A Dimethyl Mercury Inhalation Risk Screening Concentration

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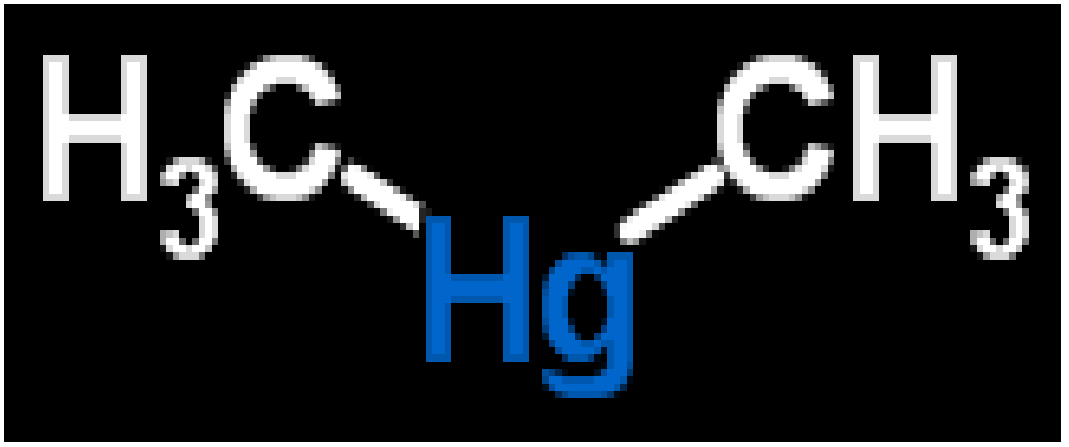
Dimethyl Mercury (DMM)



- CASRN 593-74-8
- Mass 230.659
- Log Kow 2.59
- Melting Point -43 C
- Boiling Point 92 - 94 C
- Vapor pressure 58.8 at 23.78C
- Atmospheric T1/2 = 7.865 h

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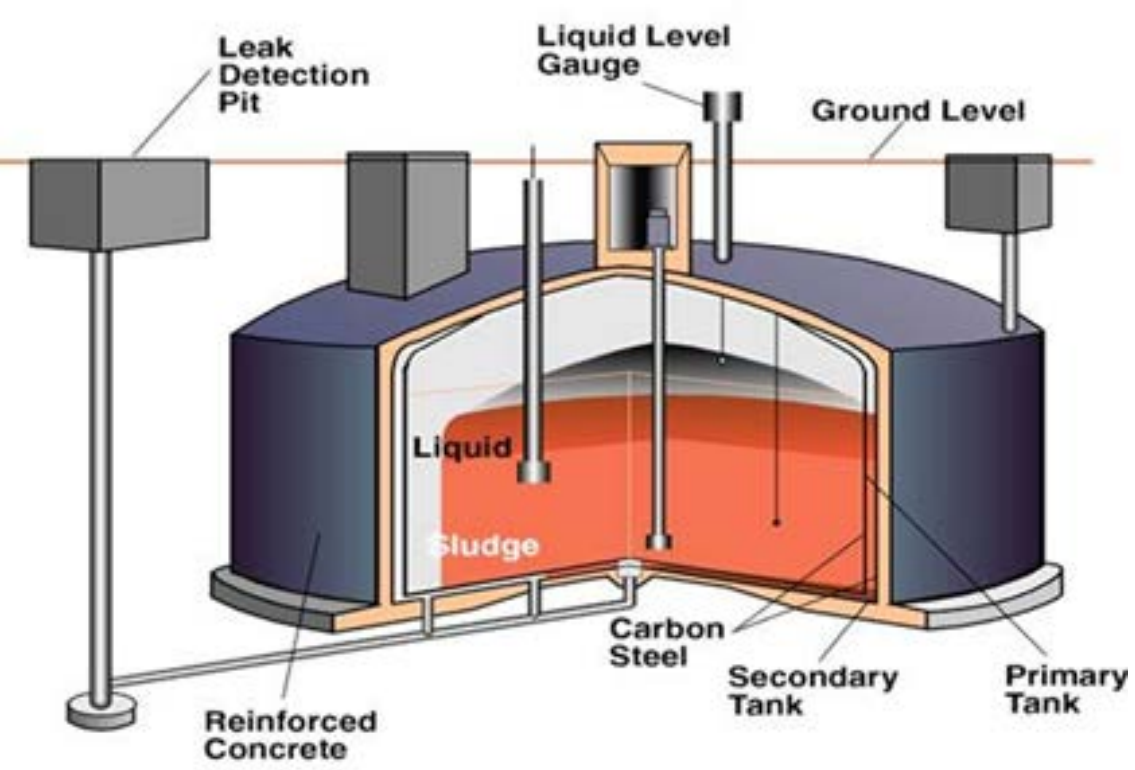
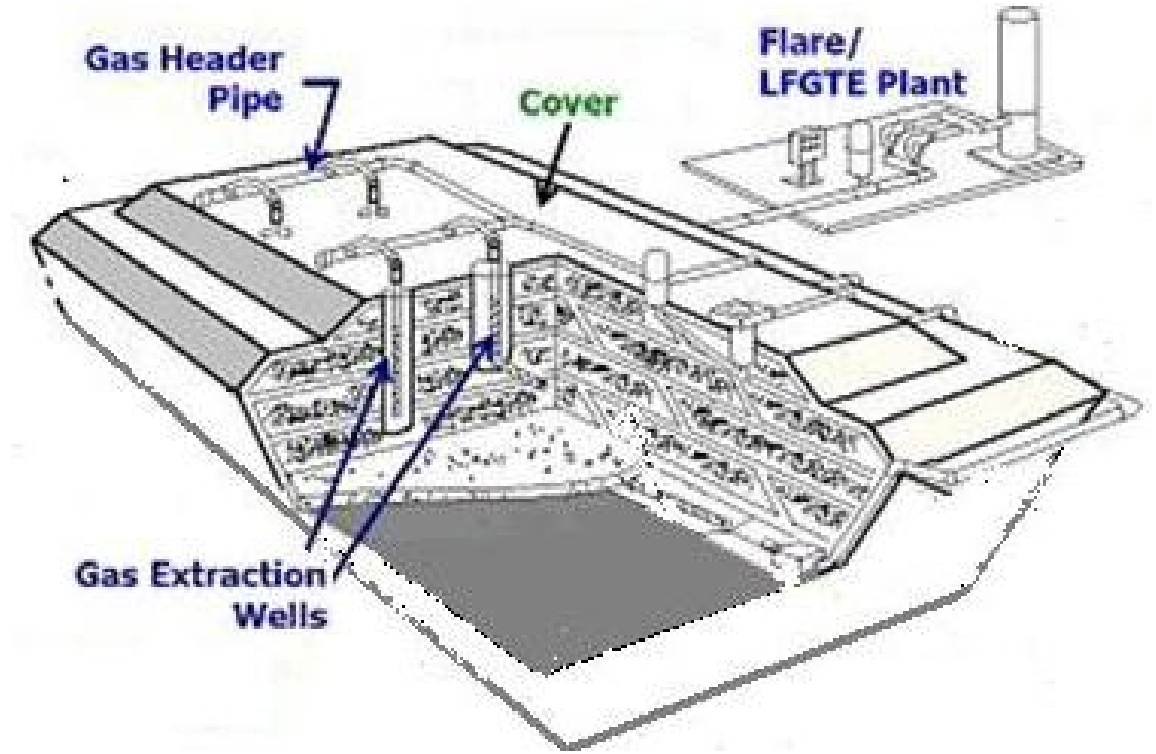
Ambient Air Location	DMM ng/m^3
Antarctica Mean	0.04 ± 0.01
Maximum	0.63
Minimum	0.00
Seattle mean	0.003 ± 0.004
Maximum	0.007
Minimum	0 .000
Mid-Atlantic Ocean	$\leq$0.1 (10% of total Hg)



Fuel rod plutonium extraction waste storage & Municipal solid waste landfills

High-level waste headspace gas in some storage tanks at Hanford: max. 251 ng/m^3



Landfills		ng/m^3
Washington	Min	7.1
	Max	46.1
Florida	Mean	30

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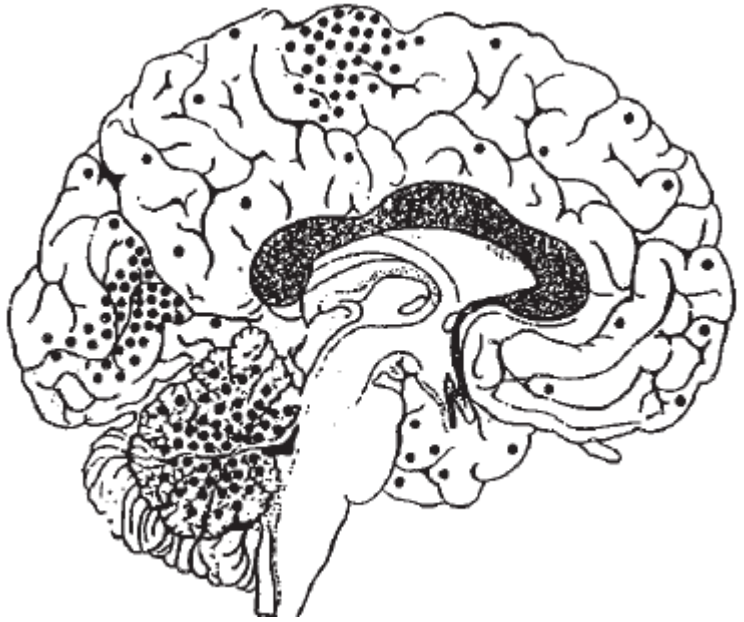
Human Case Histories

In 1864, three chemists inhaled dimethyl mercury. Two died.

In 1971, a chemist died after synthesizing 6-Kg.

In 1998, another chemist died after a dermal exposure to ≥0.44-ml.



Onset of symptoms usually 3 or more months after exposure.

Usual symptoms were sore gums; numbness of the hands, feet, lips, tongue; loss of muscular coordination with deterioration of balance and gait.

Condition rapidly worsened - deterioration speech, visual field constriction, deafness, confusion, frequent agitation, coma.

Chelation therapy failed.

Weeks to months after onset of symptoms, death by pneumonia.

Postmortems: extensive bilateral neuronal loss and gliosis in the primary visual and auditory cortices, loss of neurons and gliosis in the motor and sensory cortices, and widespread loss of several types of cerebellar neurons.

Potential for Neurodevelopmental Effects

Acute dimethyl mercury symptoms resemble those observed in acute Minamata disease

Subtle neurodevelop-mental effects of DMM are unknown

Fetal neurological development is likely the most sensitive effect

Could occur with very low maternal exposures

During the Minamata outbreak, severe neurodevelopmental effects occurred *from in utero* exposure even among asymptomatic

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Purpose

To examine if organo-mercury occupational exposure limits are sufficient to guard human fetal neurodevelopment from excessive dimethyl mercury exposure, otherwise to derive an alternative risk screening concentration

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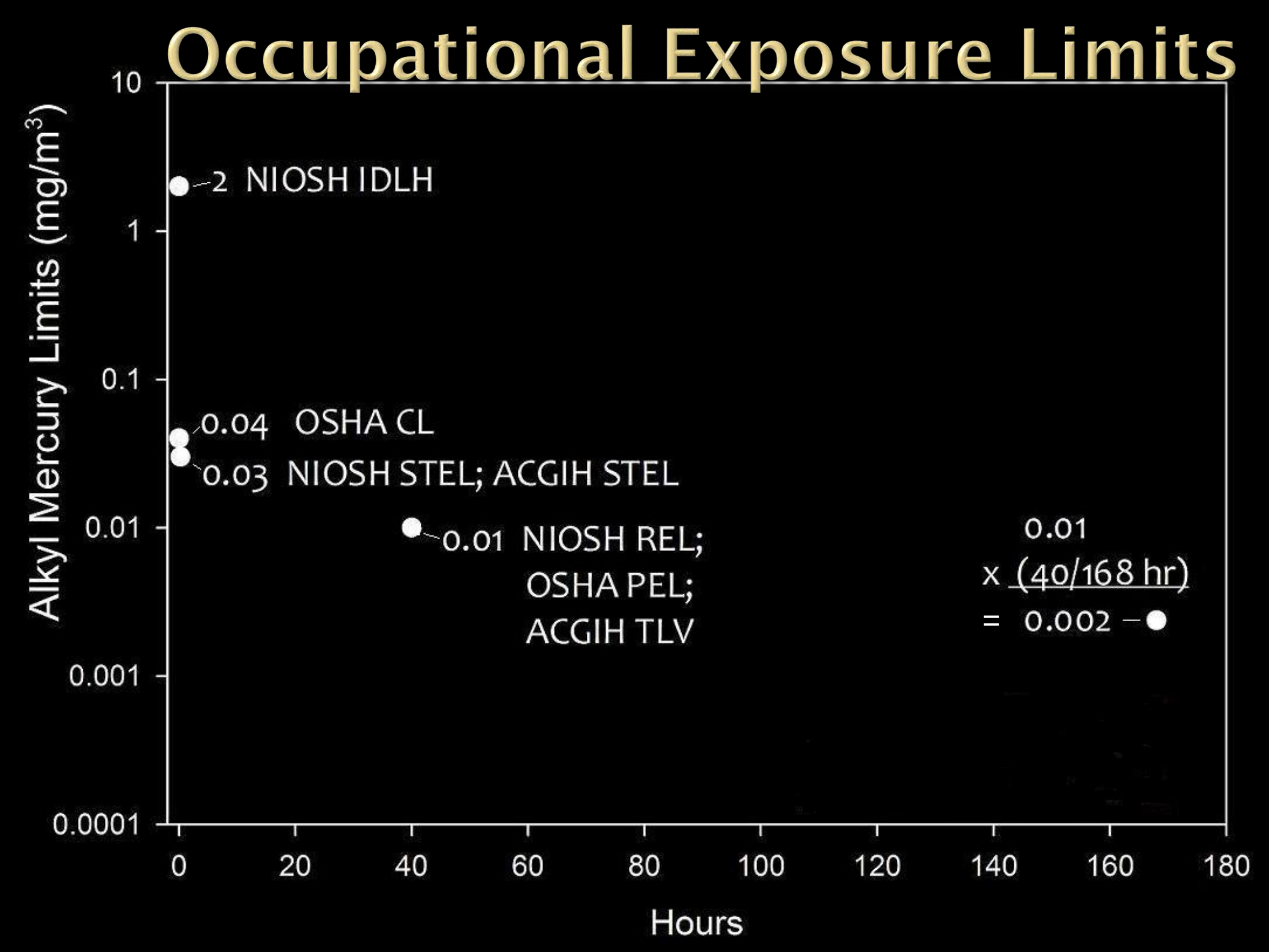
Occupational Exposure Limits



Are these Occupational Exposure Limits Applicable?

- Most alkyl mercury compounds are low volatility salts
- Apparent non-monotonic dose / time-to-onset and effects severities across different alkyl mercury compounds

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Reportedly, alkyl mercury compounds are rapidly and completely absorbed by all routes

Only 50 to 80% of inhaled dimethyl mercury (DMM) is absorbed by mice

Apparently dimethyl mercury (DMM) can diffuse in and out of the CNS, diffusion rates are unknown

Metabolic de-alkylation of alkyl mercury compounds is faster for ones with longer chain alkyl groups

Dimethyl mercury is metabolically demethylated to monomethylmercury (MMM)

Monomethylmercury reacts with Se and SH groups in endogenous molecules

Cycsteine + CH_3-Hg+ -->

methylmercury-cystine

Structure is similar to methionine

Methylmercury-cystine enters the CNS, other organs, and fetal circulation via the Large Amino acid Transporters (LAT1 and LAT2)

Methylmercury-cystine demethylates to Hg^{++} in the CNS and other organs

Offspring of dimethyl mercury-exposed pregnant rats accumulate 1.6 to 4.9 -fold more CNS mercury than the maternal CNSs do

Whole body elimination rates of injected monomethylmercury and dimethyl mercury are nearly equal in mice

DMM Neurological Effects Bioassay

In 5 Groups of male SD rats, gavaged at age 60-days then observed for 8 weeks

	Dose (mg Hg/Kg)	
ED50	65.9 ± 1.7	Equilibration test of motor coordination
NOEC	30	"
LOEC	39	"
LOEC	30	Maze learning performance

Extrapolating these to human doses

$$Dose_{human} = Dose_{rat} (BW_{human}*/BW_{rat})^{0.67 \text{ or } 0.75}$$

yields doses ranging from 5.0 - 17.6 mg Hg/Kg body weight, which are $\geq$ the proposed human lethal dose 5 mg /Kg bw

Cautious Assumptions

1. Landfill and Hanford dimethyl mercury emissions may result in repeated or continuous exposures

    But after single a inhalation exposure in mice, 81% of dimethyl mercury was exhaled within 16 hours

2. All dimethyl mercury absorbed by humans is metabolized to MMM

    But there is no information about how much absorbed DMM is metabolized to MMM by humans after a single dose or during long-term repeated or continuous exposure

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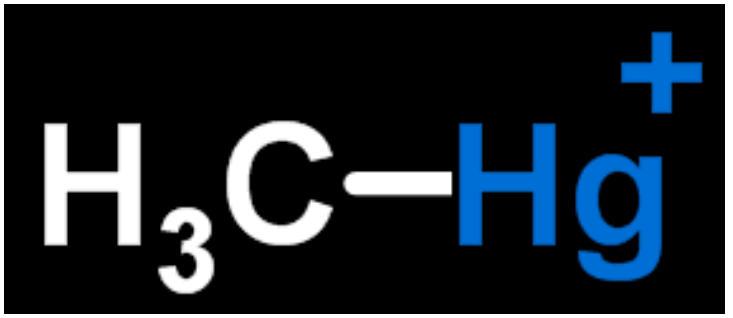
Monomethylmercury (MMM)



- No RfC
- RfD 0.1 µg/Kg-day
- RfD is based on a BMD calculated from neurodevelopmental data from the Faroe Islands longitudinal prospective study of mother-infant pairs and from supporting studies
- UF = 10, primarily for human variability and lack of a two-generation reproductive study

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Tolerable Internal Dose of Monomethylmercury

- The primary exposure route to monomethylmercury is through the GI tract: Mostly by consumption of contaminated fish
- Adult humans absorb 95% or more of the monomethylmercury in food
- Estimating the tolerable internal dose (TID) from the RfD

0.95 x 0.1 µg/Kg-d = **0.095 µg/Kg-d MMM TID**

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Tolerable Internal Dose (TID) of Dimethyl Mercury

Monomethylmercury molecular weight: 215.6239

Dimethyl mercury molecular weight: 230.6589

MW ratio: 1.0697

- Equivalent dimethyl mercury TID:

  0.095 µg/Kg-d x 1.0697 = **0.102-µg/Kg-d**

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If Dimethyl Mercury Tolerable Internal Dose is Inhaled Instead of Ingested

- During pregnancy, women have higher ventilation daily volumes than prior to pregnancy (increase up to 55% according to some estimates).

- Given the same level of physical activity, overweight and obese women breathe higher volumes of air than normal weight and underweight ones do.

- Daily volumes in pregnant overweight and obese women

percentile	m^3/day
50	23 - 25
95	32 - 35
99	41 - 47

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Body Weight

- 67-kg was the default weight of a pregnant woman EPA used for calculating the monomethylmercury RfD.

- Looking at week of pregnancy and ranges of maternal inhalation rates, ages, weights and heights - mothers likely to receive the highest internal doses are those in 9th month of pregnancy who are who are very short, and under- or over wt, aged 23 – 29.

- Under- and over- weight women seem likely have the highest internal dimethyl mercury doses, however monomethylmercury- exposed obese female macaques actually had higher CNS mercury than equally dosed normal-weight macaques.

Dimethyl Mercury Tolerable Internal Dose by inhalation

- For a woman weighing 67 Kg

  67 Kg x 0.1016 µg/Kg-d = 6.8086 µg (DMM) dimethyl mercury/d

- To absorb this by breathing 47 m^3/d, air would have to contain

$$\frac{6.8086\ \mu g\ DMM/d}{47\ m^3/d} = 0.14\ \mu g/m^3$$

- The full range across gestation, and given maternal heights 146 to 179-cm, BMIs 19.8 to 26, with 99th percentile daily air volume is 0.11- to 0.27–µg dimethyl mercury/m^3

Proposed ASIL: 0.14 µg Dimethyl Mercury/m^3 daily TWA

- ~70 fold < the lowest occupational exposure limit
- ~14 fold < the continuous concentration inferred from it
- Probably sufficient to screen for *in utero* exposure neurodevelopment hazards, even in the extreme situation of steady exposure throughout the third trimester in which a woman breathed air at the 99th percentile rate and had complete dose absorption and metabolism to monomethylmercury

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