

**Contract No:**

This document was prepared in conjunction with work accomplished under Contract No. DE-AC09-08SR22470 with the U.S. Department of Energy (DOE) Office of Environmental Management (EM).

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# **Review of Potential Dimethyl Mercury Exposures**

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February 4, 2004

Submitted to the  
Westinghouse Savannah River Company

Contract Number AC37146T



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# **DIMETHYLMERCURY**

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## Background

Mercury is a persistent and ubiquitous metal that is toxic to humans and comes in several species. Those species which are of toxicological importance are:

Inorganic Hg	
elemental/metallic	Hg <sup>0</sup>
mercurous Hg	Hg <sup>1+</sup>
mercuric Hg	Hg <sup>2+</sup>
Organic Hg	
monomethyl mercury	MeHg
dimethyl mercury	DMHg
ethylmercury	EtHg
others	

The alkyl mercuries (includes methyl) are considered to be virulent neurotoxins because of their volatility, their ability to penetrate epithelial and blood-brain barriers and their persistence in the organism (Gosselin et al. 1984).

Methylmercury compounds are formed in aquatic and terrestrial environments from the methylation by organisms of metallic and mercuric mercury.

MeHg bioaccumulates in fish and is a major source of Hg and the primary source of organic mercury in the human population. In the methylation of MeHg to DMHg, which is relatively insoluble in water, the mercury escapes to the atmosphere (see Figure 1). Other major sources of mercury involving human populations include metallic mercury vapor from dental amalgams and inorganic mercury contamination of food (see Table 1).

It should be noted that if workers are monitored for methylmercury exposures, information on dental amalgams and fish consumption should be obtained. With regard to dental amalgams, it has been estimated by the World Health Organization (WHO) that 36 restored amalgam surfaces yield an exposure of 10-12 µg of elemental mercury per day.

For fish consumption, which is the primary source of MeHg, Table 2 (Environmental Protection Agency) shows the increasing levels of MeHg in hair (a biomarker of MeHg exposure) with increased fish consumption.

Also in Table 4, a study of New Jersey fish consumers (National Research Council) shows the percentile levels of average MeHg intake (µg/day). These two tables indicate the high variability of MeHg intake among individuals depending upon their diet.

**TABLE 1**

Estimated Daily Intake and Retention of Total Hg and Hg Compounds in the General Population ( $\mu\text{g}$  per day).

Exposure	Elemental Hg Vapor	Inorganic Hg	MeHg
Air	0.03	0.002	0.008
Food Sources			
Fish	0	0.6	1-6
Non-Fish	0	3.6	0
Drinking Water	0	0.05	0
Dental Amalgams	3.8-21	0	0
Total	3.9-21(3.1-17)*	4.3(0.3)*	1-6(1-6)*

\* Retention – 95% of MeHg intake, 80% of elemental Hg vapor & 7% of inorganic Hg

From: NRC, Toxicological Effects of Methylmercury pg. 57

**TABLE 2**

Mercury Concentration in Hair by Level of Fish Consumption

Fish Consumption	1/month	1/2 weeks	1/week	1/day
Concentration in hair (ppm)	1.4	1.9	2.5	11.6

**TABLE 3**

Mercury Concentration in Blood by Level of Fish Consumption

Fish Consumption	none	2/week	2-4/week
Concentration in blood ( $\mu\text{g/L}$ )	2.0	4.8	8.4

**TABLE 4**

MeHg Intake among New Jersey Fish Consumers

Population Percentile	50%	75%	90%	95%	99%
MeHg Intake ( $\mu\text{g/day}$ )	3.1	5.8	13.1	21.1	49.9

## Absorption and Distribution

Methylmercury is highly absorbed by both the oral or inhalation route (~95%). It is not clear, however, how easily MeHg is absorbed by the dermal route in liquid phase. In one guinea pig study the absorption rate was slow (6% after 5 hours) (IARC).

Dimethylmercury, on the other hand is highly absorbed by all routes including dermal. The high dermal absorption rate is based partly upon the findings of the DMHg poisoning of the Dartmouth chemist (Nirenberg NEJM 338:1672-6 1998). This observation may contribute to the additional concern about the toxicity of DMHg. Once absorbed,

*Dimethylmercury seems to behave toward animal tissue as a chemically and physically inert substance, until it is metabolized to an ionisable metabolite. This metabolite was concluded to be methyl mercury.* (Ostlund 1969 pg. 124)

Based upon these conclusions, DMHg should be treated toxicologically as its metabolite MeHg. The concern about fish consumption and the high neurotoxicity of MeHg has generated a large amount of research literature and scientific consensus reports (eg. NRC, WHO). This information on MeHg therefore provides ample information for assessing the health effects of DMHg.

A second important aspect of the comparison between DMHg and MeHg is that not all of the absorbed DMHg is retained while awaiting metabolic conversion to MeHg. In the experiments of Ostlund, mercury was administered by intravenous injection to mice both as MeHg and DMHg. Ostlund found that the majority (~80% to 90%) of the volatile DMHg was rapidly exhaled (Figure 2). This result also was found to be the case after exposure by inhalation. Figure 3 compares the long-term retention of MeHg and DMHg, respectively. After about 6 hours the DMHg retention curve resembled that of MeHg. This implies that the toxic effects of DMHg may be only 10% to 20% of that of MeHg. We do not know if this degree of reduction is also the case in humans. Therefore one cannot definitely conclude a reduction or increase in toxicity from one species to another. It does strongly suggest, however, that treating exposure to DMHg as being equivalent to exposure to MeHg is conservative and a 5 to 10 fold safety factor may thus be present.

MeHg distributes throughout the body (5% found in blood). It readily crosses the blood-brain barrier, as well as the placental barrier. MeHg slowly demethylates to mercuric Hg. Since mercuric Hg does not readily cross the blood-brain barrier, Hg will remain in the brain (10% of the exposure). MeHg is excreted primarily in the feces (90%) as mercuric Hg. The rate of excretion is estimated to be about 1% per day or a half-life of about 2 months. Figure 4 illustrates the

physiologically based pharmacological model description for methylmercury kinetics and Figure 5 shows the comparable results for inorganic mercury.

### **Toxicity**

Methylmercury is considered to be a supertoxic compound. This is based on the definition of supertoxic if the  $LD_{50} < 5$  mg/kg (Clarkson, 1972). Since a body burden of 400 mg is considered lethal (Nierenberg, 1998), MeHg would about achieve this value of 5 mg/kg.

The main aspects of MeHg toxicity (see WHO) are

1. long latent period (several months)
2. damage primarily limited to the nervous system (especially CNS)
3. damage to the brain is highly localized
4. effects in severe cases are irreversible
5. earliest effects are non-specific, such as paresthesia, blurred vision and malaise

The critical organ for MeHg toxicity is the brain (both adult and fetal). This is contrasted with elemental mercury where the brain and the kidneys are targets. Both elemental Hg and MeHg cross the blood-brain barrier and are converted to mercuric mercury, which traps the mercury. The critical organ for mercuric mercury is the kidney, where it accumulates (NRC).

There are new studies suggesting that both the cardiovascular and immune systems might be important sites for MeHg toxicity (NRC).

A number of human studies involving exposure to a variety of mercury species have shown to increase blood pressure, as well as heart rate. Also, irregular heart rates have been observed (NRC). In a prospective cohort study of 1833 men in Finland (Salonen 1995) there was observed after seven years of follow-up a two-fold higher risk of acute myocardial infarction (AMI), as well as coronary and cardiovascular deaths among the highest tertile. The range of Hg in hair was 0 to 16 ppm with a mean of 1.9 ppm. Recently two large case control studies of myocardial infarction and MeHg body burdens were reported (Guallar et al. '02 and Yoshizawa et al. '02). These studies used mercury levels in toenails as their biomarker and measure of MeHg intake. The level of mercury in toenails is about 1/3 that found in hair. Also one may obtain exposure information further back in time compared with scalp hair due to the relative slow growth of toenails. The mercury levels were found in these studies to correlate well with reported fish consumption. The study in the U.S. (Yoshizawa '02) did not find the risk of coronary heart disease to be associated with mercury levels. The study did find a good correlation between mercury in toenails and reported daily fish consumption (see Table 5). On the other hand, the European study (Guallar '02) did find an association with myocardial infarction cases observed to

have a 15% higher level of mercury than controls. Although the question remains open it should be noted that the high MeHg exposures in Minamata did not increase coronary heart disease among the exposed people.

**TABLE 5**

Concentration of mercury in Toenails (quintile) and median level of daily Fish Consumption

Hg in Toenails (ppm)	0.29	0.34	0.44	0.62	0.75
Daily Fish Consumption (g)	20.7	26.1	30.4	37.2	51.0

Data from Yoshizawa et al 2002.

The effect of MeHg on the human immune system has not been studied. Some occupational exposures to elemental Hg have been shown to alter immune system parameters. In one study, workers exposed to  $2.8 \mu\text{g}/\text{m}^3$  (metallic Hg) workplace air with urinary Hg (0 to  $240 \mu\text{g}/\text{L}$ ) had increased T-cells, T-helper cells and T-suppressor cells. Animal studies have shown effects on the immune system after exposure to MeHg.

Although the kidney is sensitive to metallic Hg, it has rarely been reported to have been affected by organic mercury. In those cases where it has been reported, there was severe poisoning with neurological symptoms also present.

IARC has classified MeHg as a possible human carcinogen based upon several mouse studies in which male mice had increased kidney cancer at the high doses. It was pointed out, however, that the effect was seen only at doses that were toxic to the kidney and the cancer was likely to be secondary to the kidney toxicity. The effect was not seen in female mice, nor in rats of either sex.

The fetal nervous system is used by EPA for environmental standard settings of MeHg limits because of its extreme sensitivity. For the worker, however, adult CNS toxicity studies are the most relevant. Minamata studies showed a number of neurological effects in adults, many evident after 20 years since exposure. WHO estimated that 5% of adults with a blood concentration of  $200 \mu\text{g}/\text{L}$  (corresponding hair concentration is 50 ppm) would manifest paresthesia. It has been argued that the WHO value of 5% is low and the level should be between  $20 \mu\text{g}/\text{L}$  and  $200 \mu\text{g}/\text{L}$ . WHO concludes that intake of  $0.48 \mu\text{g MeHg}/\text{kg}/\text{day}$  will not result in any detectable adverse effects. A daily intake of  $3\text{--}7 \mu\text{g}/\text{kg}/\text{day}$  ( $50\text{--}125 \mu\text{g}/\text{g}$  hair) would cause adverse effects of the nervous system with about a 5% increase in the incidence of paresthesia. For the fetus, which is at particularly high risk, the WHO suggests that a 5% risk may be associated with a peak mercury level of 10 to 20 ppm in the maternal hair.



There has been a mortality study of DOE workers exposed to elemental mercury vapors at the Y-12 plant of the Oak Ridge facility. There were 2,133 workers exposed between 1953 and 1963, and were followed through 1978. Death certificates were obtained on 371 of the workers. During the early 1950's, the majority of air samples collected for tasks involving mercury exceeded the  $0.01\text{mg}/\text{m}^3$  level. The mercury workers were compared to 3,260 non-mercury workers with regard to mortality outcome. No mortality differences were observed. Actually, the non-mercury workers had increased brain and other CNS cancer deaths ( $\text{SMR} = 2.3$ ). There also was no difference in causes of mortality among those workers whose urine levels exceeded the "plant action value" of  $0.3\text{mg}/\text{L}$ . Those workers whose value exceeded  $0.6\text{mg}/\text{L}$  were reassigned to other duties (Cragle, 1984).

### Occupational Exposure Limits

The ACGIH has established for an eight hour TWA occupational exposure a TLV (threshold limit value) for alkyl mercury compounds to be  $10\text{ }\mu\text{g}/\text{m}^3$  and a STEL (short term (15 minute) exposure limit) for alkyl mercury compounds of  $30\text{ }\mu\text{g}/\text{m}^3$ . These values also agree with NIOSH's recommendations. Most other countries use these ACGIH recommended values (IARC).

The regulatory values set by OSHA (as of 07/28/2003) for mercury alkyl compounds are  $10\text{ }\mu\text{g}/\text{m}^3$  for 8-hour TWA and a ceiling value of  $40\text{ }\mu\text{g}/\text{m}^3$  (see Figure 6).

The EPA default value for human occupational volume of air inhaled during an 8 hour shift is  $10\text{ m}^3$ . This implies that a worker at the TWA exposure value of  $10\text{ }\mu\text{g}/\text{m}^3$  would take in a daily average of  $0.97\text{ }\mu\text{g}/\text{kg}/\text{day}$  of mercury.

Assuming 95% absorption and a 70 kg man;

$$0.97\text{ }\mu\text{g}/\text{kg}/\text{day} = (10\text{ }\mu\text{g}/\text{m}^3) (10\text{ m}^3) (5/7) (0.95) / 70\text{ kg}$$

Now the concentration of MeHg in blood is given by (see pg 87 NRC and EPA pg 5-17)

$$C = \frac{D \times W \times A \times F}{B \times V}$$

D = absorbed dose  $\mu\text{g}/\text{kg}/\text{day}$

W = body weight (70 kg)

A = fraction of ingested MeHg that is absorbed (0.95)

F = fraction absorbed that is in blood (0.05)

b = elimination rate constant (0.014)

V = blood volume (5)

Thus for 0.97 µg/kg/day MeHg absorption we would have

$$C = \frac{(0.97) (70) (0.95) (0.05)}{(0.014) (5)} = 46 \text{ µg/L MeHg in blood.}$$

To convert this to µg/g MeHg in hair, we have the accepted ratio of

$$\text{µg MeHg/g hair to mg MeHg/L blood} = 250.$$

Therefore, 46 µg MeHg/L blood is equivalent to 11.5 µg MeHg/g hair. A blood level of 46 µg/L will correspond to a body burden of 4.6 mg MeHg. Using a 1% daily excretion rate with 10% in urine and about 1.3 L urine per day we expect to measure about 3.5 µg/L mercury in urine.

In summary, we have for MeHg

TABLE 6

		Background*
TLV (8 hr TWA)	10 µg/m <sup>3</sup>	
Absorption	1.0 µg/kg/day	
Blood concentration	46 µg/L	8 µg/L
Hair concentration	11.5 µg/g	2 µg/g
Body burden	4.6 mg	
Urine level	3.5 µg/L	4 µg/L

These levels are in addition to general population background levels.

\*Reference values for mercury in the general population are whole blood: 8 µg/L, scalp hair: 2 µg/g and urine: 4 µg/L (WHO 1990 pg. 15).

For DMHg the absorption and thus the blood concentration and the hair concentration could be considerably less than the MeHg values as previously discussed.

Dermal absorption is believed to be high (>90%) for organic mercury as contrasted to elemental and inorganic mercury in liquid phase. The EPA, in calculating body burdens from inhalation, does not explicitly consider dermal absorption. For elemental mercury vapors, a human study (Hursh et al., 1989) suggests that dermal exposure from vapor phase could contribute an additional 1% - 2.2% of the pulmonary absorption and thus a minor addition to the total dose. (WHO reports 1% and ACGIH reports 2.2%.) These values of 1% to 2.2% assume the total body is exposed to the vapor. It is not clear whether the rate of dermal absorption of vapor phase organic mercuries compared with inorganic

mercury would be the same or possibly higher as with the liquid phase. It is safe to say that the body burden would be increased slightly from the dermal route.

It is remarkable that the value of 11.5 ppm for hair concentration from Table 6 is essentially the same as the value given in Table 2 for a diet of daily fish consumption.

Finally, it is instructive to compare the blood and urine mercury concentration levels for elemental mercury and methylmercury at the same occupational exposure level. Table 7 repeats the values for MeHg from Table 6 and includes the corresponding values for elemental mercury vapor (see WHO 1991 pg. 63). These values show the relatively high values for mercury concentrations in blood from MeHg and the reverse for mercury in urine.

TABLE 7

	MeHg	elemental Hg vapor
TLV (8 hr TWA)	10 $\mu\text{g}/\text{m}^3$	10 $\mu\text{g}/\text{m}^3$
Blood concentration	46 $\mu\text{g}/\text{L}$	5 $\mu\text{g}/\text{L}$
Urine level	3.5 $\mu\text{g}/\text{L}$	30 $\mu\text{g}/\text{L}$

#### Risk Estimates

Adverse health effects for MeHg are driven by neurotoxicity. The most sensitive site is the developing fetal brain. For the worker, however, it is useful to know the doses associated with adult CNS effects.

These neurological effects are believed to have thresholds, and thus agencies such as the EPA will calculate either a reference concentration (RfC) for inhalation or a reference dose (RfD) for ingestion. These values are determined by using an appropriate LOAEL (lowest observed adverse effect level) or a NOAEL (no observed adverse effect level) divided by uncertainty factors. For MeHg only an RfD has been calculated since it is assumed that diet is the only meaningful source of MeHg in the general populace. Using developmental outcome data, EPA estimates a LOAEL for MeHg to be: 3  $\mu\text{g}/\text{kg}/\text{day}$  (300  $\mu\text{g}/\text{L}$  blood). They further use an uncertainty factor to obtain their RfD of 0.3  $\mu\text{g}/\text{kg}/\text{day}$  (ATSDR's minimal risk level is also 0.3  $\mu\text{g}/\text{kg}/\text{day}$ ).

A newer approach used by the EPA is the benchmark dose (BMD). This approach uses all the data and estimates a dose for which there is either a 1%, 5% or 10% increase in background effect. The choice of the percentage increase over background is arbitrary and usually depends upon the amount of available toxicological data. Next, a lower 95% confidence bound on the BMD estimate is used to insure that most individuals would not be affected at the estimated dose. Again, using developmental outcomes, the NRC gave a BMD estimate of 21 ppm in maternal hair with a lower bound of 8 ppm. (EPA's BMD is

1.1  $\mu\text{g/kg/day}$ , which has been used to obtain a new RfD of 0.1  $\mu\text{g/kg/day}$ ). For neurological effects in adults (eg. paresthesia), it has been estimated that 50 ppm in hair or 200  $\mu\text{g/L}$  in blood is a no effect level for MeHg (WHO, Clarkson '97).

The WHO expert group did mention that data collected from a number of published studies identified over 100 people who had blood levels over 200  $\mu\text{g/L}$  without any adverse effects (Clarkson '97). These negative data are consistent with a maximum risk for paresthesia of about 3% (WHO 1990 pg. 84). Figure 5 (from WHO) shows the adult neurological dose-responses for body burdens of MeHg (note: a 25 – 40 mg body burden corresponds to 250 – 400  $\mu\text{g/L}$  MeHg in blood).

It has, however, been recommended by the NRC that this value may not be sufficiently protective. The WHO gave values of 10 to 20 ppm in maternal hair and 40 to 80 ppb in maternal blood for a level protective for the developing fetus.

Comparing these risk values with the worker TLV value of 10  $\mu\text{g/m}^3$  we see that a worker continually exposed at the TLV value will have a blood level less than  $\frac{1}{4}$  (i.e. 46  $\mu\text{g/L}$ ) that of the suggested 200  $\mu\text{g/L}$  level as an administrative limit for adult neurological effects.

Gosselin (1984) states that the effects of MeHg are critically dependent on dose (i.e. steep dose-response curves as shown in Figure 7). Paresthesia (the most sensitive effect) occurs at a body burden of about 40 mg while death occurs at levels greater than 200 mg.

It is generally accepted (NRC) that blood and scalp hair are the appropriate sources for MeHg exposure assessment. Methylmercury is readily accumulated by scalp hair. The concentration ratio of methylmercury between hair and blood is about 250 to 1. Methylmercury makes up about 85% of the mercury in hair with the remainder being inorganic mercury. The total mercury in hair correlates well with methylmercury in blood. It may be that some of the methylmercury entering the hair is broken down into inorganic mercury (Clarkson '97). Therefore, total mercury measured in hair is a good marker for exposure to MeHg. There are of course numerous practical difficulties with the use of scalp hair in routine human monitoring. These problems include availability of scalp hair and variability of hair growth and external exposure to agents (both mercury and others that confound mercury hair analysis), sample handling and access to qualified laboratories.

The limit of detection for total Hg in hair is in the range of 0.01 to 0.04  $\mu\text{g/g}$ . The general populace with little or no fish consumption has values in the range of 0.2 to 0.8  $\mu\text{g/g}$  (NRC). Since hair grows at the rate of about 0.6 to 1.5 cm/month, past total mercury exposures can potentially be measured.

The use of gas chromatography permits the measurement of MeHg. Also, atomic absorption spectrometry measures total mercury and can estimate organic mercury through subtraction of inorganic mercury from total mercury (EPA). The limit of detection for total Hg in blood is about 0.1 to 0.3 µg/L (NRC). The mean blood Hg concentration in populations with little or no fish consumption is about 2 µg/L.

For workers with irregular exposures to MeHg, recent exposures will result in peaks in blood Hg concentrations. A single blood sample showing increased concentration does not necessarily provide a temporal perspective. Conversely, a sample obtained between peak exposures separated by many months showing a low level of Hg in blood provides no evidence of the peak exposures. However, the half-life of total MeHg in blood is about 50 days and thus blood samples provide data on exposures received in the last several months (NRC) (note: Clarkson suggests the half-life to be about 70 days.). Because of the relatively high level concentrations in blood of MeHg compared with background levels, exposures at the TLV level should still be measurable after several half-lives or many months. For example, if the body burden was at the 4.6 mg level (Table 6) then the blood level would still be twice the reference background level (8 µg/L) after 4 months since cessation of exposure.

In Table 7 the relatively high values in urine shows why urine is the typical material to measure after elemental mercury vapor exposures. A second issue is that the elimination of inorganic mercury is complicated with different half-lives depending upon the tissue. For blood there is a first phase of elimination with a half life of 2-4 days which accounts for about 90% of the mercury in blood. The second phase half-life is about 15 to 30 days. This is compared to a whole body and kidney half-life of about 64 days. Thus blood is not a good source of exposure information from acute inorganic mercury exposures (see WHO 1991 pg. 59). Methylmercury on the other hand is rapidly distributed through the body and the decline in MeHg levels in different body parts is at about the same rate (see Clarkson 1972). The concentration of MeHg in blood (red cells) is simple first order kinetics and has essentially the same half-life as in the whole body (50-70 days). Therefore, for methylmercury exposure, blood serves as the most sensitive biomarker, due to the high initial methylmercury concentration and a long biological half life.

### **SRS Biomarker Measurements**

Data on total Hg in biological samples for 85 workers have been made during the period 06/22/2001 to 06/03/2003. Also, eight workers had repeat measures.

**TABLE 8****Number of Workers Tested**

<u>Period</u>	<u>Blood Total Hg</u>	<u>Urine Total Hg</u>
6 to 12/2001	8 (3)*	9 (3)
6 to 8/2002	0	35
11 to 12/2002	3	16 (3)
2 to 6/2003	1	25 (2)
<b>TOTAL:</b>	<b>12 (3)</b>	<b>85 (8)</b>
*repeat measure		

Although the urine Hg values were carried out, they give little or no indication of possible MeHg exposure. The reason is, as discussed previously, only about 1% of MeHg is excreted per day and about 10% of this is in the urine. This gives only about 0.1% of the body's MeHg burden excreted per day in urine. The contribution from a continual exposure to the TLV level of  $10 \mu\text{g}/\text{m}^3$  would be about 2.6 to 5.8  $\mu\text{g}/\text{L}$  in urine (assuming 0.8 to 1.8 L total urine production per day) compared with 46  $\mu\text{g}/\text{L}$  in blood (see Table 6). None-the-less MeHg exposures at the TLV level would approximately double the reference levels expected in urine (WHO reference value is 4  $\mu\text{g}/\text{L}$  for Hg in urine. see pg 15 WHO 1990). Also for screening workers it is not obvious that DMHg is the only species of mercury present. Urine provides a relatively easy marker for assessing total mercury exposure.

Mercury urine values for the workers were all within the normal range (WHO). The reported values were:

**TABLE 9****Total Mercury Concentration (urine)**

<u><math>\mu\text{g}/\text{L}</math></u>	<u>Number of workers</u>
0	63
1	5
2	9
3	6
4	2

The CDC reported in one study of 1748 women age 18 – 49 a distribution of urine levels

**TABLE 10**

**Total Mercury Concentration (urine)**

<u>Percentile</u>	<u>µg /L</u>
50%	0.8
75%	1.6
90%	3.2
95%	5.0

This distribution is in good agreement with the SRS worker values.

The total Hg blood values, which are more relevant to MeHg exposure, also appear to be within normal limits.

Of the 12 individuals measured, 5 were given a value of zero (i.e. <1 µg/L) with the other values as follows:

**TABLE 11**

**Total Mercury Concentration (blood)**

<u>µg/L</u>
1.0, 1.1, 1.6*
3.0
4.2, 5.1
11.4

\*This individual had a repeated measurement of 1.5 and 2 individuals with a value of zero were remeasured and again had values of zero.

The CDC distribution among women was as follows:

**TABLE 12**

**Total Mercury Concentration (blood)**

<u>Percentile in CDC cohort</u>	<u>µg /L</u>
50%	0.9
75%	2.0
90%	4.9
95%	7.1

The highest measured value among the SRS workers was one individual with a blood concentration value of 11.4 µg/L. This value would correspond to only ¼ the level expected from continual exposure at the TLV level (46 µg/L). This assumes no background (eg. fish, amalgams, etc.) exposure. A frequent fish consumer would report a blood concentration at about this level. Further the worker reported a urine level of only 1 µg/L which is well below the WHO reference level of 4 µg/L.

Therefore, the biomarker measurements of the 85 workers are consistent with what one would expect to observe in a non-occupationally exposed adult population.

### **Exposures**

It does not seem possible to reconstruct the actual exposures to DMHg that individual workers may have received. From the sampling that has been carried out, there is a very wide range of measured concentrations depending upon exactly where samples were taken (eg. sumps, HEPA filters, overhead samples). With engineering improvements, the DMHg levels have been reduced at their source.

Crude overestimated exposures may be possible to make. For example, a worse case estimate suggested by SRS has shown that because of limited worker exposure time, an overestimated concentration of 0.04 mg/m<sup>3</sup> on the service floor becomes an effective exposure of 0.008 mg/m<sup>3</sup>, which is within the PEL-TWA value of 0.01 mg/m<sup>3</sup> (this assumes 20% exposure per day). The issue is whether the 0.04 mg/m<sup>3</sup> value (OSHA limit) is a realistic upper bound. It seems reasonable to conclude that those locations (eg. sump, overhead, etc.) where excessive exposures occurred are not the normal breathing zone of the worker as specified by OSHA. The measurements did, however, identify sources of the contamination in the evaporators.



Measured DMHg values have not been high other than at a few places such as the overhead receiver pump. Maximum values such as  $165 \mu\text{g}/\text{m}^3$ ,  $> 84 \mu\text{g}/\text{m}^3$ ,  $138 \mu\text{g}/\text{m}^3$ ,  $>175 \mu\text{g}/\text{m}^3$  (estimated to be  $350 \mu\text{g}/\text{m}^3$ ) etc. have been measured at particular sites. A body burden of 30 mg would begin to exhibit neurological effects. This would correspond to an 8 hour TWA of about  $65 \mu\text{g}/\text{m}^3$  over a year's time. After three months' exposure, the body burden would be about  $\frac{1}{2}$  or 15 mg (see Clarkson 1972). Thus we see that for the occurrence of neurological effects, a worker would need to be continually exposed at these values for a long period of time. Also, these extreme values are not ones in the normal breathing zone of the worker. From the limited biomarker measurements, the workers clearly did not experience the high environmental levels for a significant period of time. Finally, as an example, if a worker were continually exposed at the highest recorded exposure level of  $350 \mu\text{g}/\text{m}^3$  it would take 15 hours to achieve the same body burden as a continual exposure at the TLV level of  $10 \mu\text{g}/\text{m}^3$ . (Note: From Table 6, a  $10 \mu\text{g}/\text{m}^3$  8 Hour Time Weighted Average work exposure corresponds to a daily dose of  $1.0 \mu\text{g}/\text{kg}$ . Therefore an exposure of  $350 \mu\text{g}/\text{m}^3$  corresponds to a dose of  $(35 \times 70) / (8 \times 1000) = 0.31 \text{ mg/hr}$  for the standard 70 kg man. It would thus take 15 hours ( $4.6 / 0.31$ ) at an exposure level of  $350 \mu\text{g}/\text{m}^3$  to achieve the body burden level of 4.6 mg found in Table 6).

The preference for blood when the concern is MeHg exposure is that the estimated concentrations in blood and urine for a continual exposure at the TLV level compared to the reference values of WHO is that the blood level is a factor of about 7 fold (i.e.  $(46 \mu\text{g}/\text{L} + 8 \mu\text{g}/\text{L}) / 8 \mu\text{g}/\text{L}$ ) while for urine the factor is about 2 fold (i.e.  $(3.5 \mu\text{g}/\text{L} + 4 \mu\text{g}/\text{L}) / 4 \mu\text{g}/\text{L}$ ) (see Table 6). Thus, for biological measures of MeHg exposure, blood and hair are the best materials for analysis. As explained previously, only about 0.1% of the body's MeHg burden will be excreted per day. Although there is a considerable variability in scalp hair growth, hair selectively provides levels of MeHg. It further provides an exposure history. If past MeHg exposures of a year or more are required, then toenail analysis provides an option (Yoshizawa et al. 2002). MeHg concentration in toenails is about  $\frac{1}{3}$  that of scalp hair (Plante et al. 2003). Although toenail clippings have recently been used in very large epidemiological studies of coronary heart disease and methyl mercury intake (Yoshizawa et al. 2002 & Guallar et al. 2002) there has been no recommendation that nail clippings would be appropriate for medical surveillance. In carrying out any biological measurements, background information concerning fish consumption and numbers of amalgams should also be collected.

For biological effect measures, the focus of MeHg is neurological. Although renal effects have been observed, they occur at high doses with neurological effects also present. Medical screening of exposed workers would include an exam of the nervous system including visual field and hearing.

If there is evidence that workers are being occupationally exposed to MeHg near the recommended TLV level they should probably be screened for MeHg exposures. This screening should include both periodic medical screening and blood analysis. If accidental exposure events or above-normal blood levels are found, then scalp hair analysis should also be considered.

SRS has focused on controlling MeHg exposures through engineering solutions. The proper approach is to control worker exposures instead of monitoring biomarker levels as a substitute.

### Conclusions

1. Dimethyl mercury is converted in the body to monomethyl mercury and should be considered toxicologically the same as MeHg. Because of lower retention, exposure to DMHg is likely less toxic than an equivalent exposure to MeHg.
2. The major health risk from MeHg exposure is neurological, with renal damage also a possibility. Possible cardiovascular effects are unlikely but uncertain.
3. The TLV of  $10 \mu\text{g}/\text{m}^3$  for MeHg is a reasonable limit resulting in a maximum daily intake of approximately  $1 \mu\text{g}/\text{kg}$ .
4. Biological monitoring of blood and hair are reasonable procedures for assessing MeHg intake. Background levels from amalgams and diet need to be considered.
5. The measurement of Hg in urine and blood of potentially exposed SRS workers suggests that occupational exposures of any health significance have not occurred. It is not known whether all of the potentially exposed workers were measured for mercury levels. The biological sample analyses which have been carried out suggest that it is highly unlikely that there are any workers that had biologically measurable exposures to DMHg.
6. The SRS approach of providing engineering solutions is the appropriate one. This provides the best protection for the worker as contrasted with simply monitoring the worker for mercury exposure and possible adverse health effects.
7. The measurements of mercury concentrations in the blood and urine of the SRS workers and the relatively high threshold values for neurological

effects means that the potentially exposed SRS workers are very unlikely to be at increased health risks.

8. Since a) there is not any evidence of mercury body burdens in excess of normal background levels, b) the number of potentially exposed workers is small and c) adverse neurological effects with variable baseline rates occur at relatively high levels of exposure, there is no scientific justification for carrying out an epidemiological study.
9. Based on the measured concentrations of DMHg being reported, and the improvements in reducing identified mercury emission points as well as the normal measured mercury levels in workers, it is not necessary that a medical surveillance program be required for workers. In the event that Industrial Hygiene determines sufficient task exposures may exceed the applicable limits, then personnel should be provided with blood and urine assays for mercury.

### **Recommendations**

1. If the anticipated occupational exposures are expected to be approximately at or above the TLV level of  $10 \mu\text{g MeHg/m}^3 \text{ TWA}$ , then the following precautions should be taken.
  - a) Consideration should be given to restricting workers who are especially at risk from mercury exposure. These workers would include women of childbearing age and potential, workers with neurological or renal problems, and workers with an especially high background level of mercury exposure from dental amalgams, fish consumption and other factors. For workers with renal or neurological problems the occupational physician should determine the potential health risks from anticipated DMHg exposures to the worker.
  - b) For workers who will be potentially exposed to mercury, background information should be collected including biomarkers of exposures, as well as renal functions and neurological testing. This would include both blood and urine concentrations in order to provide baseline levels of total mercury as well as an indication of the background level of methyl mercury.
  - c) If it is anticipated that worker exposures to mercury will continue, then periodic (once or twice a year) assessments of mercury blood levels should be carried out. If the levels are higher than the expected baseline plus levels from exposure at the TLV level, then hair sampling, as well as neurological testing should be performed.

For neurological testing, the most sensitive endpoints to mercury exposures should be determined by the occupational health physicians at the SRS.

2. Environmental sampling of DMHg levels at breathing zone levels should be made. The frequency should be determined by the confidence the industrial hygiene experts have in the likelihood of concentrations of DMHg being at or near the TLV level. If excursions of high concentrations take place, any potentially exposed workers should be tested for Hg body burdens as soon as possible.

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## **Attachment A**

1. Has the prioritization of energies by the WSRC team been appropriate in minimizing the exposures to workers (diagnostics versus medical surveillance enrollment)?

**Answer:**

The priority in my opinion is to immediately identify the exposure sources and both control them while minimizing worker exposure to them. Although measured concentrations exceeded acceptable limits it was understood that because of limited contact the worker was unlikely to be highly exposed (i.e. exceed TLV/TWA levels). This was confirmed by the early biomarker measurements carried out in June through December of 2001.

2. If we can get to exposure minimization through engineering solutions, primarily ventilation, should WSRC pursue real time monitoring capability?

**Answer:**

Real time occupational monitoring is generally an asset. The question is how feasible and at what cost for DMHg. Once the engineering solutions are completed, it should be possible to determine the possible ranges of occupational exposures. The amount and frequency of environmental monitoring should depend on the likelihood of exceeding acceptable exposure levels. It should be noted that the toxic effects of DMHg are delayed and cumulative (body burden of converted inorganic mercury in the brain).

3. Whether or not WSRC can minimize exposure, should WSRC pursue development of organic mercury biological monitoring capability (fecal sampling program)?

**Answer:**

Biomonitoring of DMHg should be restricted to blood samples and possibly hair samples to identify past exposure episodes. Although the fecal route is the main excretion route, there is little experience with this marker of exposure.

The half-life of methyl mercury in blood is about the same as the half-life of methylmercury in the body. Therefore, the blood biomarker with the experience of its use should be preferable to fecal analysis.

4. Can you explain the historical perspective on the variety of organizations and their criteria for DMHg:
- a. Ceiling limit defense for OSHA's value (cannot locate)
  - b. BEI for elemental as referenced in organic TLV (and excluded from the BEI)

**Answer:**

Not much attention has been focused on DMHg because it has been considered to be a laboratory chemical and not of concern either environmentally or occupationally. Fortunately, the mouse studies of Ostland have shown that it is converted to MeHg and can be treated toxicologically the same, including absorption. MeHg is of concern environmentally mainly because elemental mercury is converted to MeHg by microorganisms and bioaccumulates in fish and because it is able to penetrate the blood-brain barrier. Occupationally, methylmercury has been used as a wood preservative and a fungicide. It was the material present in the Iraq grain-poisoning episode.

ACGIH reports that based on industrial experience, Ahlmark suggested in 1948 a limit of  $10 \mu\text{g}/\text{m}^3$ . In 1970 the ACGIH essentially agreed by proposing the current TLV-TWA occupational level of  $10 \mu\text{g}/\text{m}^3$  for alkyl compounds.

In the study of Dinman et al. (1958) symptoms were not seen with air concentrations between 10 and  $100 \mu\text{g}/\text{m}^3$ . Most countries seem to have adopted the ACGIH levels for both organic and inorganic ( $50 \mu\text{g}/\text{m}^3$ ) mercury. This includes NIOSH and OSHA. I found no information as to the reasoning behind the STEL level ( $30 \mu\text{g}/\text{m}^3$ ) adopted by ACGIH nor the OSHA ceiling of  $40 \mu\text{g}/\text{m}^3$ . The values may simply be arbitrary safety factors applied to the TWA value.

I have no explanation why ACGIH refers to BEI values in their organic report, but only produce them for inorganic mercury.

5. Can you recommend any toxicological expertise we can call upon?

**Answer:**

Dr. Thomas Clarkson at the University of Rochester is the US authority.

6. Would you recommend a retrospective epidemiological study (consequences of unknown DMHg exposure profile)?

**Answer:**

With regard to epidemiological studies, one needs both sufficient numbers of individuals and increased effects. The Oak Ridge mortality study had large numbers of individuals and high doses (i.e. 858 employees with 134 deaths with urine levels greater than 300 µg/L) but showed no increase in mortality among the highly exposed mercury workers. This is contrasted with the 4 µg/L or less urine levels for the 85 SRS workers. Neurological effects (eg. paresthesia) are estimated to begin occurring at body burden levels of 25 – 40 mg with hearing losses occurring at even higher levels. Without some indication of body burdens greater than the general public, there is no likelihood of seeing increased effects due to DMHg exposure. Therefore an epidemiological study would not be of scientific interest. A retrospective study could be developed but it would be primarily for administrative purposes.

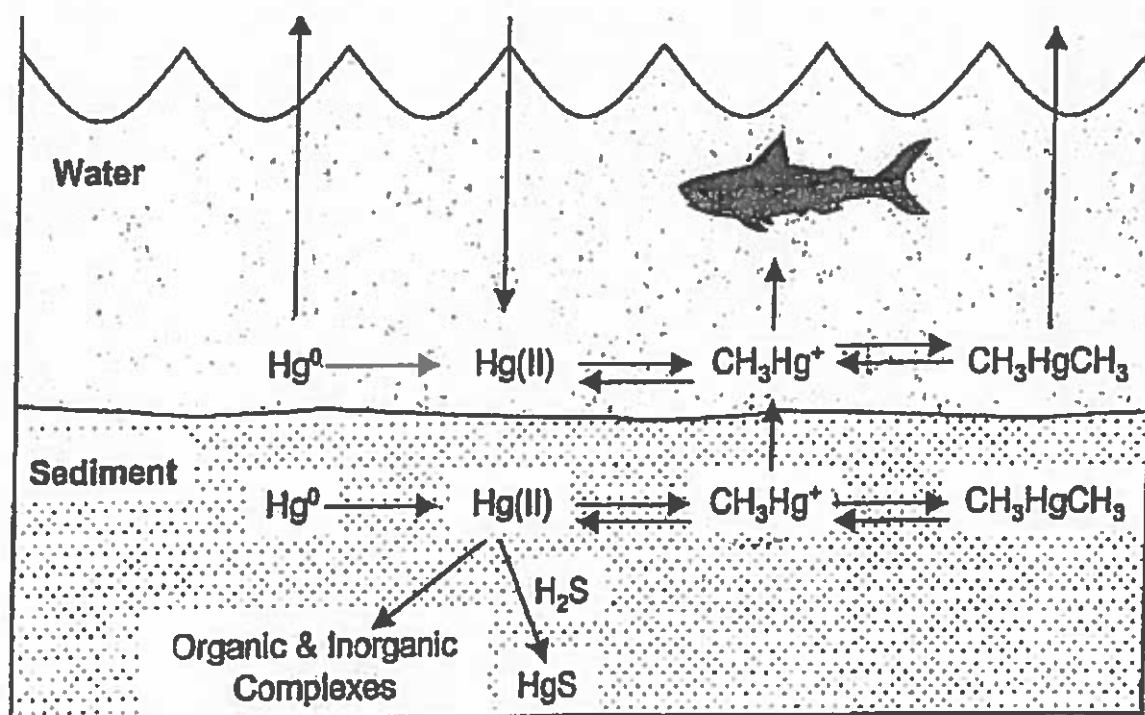
7. Would you recommend a prospective epidemiological study (consequences of Hg species exposure at low levels and fetal/employee hearing loss)?

**Answer:**

The answer to this question is the same as the answer to the previous question. If there had been exposures large enough to produce early neurological effects those effects should now be measurable. There is even less reason for doing a prospective study than a retrospective study.



Figure 1

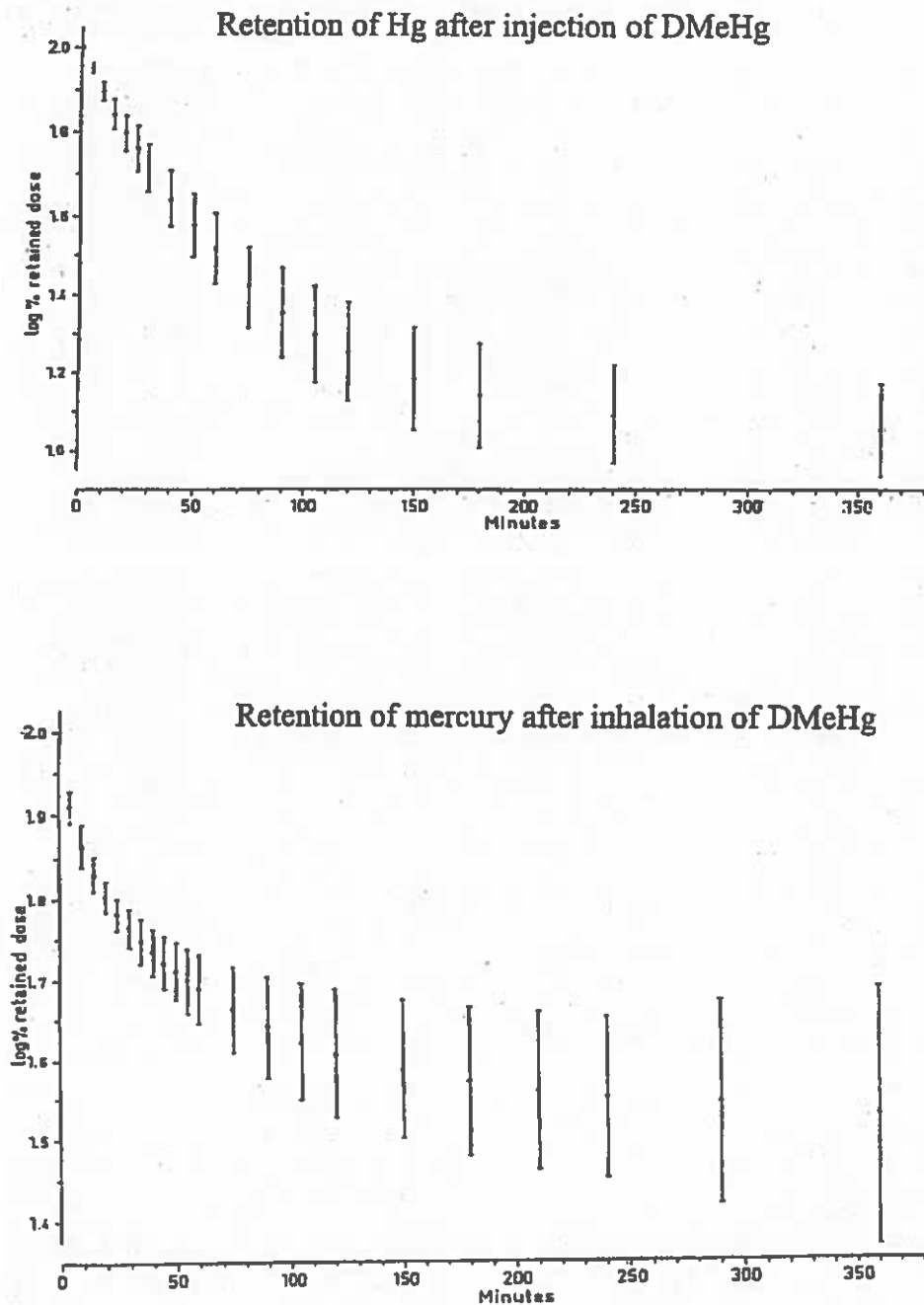


Cycling of Hg in aquatic system.  $\text{CH}_3\text{Hg}^+$ , methylmercury ion;  $\text{CH}_3\text{HgCH}_3$ , dimethylmercury;  $\text{Hg(II)}$ , mercuric mercury;  $\text{Hg}^0$ , elemental mercury;  $\text{H}_2\text{S}$ , hydrogen sulfide;  $\text{HgS}$ , cinnabar. Source: Adapted from EPA 1997b.

From: NRC Toxicological Effects of Methylmercury 2000 pg 17

## Figure 2

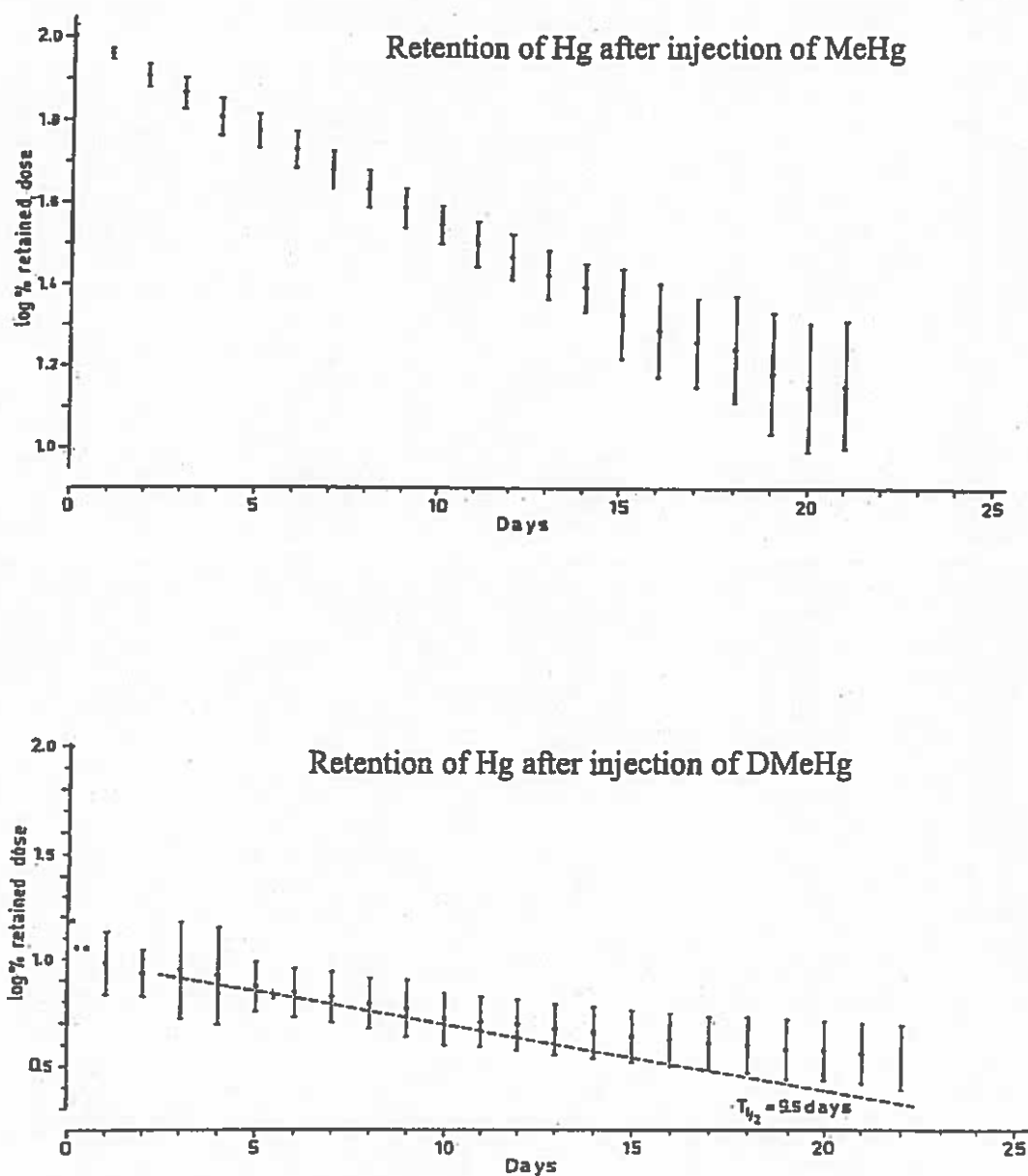
### DMeHg and MeHg mouse studies



From: Ostlund K. Acta Pharmacologica et Toxicologica Vol 27 1969 pgs 9-125.  
Figures 37 & 39

## Figure 3

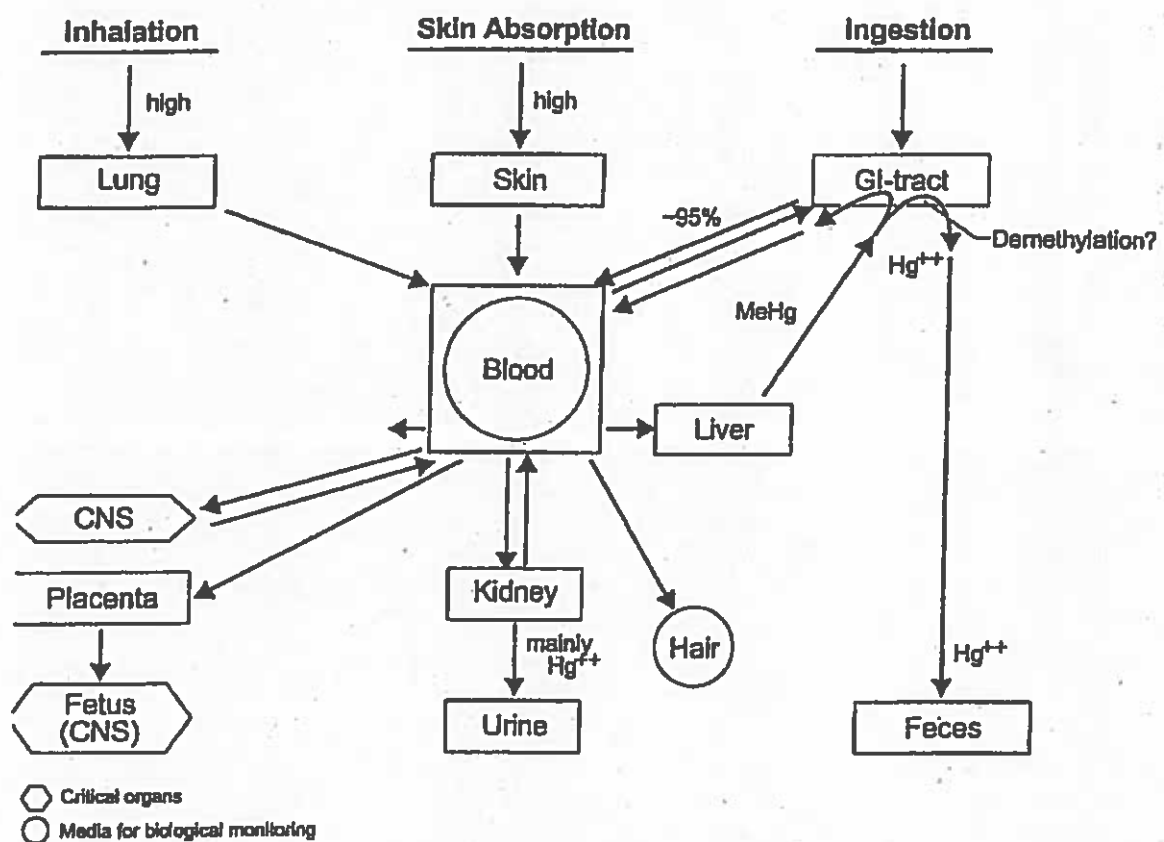
### DMeHg and MeHg mouse studies



From: Ostlund K. Acta Pharmacologica et Toxicologica Vol 27 1969 pgs 9-125.  
Figures 22 & 38

# Figure 4

## Methylmercury Kinetics

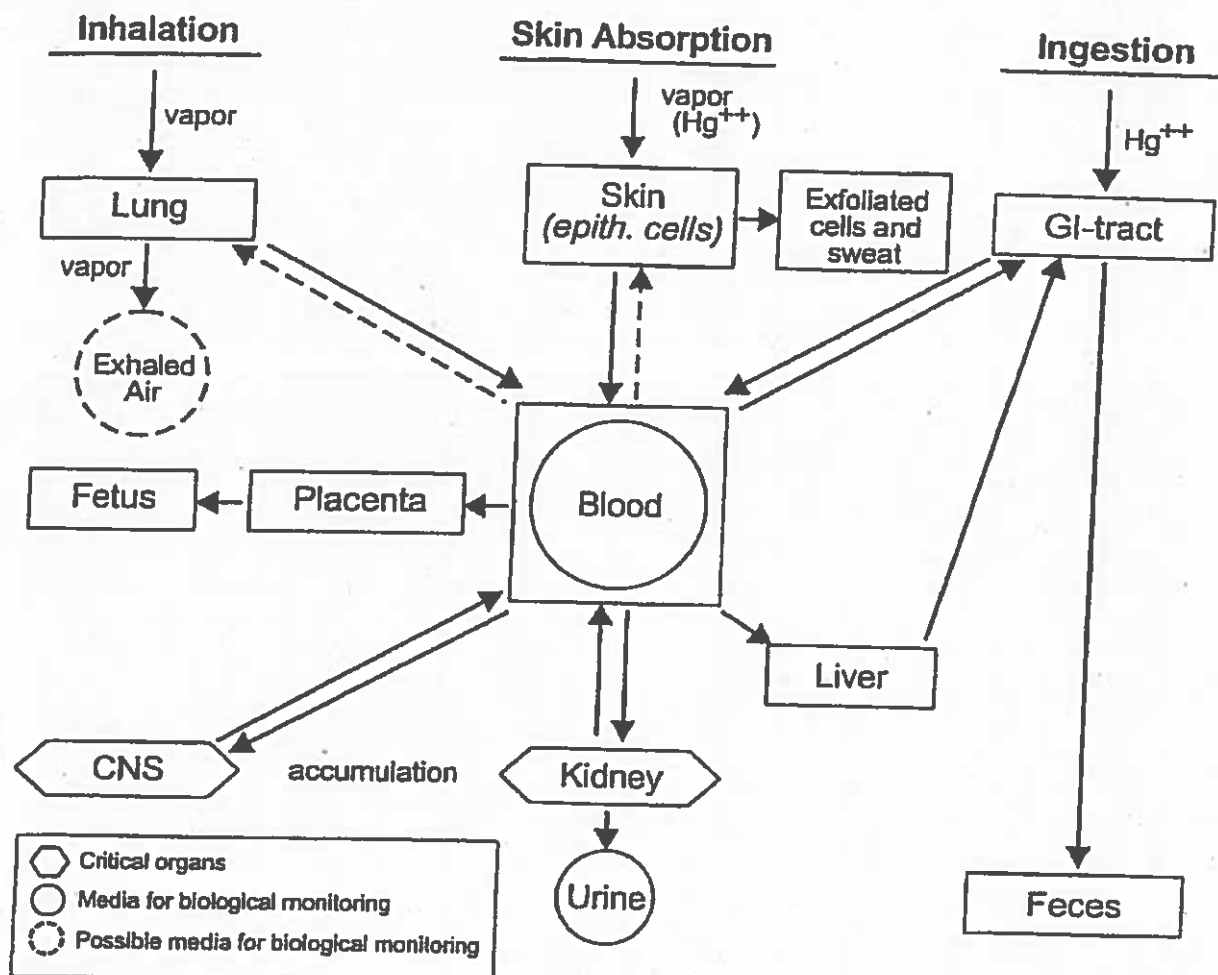


Methylmercury kinetics. Source: Elinder et al 1988. Reprinted with permission from *Biological Monitoring of Toxic Metals*; copyright 1988, Plenum Publishing Corporation.

From: NRC Toxicological Effects of Methylmercury 2000 pg 44


Figure 5

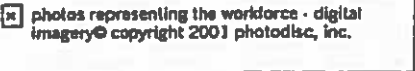
Inorganic Mercury Kinetics




From: NRC Toxicological Effects of Methylmercury 2000 pg 47

# Figure 6



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## Exposure Limits

	Mercury, Alkyl Compounds	Mercury, Aryl Compounds	Mercury, Inorganic Compounds
<b>OSHA</b>			
8-Hour TWA	0.01 mg/m <sup>3</sup>	-	-
Ceiling	0.04 mg/m <sup>3</sup>	0.1 mg/m <sup>3</sup>	0.1 mg/m <sup>3</sup>
<b>NIOSH</b>			
8-Hour TWA	0.01 mg/m <sup>3</sup> , Skin	0.05 mg/m <sup>3</sup> , Skin	0.05 mg/m <sup>3</sup> , Skin
ST/Ceiling	0.03 mg/m <sup>3</sup> , (ST) Skin	0.1 mg/m <sup>3</sup> , (Ceiling) Skin	0.1 mg/m <sup>3</sup> , (Ceiling) Skin
IDLH	2 mg/m <sup>3</sup>	10 mg/m <sup>3</sup>	10 mg/m <sup>3</sup>
<b>ACGIH</b>			
8-Hour TWA	0.01 mg/m <sup>3</sup> , Skin	0.1 mg/m <sup>3</sup> , Skin	0.025 mg/m <sup>3</sup> , Skin
Short Term	0.03 mg/m <sup>3</sup> , Skin	-	-

Revised: 28 July 2003

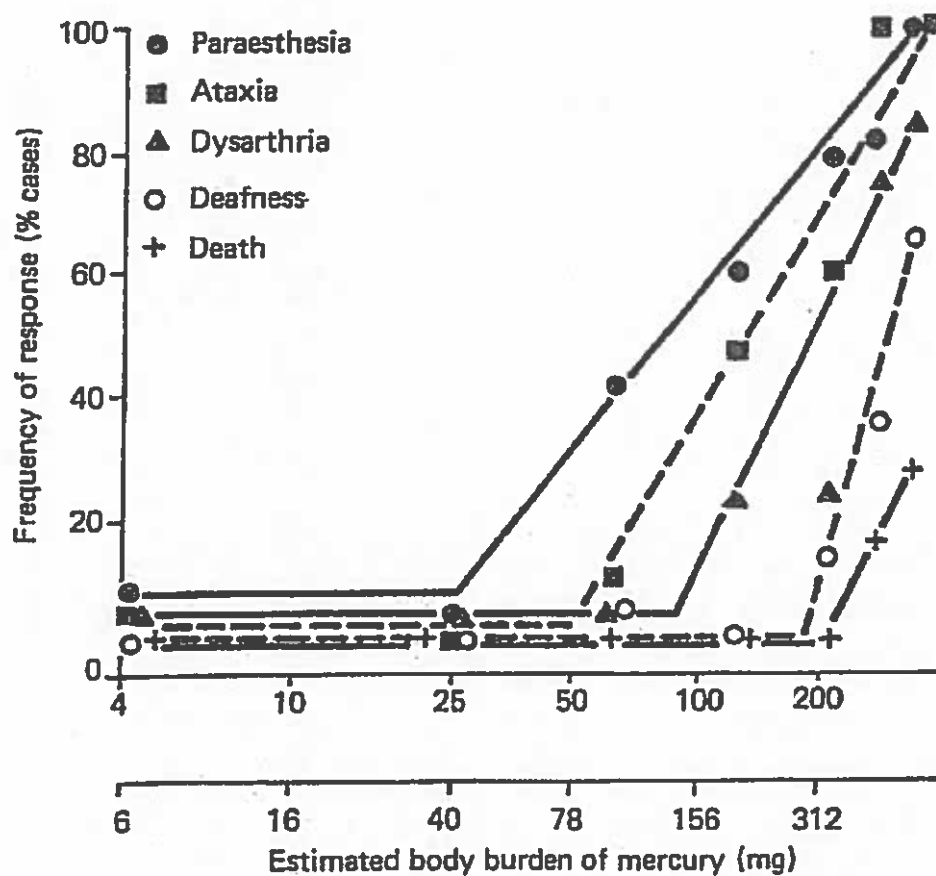
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# Figure 7



The relationship between frequency of signs and symptoms and the estimated body burden of methylmercury. From: Bakir et al., 1973. Both scales of the abscissa refer to body burden of methylmercury at the cessation of exposure. The two scales represent different methods of calculating the body burden as discussed in Environmental Health Criteria 1: Mercury (WHO, 1976b).