# TOXICITY SUMMARY FOR METHYL MERCURY

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## EXECUTIVE SUMMARY

Methyl mercury is formed by biotic and abiotic methylation of mercury (McComish and Ong, 1985). Methyl mercury has been used as a fungicide, disinfectant, and in industrial processes (Singer and Nowak, 1980; Berlin et al., 1983).

Methyl mercury is highly toxic and is readily absorbed by the body following ingestion or inhalation (Aberg et al., 1969; Meittenen, 1973; Berlin et al., 1983). Methyl mercury may be metabolized to inorganic mercury by the liver and kidneys, with further transformation occurring to form the divalent cation (ATSDR, 1989). Methyl mercury is excreted as inorganic mercury, primarily in the feces (Norseth and Clarkson, 1971).

The target organ for methyl mercury toxicity is the central nervous system (CNS), especially the brain, and may occur at doses as low as 3 μg/kg in humans (WHO, 1976). Methyl mercury is neurotoxic to several species of experimental animal and to humans. The $LD_{50}$ values for various rodent species range from 21 to 57.6 mg/kg (RTECS, 1986). Manifestation of toxic effects (neurobehavioral alterations and degenerative changes in the central and peripheral nervous system) is probably a function of accumulation of critical levels of mercury (Goyer, 1991). Histopathologic correlates have been identified in the brains of humans and animals prenatally exposed to methyl mercury (Choi et al., 1987; Hughes and Annua, 1976).

Exposure to methyl mercury in the diet (fish and contaminated grain) has caused epidemic poisonings in Iraq and Japan, characterized by severe developmental effects (impaired motor and cognitive functions) in infants of exposed mothers (Bakir et al., 1973; Amin-Zaki et al., 1974; WHO, 1976). The primary target organ for oral exposure to methyl mercury is the brain; the effects on this organ accounting for the developmental toxicity of the chemical (Magos, 1980; Goyer, 1991). Data on the effects of inhalation exposure to methyl mercury are lacking for both humans and animals.

A reference dose (RfD) of 3E-04 mg/kg/day has been calculated by the U.S. EPA and is based on the intake that would be required to produce a blood mercury level of 200 μg/mL, which is a level associated with minimal health effects in humans (U.S. EPA, 1991; U.S. EPA, 1990). In deriving the RfD, an uncertainty factor of 10 was applied for extrapolation from a LOAEL to NOAEL. Confidence in the RfD is medium.

An inhalation reference concentration (RfC) for methyl mercury is not available.

No data were available for assessing the carcinogenic potential of methyl mercury.

# 1. INTRODUCTION

Mercury may undergo biotic and abiotic methylation to form methyl mercury (McComish and Ong, 1988). Commercially produced methyl mercury (CAS No. 2269-92-6) has been used as a fungicide, seed disinfectant, alkylating agent in organic synthesis of other organometallic compounds, and as a preservative in paints (Singer and Nowak, 1980; Berlin, 1983).

# 2. METABOLISM AND DISPOSITION

## 2.1. ABSORPTION

Data are available showing that methyl mercury is readily absorbed from the gastrointestinal tract of humans and animals. Based on retention and excretion data from humans, Aberg et al. (1969) reported that 95% of a single oral dose of methylmercuric nitrate was absorbed. Efficient absorption of methyl mercury was also demonstrated in another study using human volunteers receiving an oral dose of protein-bound methyl mercury (Miettinen, 1973). Up to 80% of volatile methyl mercury compounds such as methyl mercury chloride vapor may be absorbed upon inhalation (Berlin, 1983). Dermal absorption of methyl mercury is known to occur in both humans and animals but quantitative data are lacking.

## 2.2. DISTRIBUTION

Methyl mercury is transported in red blood cells with a small fraction being bound to plasma proteins (Berlin, 1983). The compound readily penetrates membranes resulting in widespread distribution in the body; however, higher concentrations (up to 10% of total dose) accumulate in the central nervous system (CNS). In the CNS, methyl mercury remains in the organic form but in other tissues is converted and stored as inorganic mercury with the highest concentrations generally occurring in the liver and kidney. Methyl mercury readily traverses the placenta and results in higher levels of the compound in fetal relative to maternal blood (ATSDR, 1989). Incorporation of methyl mercury in hair during hair formation in the follicle results in concentrations that are up to 250 times greater than that in other tissues. A report by Dutczak et al. (1991) provided data from guinea pigs, hamsters and a macaque monkey indicating extensive absorption of methyl mercury by the gall bladder and subsequent biliary-hepatic cycling of the compound, which may contribute to the long biologic half-life of methyl mercury.

## 2.3. METABOLISM

Methyl mercury may be metabolized to inorganic mercury by the liver and kidneys, with the inorganic form then entering an oxidation-reduction cycle in the red blood cells, lungs, and liver resulting in formation of the divalent cation ($Hg^{++}$) (ATSDR, 1989). Methyl mercury remaining in the gastrointestinal tract is converted to inorganic mercury by the intestinal flora (Nakamura et al., 1977; Rowland et al., 1980). Available data suggest that metabolism of methyl mercury is similar in animals and humans (ATSDR, 1989).

## 2.4. EXCRETION

Methyl mercury is excreted primarily in the feces as inorganic mercury (Norseth and Clarkson, 1971). This is the result of biliary excretion of the compound and subsequent conversion to he inorganic form by intestinal flora. Some of the methyl mercury excreted in the bile may also be reabsorbed thereby creating enterohepatic circulation of the organic form. Less than 1% of the body burden of methyl mercury is excreted daily, resulting in a biological half-life of approximately 70 days (Berlin, 1983). Over a 4-day period, a human volunteer excreted only about 6% of the ingested dose of radiolabeled, protein-bound methyl mercury, the biological half-life ultimately being 76 days (Miettinen, 1973). Methyl mercury is also secreted in breast milk with concentrations being about 5% of that in the blood. Removal of inorganic mercury via exhalation, saliva, and sweat results from the metabolism of the organic form (ATSDR, 1989).

# 3. NONCARCINOGENIC HEALTH EFFECTS

## 3.1. ORAL EXPOSURES

### 3.1.1. Acute Toxicity

#### 3.1.1.1. Human

Berlin (1983) noted that there are no differences between acute and chronic effects of methyl mercury; the toxic effects occurring when a toxic level has accumulated. According to the World Health Organization (WHO, 1976), the earliest effects of methyl mercury in humans occur when blood concentrations are between 200 and 500 ng/mL. These blood concentrations correspond to body burdens of 30 to 50 mg Hg/70 kg and are equivalent to daily intakes of 3 to 7 µg/kg. It is important to note that the onset of methyl mercury poisoning may be delayed for weeks or even months depending on the total body accumulation of the compound.

#### 3.1.1.2. Animal

Oral $LD_{50}$ values of 29.9 mg/kg, 57.6 mg/kg, and 21 mg/kg have been reported for rats, mice, and guinea pigs, respectively (RTECS, 1986). Acute toxic effects including neurological effects (behavioral alterations, brain cell death) have been reported for animals orally exposed to various methyl mercury compounds, including methylmercuric chloride, methylmercuric hydroxide, methylmercuric acetate, and methylmercuric dicyandiamide (ATSDR, 1989).

### 3.1.2. Subchronic Toxicity

#### 3.1.2.1. Human

Depending on the exposure and subsequent accumulation of methyl mercury in the body, toxic effects may appear within weeks or months (Clarkson, 1989). As noted by Berlin (1983), severity of exposure will determine the onset of toxic effects, and that toxicity may occur following less than chronic exposure (see Section 3.1.3.1.). The signs and symptoms include sensory disturbances, constricted visual field, deafness, and motor aberrations. Primary targets for methyl mercury damage in adult humans are the cerebellum, calcarine fissure, and the precentral gyrus of the brain.

#### 3.1.2.2. Animal

Subchronic exposure of cats to methyl mercury at doses of 0.01 mg/kg/day for 11 months, or 0.45 mg/kg/day for 83 days caused behavioral and pathological changes in nervous tissue (U.S. EPA, 1985). Similar effects were also reported for rats given methyl mercury dicyandiamide at 1 mg/kg/day for 8 weeks (Magos et al., 1972). An impairment of spatial vision at high and low luminescence was observed in newborn cynomolgus monkeys fed methyl mercury at 0.05 mg/kg/day for 3-4 years. Evans et al. (1977) reported reduced visual sensitivity, restricted visual field, intention tremors, somasethic impairment, and incoordination in monkeys receiving 100 day-exposure to methyl mercury doses that produced steady-state blood mercury levels of 100-400 μg/dL.

Wakita (1987) reported an increase in systolic blood pressure in rats receiving methylmercuric chloride by gavage at 0.4 mg Hg/kg/day for 3-4 weeks. The effect persisted for at least 9 months.
Gavage administration of methylmercuric chloride at a dose of 1 mg/kg (0.8 mg Hg/kg) to rats for up to 11 weeks resulted in neuronal degeneration of the cerebellum and dorsal route ganglia, and clinical signs of neurotoxicity (Chang and Hartmann, 1972). Hind leg weakness and degenerative changes in the corpus striatum, cerebral cortex, thalamus, and hypothalamus were seen in mice receiving methyl mercury by gavage at doses of 1.0 or 4.0 mg/kg/day (0.8 or 3.2 mg Hg/kg/day) for 60 days (Berthoud et al., 1976).

### 3.1.3. Chronic Toxicity

#### 3.1.3.1. Humans

The chronic toxicity of methyl mercury is best exemplified by the epidemic poisonings in Iraq, and Minamata and Niigata, Japan. In Iraq, over 6000 individuals were hospitalized and 459 individuals died as a result of consuming bread prepared with flour made from wheat and barley treated with a methylmercurial fungicide (Bakir et al., 1973). Methyl mercury concentration in the wheat flour ranged from 4.8-14.6 μg/g (mean=9.1 μg/g). The clinical symptoms included paresthesia, visual disorders, dysarthria, and deafness. The most severe cases resulted in coma and death due to CNS failure. Based on data obtained during this incident, a dose-response relationship between blood mercury levels (<10 μg/dL to 500 μg/dL), and frequency and severity of symptoms showed that mild symptoms occurred at the lower blood mercury levels and that deaths occurred at levels >300μg/dL.

In Minamata and Niigata, Japan, methyl mercury poisoning resulted from the ingestion of fish that had accumulated methyl mercury and other mercury compounds that were released from industrial sources into surface waters (WHO, 1976).

#### 3.1.3.2. Animals

Charbonneau et al. (1976) fed methyl mercury to cats for 2 years and found that doses as low as 0.046 mg Hg/kg/day impaired reflexes and diminished sensitivity to pain. At higher doses, these effects became progressively more severe to the point of convulsions. Histopathological correlates included degenerative changes in the dorsal root ganglia, and sensory nerve pathways.

Incoordination and weakness was observed in three of 16 kittens fed tuna containing methyl mercury (dose equivalent to 0.015 mg Hg/kg/day) for 11 months (Chang et al., 1974). However, degenerative changes in the cerebellum and cerebral cortex were found in most of the treated kittens.

Mice given methyl mercury (0.8 mg Hg/kg/day) in the drinking water for 110 days followed by 8-16 mg Hg/kg/day for 14 months exhibited unspecified neurotoxic effects (Ganser and Kirschner, 1985). Rice and Gilbert (1982) reported impaired spatial vision for monkeys given methyl mercury at a dose of 0.05 mg/kg/day (0.04 mg Hg/kg/day) from birth until 3-4 years of age.

### 3.1.4. Developmental and Reproductive Toxicity

#### 3.1.4.1. Human

Relative to the effects on the adult brain, the effects of methyl mercury on the developing brain *in utero* are more diffuse and may involve derangement of cortical cells layers and ectopic neurons. Depolymerization of microtubular structures by methyl mercury may be a possible mechanism for these prenatal effects (Clarkson, 1989).

Although no evidence of teratogenicity was observed, Amin-Zaki et al. (1974) found other severe developmental effects (impaired motor and mental function, hearing loss and blindness) in infants of mothers exposed to methyl mercury via contaminated grain during the Iraqi epidemic. The most severely affected infants had mercury blood levels ranging from 319 to 422 μg Hg/dL. It is also important to note that a 45% mortality rate was reported for pregnant women with signs of mercury poisoning versus a 7% mortality rate for the general population.

Harada (1978) reported that at about 6 months of age 13 of the 220 infants prenatally exposed to methyl mercury during the Minamata Bay incident showed signs of mercury poisoning characterized by instability of the neck, convulsions, and severe neurological and mental impairment.

Choi et al. (1978) reported abnormal cytoarchitecture of the brain in infants prenatally exposed to methyl mercury. No other significant anatomical defects have been reported.

#### 3.1.4.2. Animal

A 100% incidence of neonatal deaths and failure of dams to deliver was reported for rats receiving dietary methylmercuric chloride equivalent to 5 mg Hg/kg/day (Khera and Tabacova, 1973). The investigators reported no maternal toxicity.

Ultrastructural changes in the nervous system of mice exposed *in utero* to methylmercuric hydroxide (up to 10 mg Hg/kg/day) were reported by Hughes and Annau (1976). A dose of 3 mg Hg/kg/day produced significant behavioral changes in the mice. Ultrastructural changes in the nervous system have also been reported for rats prenatally exposed to methylmercuric chloride (4 mg Hg/kg/day) (Chang et al., 1977).

Exposure of rats to methyl mercury in the drinking water (0.25-0.50 mg Hg/kg/day) from one month prior to mating to the end of gestation resulted in ultrastructural changes the livers of the fetuses (Fowler and Woods, 1977).

In their study using monkeys exposed from birth to 3 or 4 years of age (Section 3.1.3.1.), Rice and Gilbert (1982) noted that the young, developing monkeys were especially vulnerable to the toxic effects of

methyl mercury on visual function as demonstrated by the low dose at which these effects occurred.

Pregnant monkeys (*Macaca fascicularis*) given methyl mercury in apple juice (50 or 90 μg methyl mercury/kg/day resulted in blood mercury levels of 1.0±0.13 ppm or 2.0±0.33 ppm, respectively) exhibited a decrease in pregnancy rate and increased abortion rate for mercury blood levels above 1 ppm (Mottet et al., 1985).

### 3.1.5. Reference Dose

#### 3.1.5.1. Subchronic

ORAL $RfD_s$: 3E-4 mg/kg/day (U.S. EPA, 1991)
UNCERTAINTY FACTOR: 10
NOAEL: None
LOAEL: 200 ng mercury/mL of blood equivalent to 0.003 mg/kg/day

#### 3.1.5.2. Chronic

ORAL $RfD_c$: 3E-4 mg/kg/day (U.S. EPA, 1990; U.S. EPA, 1991)
UNCERTAINTY FACTOR: 10
MODIFYING FACTOR: 1
NOAEL: None
LOAEL: 200 ng mercury/mL of blood equivalent to 0.003 mg/kg/day

CONFIDENCE:
Study: Medium
Data base: Medium
RfD: Medium

VERIFICATION DATE: 12/02/85, revised 12/01/88

PRINCIPAL STUDY: Clarkson et al., 1976; Nordberg and Strangert, 1976; WHO, 1976.

COMMENTS: The RfD is based on the fact that the earliest effects of mercury poisoning in humans (both pre- and postnatal exposures) have been shown to occur when blood concentrations are between 200 and 500 ng Hg/mL. A blood concentration of 200 ng Hg/mL corresponds to a body burden of 30 mg Hg/70 kg, which is equivalent to an intake of 3 μg Hg/kg/day. (WHO, 1976).

## 3.2. INHALATION EXPOSURES

### 3.2.1. Acute Toxicity

#### 3.2.1.1. Human

No data were located regarding the acute inhalation toxicity of methyl mercury in humans.

However, any repeated short-term exposure to methyl mercury would conceivably contribute to the body burden of mercury, especially considering the relatively slow removal of methyl mercury from target tissues.

#### 3.2.1.2. Animal

No data are available regarding the acute inhalation toxicity of methyl mercury in animals.

### 3.2.2. Subchronic Toxicity

Information on the subchronic inhalation toxicity of methyl mercury in humans and animals was unavailable. However, as indicated in 3.2.1.1., any repeated short-term exposure to methyl mercury would conceivably contribute to the body burden of mercury and subsequent manifestation of toxicity.

### 3.2.3. Chronic Toxicity

#### 3.2.3.1. Human

No data are available regarding the chronic inhalation toxicity of methyl mercury in humans. As indicated in 3.2.2., any exposure to methyl mercury would conceivably contribute to the body burden of mercury and the subsequent manifestation of toxic effects.

#### 3.2.3.2. Animal

No data are available regarding the chronic inhalation toxicity of methyl mercury in animals.

### 3.2.4. Developmental and Reproductive Toxicity

#### 3.2.4.1. Human

No data are available regarding the developmental and reproductive toxicity of methyl mercury in humans following inhalation exposure.

#### 3.2.4.2. Animal

No data are available regarding the developmental and reproductive toxicity of methyl mercury in animals following inhalation exposure.

### 3.2.5. Reference Concentration

#### 3.2.5.1. Subchronic

Not calculated.

#### 3.2.5.2. Chronic

Not calculated.

### 3.3. OTHER ROUTES OF EXPOSURE

#### 3.3.1. Acute Toxicity

Information on the acute toxicity of methyl mercury by other routes in humans or animals was not available.

#### 3.3.2. Subchronic Toxicity

Information on the subchronic toxicity of methyl mercury by other routes in humans or animals was not available.

#### 3.3.3. Chronic Toxicity

Postnatal mercury poisoning may occur via exposure to methyl mercury in breast milk.

#### 3.3.4. Developmental Toxicity

No information regarding the developmental toxicity of methyl mercury by other routes in humans or animals was available.

### 3.4. TARGET ORGANS/CRITICAL EFFECTS

#### 3.4.1. Oral Exposures

##### 3.4.1.1. Primary Target(s)

1. CNS: The primary target for methyl mercury toxicity is the brain. Data indicate that the fetal brain is more sensitive than that of the adult (Magos, 1980). Methyl mercury-induced developmental toxicity also involves the central nervous system.

##### 3.4.1.2. Other Target(s)

No information was available indicating additional target organs for methyl mercury.

#### 3.4.2. Inhalation Exposures

Inhalation exposure to methyl mercury has not been shown to be a significant route of exposure. However, due to the rapid absorption of methyl mercury by biological systems and its affinity for the CNS, it may be assumed that the critical organ (CNS) would be the same as for oral exposure.

## 4. CARCINOGENICITY

### 4.1. Oral Exposures

#### 4.1.1. Human

Information on the carcinogenicity of methyl mercury in humans is not available.

#### 4.1.2. Animal

Mitsumori et al. (1981) reported renal tumors (13/16; 2 adenomas and 11 adenocarcinomas) in male but not female mice fed methyl mercury chloride (15 ppm) for 53 weeks. No additional information was available regarding the carcinogenicity of methyl mercury.

### 4.2. Inhalation Exposure

Information on the carcinogenicity of methyl mercury in humans and animals following inhalation exposure is not available.

### 4.3. Other Routes of Exposure

Information on the carcinogenicity of methyl mercury in humans and animals is not available.

### 4.4. Weight-of-Evidence

The potential carcinogenicity of methyl mercury has not been evaluated by the U.S. EPA and, therefore, does not receive a weight-of-evidence classification.

### 4.5. Carcinogenicity Slope Factor

Not calculated.

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