rats after five daily oral doses (by gavage) of 8.0 mg Hg/kg b.w., given either as methyl- or ethylmercury. (Data were extracted from Magos et al., 1985)

		Brain: blood Hg conc. ratio.	
time after last treatment	sex	MeHg	EtHg
3 days	male	0.066	0.029
	female	0.089	0.023
10 days	male	0.078	0.028
	female	0.116	0.026

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Thus applying the relationship between blood and brain mercury established for methylmercury to blood mercury concentration after exposure to ethylmercury would overestimate brain mercury concentration more than two-fold.

Table 5 shows the kidney: blood mercury ratios in rats, a species which responds to ethylmercury with more renal damage and accumulate in their kidneys more mercury than methylmercury treated rats.

TABLE 5. Kidney: blood mercury concentration ratios in rats after five daily oral doses (by gavage) of 8.0 mg Hg/kg b.w., given either as methyl- or ethylmercury. (Data were extracted from Magos et al., 1985)

time after last treatment	sex	Kidney: blood Hg conc. ratio.	
		MeHg	EtHg
3 days	male	0.57	0.18
	female	0.51	0.21
10 days	male	0.66	0.43
	female	0.60	0.25

Table 5 shows that in spite of the higher kidney uptake of ethyl- than in methylmercury treated rats (see Table 3), the kidney: blood mercury concentration ratio was higher in methylmercury treated rats. The reason for this anomaly is that renal uptake in proportion of blood mercury concentration was lower in ethyl- than in methylmercury exposed rats. Consequently, the application the kidney: blood mercury ratio found in methylmercury exposed rats to the blood mercury of ethylmercury exposed rats would result in the overestimation of renal mercury concentration and consequently the risk of renal damage.

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