

# Mercury Reference Exposure Levels DRAFT

(Hg<sup>0</sup> Elemental; Quicksilver)

CAS 7439-97-6

## 1. Summary

Elemental mercury exposures adversely affect several organ systems. The effects of acute, high level inhalation exposures first appear in the lungs as pulmonary dysfunction, possibly followed by respiratory failure leading to death. At lower levels of exposure, the kidneys and brain, especially the developing brain, are more sensitive targets. Short term maternal exposure to mercury vapor during pregnancy may result in long lasting neurobehavioral effects in the offspring, an effect upon which the acute REL is based. Chronic, low level exposures also adversely affect the central nervous system and manifest as motor deficits (tremors, unsteady gait, performance decrements), mood changes (irritability, nervousness), poor concentration, short-term memory deficits, tremulous speech, blurred vision, paresthesia, and decreased nerve conduction. Renal and cardiovascular functions are also impaired with long term exposure. This REL focuses on inhalation exposures. There is a large body of literature on methylmercury poisoning as well as the toxicology of ingested mercury. Much of the latter is reviewed in OEHHA's documentation of the Public Health Goal for drinking water (OEHHA, 1999)

### 1.1 Mercury Acute REL

*Reference Exposure Level*  
*Critical effect(s)*  
*Hazard Index target(s)*

**0.6 µg Hg/m<sup>3</sup> (0.07 ppb Hg<sup>0</sup>)**  
CNS disturbances in offspring  
Nervous system

### 1.2 Mercury 8-Hour REL

*Reference Exposure Level*  
*Critical effect(s)*  
*Hazard Index target(s)*

**0.06 µg Hg/m<sup>3</sup> (0.007 ppb Hg<sup>0</sup>)**  
Impairment of neurobehavioral functions in humans  
Nervous system

### 1.3 Mercury Chronic REL

*Reference Exposure Level*  
*Critical effect(s)*  
*Hazard Index target(s)*

**0.03 µg Hg/m<sup>3</sup> (0.004 ppb Hg<sup>0</sup>)**  
Impairment of neurobehavioral functions in humans  
Nervous system

## 2. Physical & Chemical Properties - Elemental Mercury

<i>Description</i>	Silver-white, heavy, mobile, odorless, liquid metal
<i>Molecular formula</i>	Hg <sup>0</sup>
<i>Molecular weight</i>	200.59 g/mol
<i>Density</i>	13.53 g/cm <sup>3</sup> @ 25° C
<i>Boiling point</i>	356.73° C
<i>Melting point</i>	-38.7° C
<i>Vapor pressure</i>	2 x 10 <sup>-3</sup> mm Hg @ 25° C
<i>Solubility</i>	soluble in nitric acid, to some extent in lipids, and up to 0.28 µmol in water @ 25° C
<i>Odor threshold</i>	odorless
<i>Conversion factor</i>	1 ppm in air = 8.34 mg/m <sup>3</sup> @ 25° C

## 3. Occurrence and Major Uses

Mercury and mercury-containing compounds are widely used in diverse applications. Thermometers, barometers and thermostats take advantage of mercury's uniform temperature-dependent volume expansion over a broad temperature range. It is used in mercury arc and fluorescent lamps, as a catalyst in oxidation of organic compounds, in the extraction of gold and silver from ores, and as a cathode in electrolysis. It is also used in pulp and paper manufacturing, as a component of batteries, in dental amalgams, and in the manufacture of switching devices such as oscillators, the manufacture of chlorine and caustic soda, as a lubricant, and as a laboratory reagent. To a lesser extent mercury has been used as a grain fumigant, in pharmaceuticals, agricultural chemicals, and as a preservative (ACGIH, 1986).

The annual statewide emissions of mercury from mobile, stationary and natural sources reported in the California Toxics Inventory for 2004 were estimated to be 18 tons (CARB, 2005a). Statewide ambient levels of mercury in 2002 were 1.7 ng/m<sup>3</sup> (CARB, 2005b). Mercury emitted in the metallic form is slowly oxidized in the atmosphere to the ionic mercurous and mercuric (+1 and +2) forms, which are much more soluble in water. These forms dissolve in raindrops and are deposited onto land and water. Much of this precipitation enters sediment of streams or other water bodies, where it is converted to methylmercury and can be accumulated by fish. Thus human exposure to air-borne mercury may be direct, via inhalation, and indirect, through a diet containing contaminated fish. For the purposes of evaluating a Reference Exposure Level, however, we focus on studies of inhalation exposure to mercury.

## 4. Metabolism / Toxicokinetics

Inhalation exposure to mercury is usually to vapors of the elemental form. However, combustion processes may also emit mercury salts (chlorides and oxides). Thus inhalation exposure to these forms also occurs. Exposure to the inorganic forms of mercury, the mercurous and mercuric salts, also occurs via the oral route. However, absorption from the intestinal tract is much less

efficient (2-38%) than from the lungs (70-80%) (ATSDR, 1999). To protect against oral exposure to inorganic mercury via drinking water, OEHHA (1999) has developed a public health goal (PHG) of 0.0012 mg/L (1.2 ppb) as a level of exposure expected to pose no significant health risk to individuals consuming the water on a daily basis. The difference between the PHG and the REL values reported in this document in part reflects differences in the toxicokinetics by the different routes of exposure. For inhalation exposure to mercury vapor, modeling based on human and experimental animal studies suggests that approximately 80% of inhaled mercury is deposited in the respiratory tract, of which about 70% is rapidly absorbed into the blood with a half-time of around 1 min. The remainder is absorbed more slowly with half-times of 8 hr to 5 days (Leggett et al., 2001). Absorption is markedly decreased if the breathing is done only through the mouth (Teisinger and Fiserova-Bergerova, 1965). It is not clear whether this difference is related to the direct uptake of mercury from nasal passages but mercury is known to be transported via olfactory nerves directly to the brain (Tjalve and Henriksson, 1999). In the blood, elemental mercury ( $\text{Hg}^0$ ) may be oxidized by catalase and peroxidase to the more toxic inorganic forms. Cellular membranes and the blood-brain barrier are readily permeable to  $\text{Hg}^0$ , but much less so to the inorganic forms. Residual  $\text{Hg}^0$  in the blood may enter target cells and be oxidized to the mercuric form intracellularly, effectively trapping it in the cells. The biological half-life of mercury in the human head is reported to be 21 days, and 64 days in the kidney (Hursh et al., 1976). Mercury is eliminated in urine, feces and exhaled air.

Mercury exerts its toxicity through several mechanisms mainly related to the high affinity of the mercuric ion for sulfhydryl groups. By binding to non-protein sulfhydryls such as glutathione and N-acetyl cysteine, mercury alters intracellular thiol status, thus promoting oxidative stress and lipid peroxidation. Mercury interacts with the mitochondrial electron transport chain resulting in increased  $\text{H}_2\text{O}_2$ . There is a concomitant depletion of mitochondrial glutathione, depolarization of the inner mitochondrial membrane, and increased susceptibility of the mitochondrial membrane to peroxidation. Mitochondrial function is thus impaired and oxidative stress increased (Lund et al., 1993). In addition to mercury's pro-oxidant effects, the binding of mercury by sulfhydryl-containing proteins disrupts a broad range of critical cellular functions such as microtubule polymerization (Yole et al., 2007), DNA transcription (Rodgers et al., 2001), glutamine synthesis (Allen et al., 2001), and calcium homeostasis (Yole et al., 2007). These effects may lead to cell dysfunction and death, an effect that is exacerbated by mercury's ability to promote auto-immune responses (Rowley and Monestier, 2005). Indeed, among genetically susceptible individuals, much of the renal pathology associated with mercury exposure has been attributed to auto-antibodies to renal proteins (Hua et al., 1993). Disruption of cellular processes during development can have severe and long-lasting effects. This is especially true during the growth and organization of the central nervous system as it is critically dependent on cell division and neuronal migration. These processes in turn depend on microtubule polymerization which is powerfully inhibited by both the mercuric ion and methylmercury.

## 5. Acute Toxicity of Mercury

### 5.1 Acute Toxicity to Adult Humans

The respiratory tract is the first organ system affected in cases of acute inhalation poisoning (Levin et al., 1988). Acute exposure to  $\text{Hg}^0$  can lead to shortness of breath within 24 hours and a

rapidly deteriorating course leading to death due to respiratory failure (Kanlun and Gottlieb, 1991; Asano et al., 2000). In a case report, Kanlun and Gottlieb (1991) observed four individuals from a private home where silver was being smelted from dental amalgam containing an unknown amount of  $\text{Hg}^0$ . All individuals died 9-23 days post-exposure from respiratory distress despite treatment with dimercaprol, a mercury chelator. Autopsy revealed acute lung injury characterized by necrotizing bronchiolitis with edema, emphysema, and obliteration of alveolar spaces with extensive interstitial fibrosis. The concentrations of mercury to which the individuals were exposed and the duration of exposure are not known.

Central nervous system (CNS) effects such as tremors or increased excitability are sometimes seen in cases of acute accidental exposures (Netterstrom et al., 1996). Long-term effects from a single exposure to  $\text{Hg}^0$  were reported in 6 male workers exposed to an estimated concentration of  $44 \text{ mg Hg/m}^3$  for a period of several hours (McFarland and Reigel, 1978). Long-term CNS effects included nervousness, irritability, lack of ambition, and loss of sexual drive for several years. Shortness of breath also persisted for years in all cases. Acute inhalation exposure to  $\text{Hg}^0$  vapors from broken thermometers resulted in generalized skin eruptions in 15 individuals (Nakayama et al., 1983). The doses and durations of exposure were not estimated.

A similar symptomatology was reported by Sexton et al. (1978) following the spillage of 100-300 ml of elemental mercury in two mobile homes that exposed 11 people to mercury vapor for one to two months. Following one to two weeks of exposure, the most intensely exposed residents, three teenage girls, reported the onset of anorexia, painful mouth, abdominal cramps, mild diarrhea, bleeding gingiva, irritated eyes, insomnia, difficulty concentrating and general restlessness. Prior to the girls' hospitalization, changes in academic performance, handwriting and personality were noted by the girls' teachers. A similar constellation of symptoms including intention tremor was subsequently observed in the other eight exposed residents. Skin rashes of varying severity were also seen among five of the residents. Blood mercury levels ranged from 183 to 620 ng/ml (normal is  $< 5 \text{ ng/ml}$ ). The highest air mercury level measured in one of the vacated and sealed trailers was  $1.0 \text{ mg/m}^3$  five months after the initial spill. Neurological exams at two to four months following termination of exposure were normal for eight of the residents. However, at four months, two of the intensely exposed girls still showed neurological abnormalities as manifested in difficulties copying simple diagrams, and abnormal electroencephalograms.

The acute effects of inhalation exposure to mercury may be compounded by simultaneous dietary intake of methylmercury. The use of mercury amalgamation in the recovery of gold in the Amazon Basin has resulted in locally elevated mercury levels both in indoor air in gold shops ( $250\text{-}40,600 \text{ ng/m}^3$ ), and in ambient urban air ( $20\text{-}5,800 \text{ ng/m}^3$ ) (Hacon et al., 1995), thus increasing the opportunities for both acute and long-term exposures. At the same time, gold extraction activities have caused mercury contamination of waterways resulting in a concomitant increase in methylmercury in the diet from the consumption of contaminated fish (Cordier et al., 1998). Adverse neurological and otological effects have been associated with elevated blood mercury levels in both adults and children in this environment (Counter et al., 1998).

### *Predisposing Conditions for Mercury Toxicity*

**Medical:** Persons with preexisting nervous system disorders or kidney diseases might be at increased risk of mercury toxicity. Also at higher risk are persons previously sensitized to mercury (Lerch and Bircher, 2004), and those with genetic susceptibility to mercury-induced hypersensitivity (Warfvinge et al., 1995). Developing organisms (fetuses and infants) are especially susceptible to the neurotoxicity of mercury (USEPA, 1997).

**Other:** People who consume significant amounts of fish from areas with advisories for daily fish intake due to mercury contamination may be more susceptible to the chronic toxicity of airborne mercury due to existing body burden.

## **5.2 Acute Toxicity to Infants and Children**

The data regarding the toxic effects of acute exposure of children to  $\text{Hg}^0$  are largely limited to case reports with little or no information on actual exposure levels. In children who inhale high levels of toxic  $\text{Hg}^0$  vapors, pulmonary dysfunction is the primary cause of mortality. For example, autopsy of a 4-month-old child who died following acute exposure to  $\text{Hg}^0$  vapors revealed pulmonary and general edema, nephrotic degeneration, ventricular dilation, and a greyish, necrotic appearance in the digestive mucosa (Campbell, 1948). In another case study, severe interstitial pneumonitis, erosion of the bronchial epithelium, membrane lesions of the alveoli and alveolar ducts, and significantly elevated Hg in the kidneys and liver were documented by Matthes et al. (1958) following the deaths of three children aged 4, 20, and 30 months from acute  $\text{Hg}^0$  vapor exposure in the home. Cases of CNS disturbances, including irritability, insomnia, malaise, anorexia, fatigue, ataxia, and headache have been reported in children exposed to vapor from spilled elemental mercury in their homes (Florentine and Sanfilippo, 1991).

## **5.3 Acute Toxicity to Experimental Animals**

As reported for humans, acute inhalation exposure of experimental animals to high levels of mercury is associated with pulmonary toxicity. However, the effects of mercury inhalation following short term exposure have also been examined in the context of neurotoxicity, notably neurobehavioral effects, and mercury deposition and distribution in the nervous system, as well as pathological changes in various organs.

Pathological changes in lung tissues similar to those reported in humans (edema, fibrosis, and necrosis of alveolar epithelium and hyaline membranes) were observed by Livardjani et al. (1991) in rats exposed to 26 mg (3.1 ppm)  $\text{Hg}/\text{m}^3$  for 1 hour, or 27 mg (3.2 ppm) for 2 hours. A dose-dependence of lung pathology and mortality was reported. No mortality was observed during the subsequent 15 days following the 1 hour exposure, while 50% mortality and more severe lesions were seen during the first 5 days following the 2 hour exposure.

In a study of pulmonary effects of mercury inhalation, as well as the possible role of metallothionein (MT), Yoshida et al. (1999) exposed both MT-null and wild-type mice to 6.6 - 7.5  $\text{mg}/\text{m}^3$  (0.79 - 0.90 ppm) mercury vapor for 4 hours on 3 consecutive days. Examination of

the lungs 24 hours after exposure revealed severe congestion, atelectasis (incomplete expansion of the lung), and mild hemorrhage of the alveoli in MT-null mice, along with 60% mortality. Among wild-type mice, these pulmonary effects were much less severe, pulmonary MT expression was markedly increased, and no lethality was observed. Mercury was found bound to MT in the lungs of wild-type, but not in MT-null mice. MT thus appears to ameliorate the effects of mercury inhalation.

The neurobehavioral manifestations in the offspring of mice with maternal exposure to mercury vapor during pregnancy suggest damage to motor control and learning centers. In the study upon which the acute REL derivation is based, Danielsson et al. (1993) exposed pregnant rats (12 per group) by inhalation to 1.8 mg/m<sup>3</sup> (0.22 ppm) of Hg<sup>0</sup> vapor for 1 hour/day (0.07 mg/kg/d) or 3 hours/day (0.2 mg/kg/d) during gestational days 11-14 and 17-20. The dose level was selected to avoid maternal toxicity. Tests of motor activity (locomotion, rearing, rearing time, total activity) in the offspring at 3 months of age revealed significant dose-dependent deficits compared to controls ( $p < 0.01$ ). When tested at 14 months of age, the hypoactivity seen at 3 months was no longer apparent and, in the 0.2 mg/kg/d dose group, was replaced with significant hyperactivity (Table 5.3.1).

**Table 5.3.1 Effects of Prenatal Metallic Mercury on Motor Activity**

Activity	Day	3 months			14 months		
		Control (SEM)	0.07 mg/kg/d	0.2 mg/kg/d	Control (SEM)	0.07 mg/kg/d	0.2 mg/kg/d
Locomotion	1	2785 (135)	2141 (104)*	2212 (135)*	1862 (119)	1289 (167)	1767 (127)
	2	2069 (127)	1432 (119)*	1385 (143)*	1194 (111)	1218 (104)	1512 (119)
	3	1719 (175)	1663 (191)	1090 (135)*	1162 (111)	915 (135)	1369 (119)
Rearing	1	404 (25)	321 (25)*	338 (25)*	204 (22)	143 (20)	210 (27)
	2	312 (29)	190 (20)*	161 (25)*	87 (22)	110 (28)	123 (22)
	3	247 (29)	238 (18)	157 (32)*	84 (18)	98 (25)	106 (18)
Rearing time	1	431 (19)	243 (20)*	232 (22)*	159 (21)	78 (24)	167 (26)
	2	269 (21)	138 (23)*	160 (24)*	66 (19)	99 (24)	114 (23)
	3	212 (21)	179 (23)	138 (21)*	87 (17)	76 (22)	138 (24)
Total activity	1	4854 (271)	3836 (318)*	3979 (302)*	3565 (302)	2435 (223)*	3151 (271)
	2	3804 (223)	2737 (239)*	2817 (350)*	2308 (255)	2324 (302)	3151 (334)*
	3	3183 (318)	3183 (350)	2132 (318)*	2228 (255)	2069 (271)	2546 (2711)

\* $p < 0.01$  Data estimated from Danielsson et al. (1993) Figure 1.

Significant learning deficits (swim maze performance) were observed in the 0.2 mg/kg/d-exposed, but not the lower-exposure rats tested at 15 months of age ( $p < 0.05$ ) (Table 5.3.2). The brain concentrations of mercury in the 0.2 mg/kg/d dose group (0.012 mg/kg) were 2.5-fold higher than in the 0.07 mg/kg/d dose group (0.005 mg/kg), and 12-fold higher than in the control group (0.001 mg/kg).

**Table 5.3.2 Prenatal Metallic Mercury and Learning Deficits**

Morris maze	Day	7 months			15 months		
		Control	0.07 mg/kg/d	0.2 mg/kg/d	Control	0.07 mg/kg/d	0.2 mg/kg/d
	1	53	48	46	42	40	29
	2	30	41	26	29	21	13*

\*p<0.01 Data estimated from Danielsson et al. (1993) Figure 3.

These data indicate adverse effects of mercury exposure on the developing brain, but it is not clear at what nervous tissue levels effects first manifest.

To evaluate mercury deposition in neurons at low exposure levels, Pamphlett and Coote (1998) exposed female BALB/c mice to mercury vapor at 25  $\mu\text{g}/\text{m}^3$  (0.003 ppm) for 2-20 hr, or to 500  $\mu\text{g}/\text{m}^3$  (0.06 ppm) for 5-240 min. At 25  $\mu\text{g}/\text{m}^3$ , mercury was first found in the perikarya of scattered large motor neurons in the lateral anterior horn of the spinal cord after 12 hr of exposure. Exposure at this level for 16 and 20 hr resulted in labeling of most of the large neurons of this area. By comparison, mercury was found in renal tubular epithelium after only 2 hr of exposure. Mice that survived longer than 6 weeks showed no mercury in the renal epithelia while mercury persisted in the brainstem motor neurons up to 30 weeks. At the higher dose of 500  $\mu\text{g}/\text{m}^3$ , mercury labeling of spinal motor neurons was seen after only 30 min. The doses that resulted in mercury uptake into mouse motor neurons in these experiments are similar to those that workers in mercury-using occupations may receive in the course of a few hours. While the toxicological significance of the observed mercury labeling was not addressed in these mice, the accumulation of mercury in the motor neurons is consistent with the behavioral alterations reported above.

The effects of short term, high level exposure to mercury are not limited to pulmonary and nervous tissues. Severe cellular degeneration and necrosis were observed in the kidneys, brain, colon, and heart tissue of 2 rabbits exposed for 4 hours to 29.7 mg Hg/ $\text{m}^3$  (3.6 ppm) (Ashe et al., 1953). Exposure of rabbits to 31.3 mg Hg/ $\text{m}^3$  (3.8 ppm) for 1 hour resulted in moderate pathological changes (unspecified), but no necrosis, in the brain and kidney. In contrast, heart and lung tissues showed mild pathologic changes (Ashe et al., 1953). Increased duration (6 hours/day for 5 days) of exposure at this concentration was lethal.

## 6. Chronic Toxicity of Mercury

### 6.1 Chronic Toxicity to Adult Humans

This section briefly summarizes a large body of literature on mercury toxicity, emphasizing studies of inhalation exposure useful in the development of the 8-hr and chronic reference exposure levels. The reader is referred to OEHHA (1999) for more information on measuring toxicity by the oral route of exposure. The effects of chronic exposure to mercury vapor have been known for centuries and are most pronounced in the central nervous system. Toxic effects

include tremors (mild or severe), unsteady gait, irritability, poor concentration, short-term memory deficits, tremulous speech, blurred vision, performance decrements, paresthesia, and decreased nerve conduction (Smith et al., 1970; Langolf et al., 1978; Fawer et al., 1983; Piikivi et al., 1984; Albers et al., 1988; Kishi et al., 1993). While some motor system disturbances can be reversed upon cessation of exposure, memory deficits may be permanent (Kishi et al., 1993). Studies have shown effects such as tremor and decreased cognitive skills in workers exposed to approximately  $25 \mu\text{g}/\text{m}^3$  (0.003 ppm) mercury vapor (Piikivi et al., 1984; Piikivi and Hanninen, 1989; Piikivi and Toulonen, 1989) (see discussion below).

The kidney is also a sensitive target organ of mercury toxicity. Effects such as proteinuria, proximal tubular and glomerular changes, albuminuria, glomerulosclerosis, and increased urinary N-acetyl- $\beta$ -glucosaminidase have been seen in workers exposed to approximately  $25\text{-}60 \mu\text{g}/\text{m}^3$  (0.003 - 0.007 ppm) mercury vapor (Roels et al., 1982; Bernard et al., 1987; Barregard et al., 1988; Piikivi and Ruokonen, 1989).

Chronic exposure to mercury vapors has also resulted in cardiovascular effects such as increased heart rate and blood pressure (Piikivi, 1989; Fagala and Wigg, 1992; Taueg et al., 1992), and in leukocytosis and neutrophilia (Fagala and Wigg, 1992).

A number of other studies with similar exposure levels also found adverse psychological and neurological effects in exposed versus unexposed individuals. Fawer et al. (1983) measured intention tremor with an accelerometer attached to the third metacarpal of the right hand in 26 male workers (mean age of 44 years) exposed to low concentrations of mercury vapor. The men worked either in a chloralkali plant ( $n = 12$ ), a fluorescent tube manufacturing plant ( $n = 7$ ), or in acetaldehyde production ( $n = 7$ ). Twenty-five control subjects came from different parts of the same plants and were not occupationally exposed to mercury. The average exposure as measured by personal air sampling was  $0.026 \text{ mg}/\text{m}^3$  (0.003 ppm) and the average duration of exposure was 15 years. The measurements of intention tremor were significantly higher in exposed workers than in controls ( $p = 0.011$ ). Using the average exposure as a LOAEL and adjusting for occupational ventilation rates and workweek, the resultant LOAEL is  $0.009 \text{ mg}/\text{m}^3$  (0.001 ppm).

Piikivi and Tolonen (1989) studied the effects of long-term exposure to mercury vapor on electroencephalograms (EEGs) of 41 chloralkali workers exposed for a mean of 15.6 years as compared to 41 matched controls. EEGs were analyzed both qualitatively and quantitatively. In the qualitative analysis, EEGs were interpreted visually with classification of normality and abnormality based on a previously established scale that separated focal, generalized and paroxysmal disturbances into four classes (normal, or mildly, moderately, or severely disturbed). Exposed workers, who had blood mercury levels of  $11.6 \mu\text{g}/\text{L}$ , tended to have an increased number of EEG abnormalities and brain activity was found to be significantly lower than matched controls ( $p < 0.001$ ). The abnormalities were most prominent in the parietal cortex, but absent in the frontal cortex. The authors used a conversion factor calculated by Roels et al. (1989) to extrapolate from blood mercury levels of  $12 \mu\text{g}/\text{L}$  to an air concentration of  $25 \mu\text{g}/\text{m}^3$  (0.003 ppm).

Another study by Piikivi (1989) examined subjective and objective symptoms of autonomic dysfunction in the same 41 chloralkali workers described above. The exposed workers had mean blood levels of 11.6  $\mu\text{g/L}$  corresponding to a TWA exposure of 25  $\mu\text{g Hg/m}^3$  in air (Roels et al., 1987). The workers were tested for pulse rate variation in normal and deep breathing, the Valsalva maneuver, vertical tilt, and blood pressure responses during standing and isometric work. The only significant difference in subjective symptoms was an increased reporting of palpitations in exposed workers. The objective tests demonstrated an increase in pulse rate variations at 30  $\mu\text{g Hg/m}^3$  (0.006 ppm; extrapolated from blood levels based on methods of Roels et al. (1987)), which is indicative of autonomic reflex dysfunction.

Piikivi and Hanninen (1989) studied subjective symptoms and psychological performance on a computer-administered test battery in 60 chloralkali workers exposed to approximately 25  $\mu\text{g/m}^3$  mercury vapor for a mean of 13.7 years. The subjective symptoms, evaluated by questionnaire, included the frequency or intensity of memory disturbances, difficulties concentrating, sleep disorders, and hand tremors. In addition a mood scale was used to evaluate tension, depression, anger, fatigue, and confusion. The psychomotor tests included finger tapping, eye-hand coordination, symbol digit substitution, pattern comparison, and a continuous performance test. Memory and learning effects were captured on tests of associate learning, associate memory, pattern memory, and serial digit learning. A statistically significant increase in subjective symptoms of sleep disturbance and memory disturbance was noted in the exposed workers ( $p < 0.001$ ), as were increased anger, fatigue and confusion ( $p < 0.01$ ). There were no differences in objective measures of memory, learning, or motor abilities, with the exception of poorer eye-hand coordination ( $p < 0.001$ ).

A study by Ngim et al. (1992) assessed neurobehavioral performance in a cross-sectional study of 98 dentists exposed to a TWA concentration of 14  $\mu\text{g Hg/m}^3$  (range 0.7 to 42  $\mu\text{g/m}^3$ ) compared to 54 controls with no history of occupational exposure to mercury. Exposed dentists were matched to the control group for age, amount of fish consumption, and number of amalgam fillings. Air concentrations were measured with personal sampling badges over typical working hours (8-10 hours/day) and converted to a TWA. Blood samples were also taken (average 9.8  $\mu\text{g/L}$ ). The average concentration in air was estimated at 23  $\mu\text{g Hg/m}^3$  when the methods of Roels et al. (1987) were used. The average duration in this study of dentists was only 5.5 years, shorter than the above studies. The performance of the dentists was significantly worse than controls on a number of neurobehavioral tests measuring motor speed (finger tapping), visual scanning, visuomotor coordination and concentration, visual memory, and visuomotor coordination speed ( $p < 0.05$ ). These neurobehavioral changes are consistent with central and peripheral neurotoxicity commonly observed in cases of chronic mercury toxicity.

Liang et al. (1993) investigated workers in a fluorescent lamp factory with a computer-administered neurobehavioral evaluation system and a mood-inventory profile. The cohort consisted of 88 individuals (19 females and 69 males) exposed for at least 2 years prior to the study. Exposure was monitored with area samplers and ranged from 8 to 85  $\mu\text{g Hg/m}^3$  across worksites. The average level of exposure was estimated at 33  $\mu\text{g Hg/m}^3$  and the average duration of exposure was estimated at 15.8 years. The exposed cohort performed significantly worse than the controls on tests of finger tapping, mental arithmetic, two digit searches,

switching attention, and visual reaction time ( $p < 0.05-0.01$ ). The effects on performance persisted after controlling for chronological age as a confounding factor.

## 6.2 Chronic Toxicity to Infants and Children

A number of case studies indicate that long-term exposure to  $Hg^0$  in children is associated with severe arterial hypertension, acrodynia, seizures, tachycardia, anxiety, irritability and general malaise (Sexton et al., 1978; Torres et al., 2000). These symptoms are consistent with the brain and kidneys as the principal target organs for  $Hg^0$ . By comparison, for methylmercury (MeHg), the brain is the most toxicologically relevant organ. An extensive literature supports the association between chronic MeHg exposure and neurological and developmental deficits in children (Choi, 1989; Harada, 1995; Grandjean et al., 1999). Unlike inorganic mercury, both  $Hg^0$  and MeHg easily cross cell membranes, the blood brain barrier, and the placenta (Ask et al., 2002). Intracellular oxidation of  $Hg^0$  and the slower demethylation of MeHg both lead to the mercuric ion that binds cellular macromolecules, trapping it within the cell and contributing to the toxicity associated with exposures to the respective forms. While the complete mechanisms of toxicity for the two forms are not well understood and are likely not identical, there are important similarities. Methylmercury and the mercuric ion formed from  $Hg^0$  avidly bind to protein sulfhydryls and may inactivate enzymes. Disruption of protein synthesis has been reported after exposure to either  $Hg^0$  or MeHg, although the former is the more powerful inhibitor (NAS, 2000). The neurotoxic effects observed in adult rats following *in utero* exposure to  $Hg^0$ , MeHg, or both, are reportedly similar with MeHg potentiating the effects of  $Hg^0$  (Fredriksson et al., 1996). Given the high susceptibility of children to MeHg and the apparent similarities in mechanisms with  $Hg^0$ , children are expected to be more susceptible to  $Hg^0$  toxicity as well.

There is a considerable body of evidence from human poisoning episodes that mercury exposure *in utero* and postnatally results in developmental neurotoxicity (McKeown-Eyssen et al., 1983; Grandjean et al., 1994; Harada, 1995; Grandjean et al., 1997). Thus, infants and children are susceptible subpopulations for adverse health effects from mercury exposure. These effects fall into several general categories: 1) effects on neurological status (Castoldi et al., 2001); 2) age at which developmental milestones are achieved (Marsh et al., 1979); 3) infant and preschool development (Kjellstrom et al., 1986; Kjellstrom et al., 1989); 4) childhood development (age 6 and above) (Grandjean et al., 1997); and 5) sensory or neurophysiological effects (Murata et al., 1999). These studies and others are extensively reviewed by the U.S. EPA (2000) and the NAS (2000)

Whereas MeHg and elemental mercury readily cross the blood-brain barrier and the placental barrier, the mercuric ion ( $Hg^{2+}$ ) does not readily cross these barriers. However, in fetuses and neonates mercuric species concentrate more in the brain because the blood-brain barrier is incompletely formed. Methylmercury and elemental mercury are lipophilic and are distributed throughout the body. In adults mercuric species accumulate more in the kidney. However, in neonates mercuric species do not concentrate in the kidneys but are more widely distributed to other tissues (NAS, 2000). It is possible that the increased distribution of mercuric species to the brain in fetuses and neonates accounts for some of the sensitivity of the brain to mercury during

these developmental periods. The sensitivity of the fetal brain might also be due to the high proportion of dividing and differentiating cells during neuronal development in the fetal and neonatal periods. These dividing cells may be more sensitive to damaging effects of mercury-protein complexes. Furthermore, neurodevelopment is a “one-way street”. Disruption along the route results in permanent deficits. Methylmercury can also alter the relative levels of thyroid hormones to which the fetus is exposed and upon which normal neurodevelopment depends.

In addition to prenatal and postnatal dietary exposure, neonates may receive added postnatal dietary exposure to mercuric species and MeHg from breast milk (Drexler and Schaller, 1998; Sundberg et al., 1999). Animal data suggest that suckling rats retain a higher percentage of ingested organic mercury than do adults, with much higher concentrations in the brain (Kostial et al., 1978). School children can be accidentally exposed to elemental mercury which is a curiosity and an attractive nuisance (George et al., 1996; Lowry et al., 1999). Younger children may also be exposed when elemental mercury is spilled on floors and carpets where they are more active.

### 6.3 Chronic Toxicity to Experimental Animals

Studies of the effects of mercury in experimental animals generally employ mercury levels in excess of those to which humans are exposed in most settings, thus limiting their ability to model the consequences of long-term, low level exposures. To address this issue, and to test for a role of metallothionein (MT) in mitigating mercury's effects, Yoshida et al. (2004) exposed wild type and MT-null mice to mercury vapor at  $0.06 \text{ mg/m}^3$  (0.007 ppm), 8 hr/day for 23 weeks. Neurobehavioral effects in open field and passive avoidance tests were evaluated at 12 and 23 weeks, and brain levels of mercury were determined. Mercury levels in the brains of mice were 0.66 and  $0.97 \text{ } \mu\text{g/g}$  tissue for MT-null and wild type, respectively. For comparison, the authors cite human brain mercury levels ranging from  $0.3 \text{ } \mu\text{g/g}$  in dental personnel to  $33 \text{ } \mu\text{g/g}$  in retired mercury miners. Mercury-exposed mice showed enhanced motor activity that was statistically significant for both strains at 12 weeks ( $p < 0.01$ ), and for the MT-null mice at 23 weeks ( $p < 0.05$ ). In a learning task (passive avoidance of an electric shock), there were no significant differences between controls and either strain of mouse at 12 weeks of exposure. However, after 23 weeks of exposure, MT-null, but not wild type mice, showed significantly less avoidance than controls ( $p < 0.05$ ) suggesting impaired long-term memory. These data suggest that long-term mercury exposure that results in brain levels of mercury comparable to those seen in occupationally-exposed humans, causes changes in neurobehavior, an effect that is exacerbated by low levels of MT. For comparison, Fawer et al (1983) reported increased intention tremor in human workers exposed to an average of 0.003 ppm for an average of 15 years (Section 6.1).

There is a substantial body of work delineating the neurotoxic effects of MeHg exposure on animals exposed in utero. A comparison between mercury vapor and MeHg, separately and in concert, was conducted in rats. Fredriksson et al. (1996) exposed pregnant rats to MeHg by gavage ( $2 \text{ mg/kg/d}$  during days 6-9 of gestation), and metallic mercury ( $\text{Hg}^0$ ) vapor by inhalation ( $1.8 \text{ mg/m}^3$  (0.22 ppm) for 1.5 h per day during gestation days 14-19), or both. Controls received the combined vehicles for each of the two treatments. The dose by inhalation was approximately  $0.1 \text{ mg Hg}^0/\text{kg/day}$ . No differences were observed among groups in clinical observations and developmental markers up to weaning. Tests of behavioral function, performed at 4-5 months of age, included spontaneous motor activity, spatial learning in a circular bath, and instrumental

maze learning for food reward. Offspring of dams exposed to  $\text{Hg}^0$  showed hyperactivity over all three measures of motor activity: locomotion, rearing and total activity. This effect was enhanced in the animals of the MeHg +  $\text{Hg}^0$  group. Compared to either the control or MeHg groups in the swim maze test, rats in the MeHg +  $\text{Hg}^0$  and  $\text{Hg}^0$  groups took longer to reach a submerged platform whose location they had learned the previous day. Similarly, both the MeHg +  $\text{Hg}^0$  and  $\text{Hg}^0$  groups showed more ambulations and rearings in the activity test prior to the learning trial in the enclosed radial arm maze. During the learning trial, these same animals showed longer latencies and made more errors in acquiring the food reward. Generally, the results indicated that prenatal exposure to  $\text{Hg}^0$  caused alterations to both spontaneous and learned behaviours, suggesting some deficit in adaptive functions. In these experiments, exposure to MeHg was not observed to alter these functions but rather appeared to potentiate the effects of  $\text{Hg}^0$ .

The similarities in the effects of MeHg and  $\text{Hg}^0$  imply similar targets in the brain, which appears to be the case. Pregnant squirrel monkeys were exposed to mercury vapor (0.5 or 1  $\text{mg}/\text{m}^3$  (0.06 or 0.12 ppm)) for 4 or 7 hours per day starting in the fifth to the seventh week of gestation and generally ending between 18 and 23 weeks of gestational age (Warfvinge, 2000). The concentration of mercury was found to be higher in maternal (0.80-2.58  $\mu\text{g}/\text{g}$  tissue) than in offspring (0.20-0.70  $\mu\text{g}/\text{g}$ ) brains, but with similar cerebellar distributions. In this study, mercury was localized mainly to Purkinje cells and Bergmann glial cells, similar to the distribution seen after MeHg exposure. The nuclei affected in these and other studies are part of the motor system.

In rats exposed to mercury vapor at  $\sim 1 \text{ mg}/\text{m}^3$  (0.12 ppm) for 6 h/d, 3 d/wk for 5 wk (low dose), or 24 h/d, 6 d/wk for 5 wk (high dose), an exposure duration-dependent loss of Purkinje cells and proliferation of Bergmann glial cells were observed (Hua et al., 1995). Whereas mercury accumulated to a higher degree in kidney compared to brain, the mercury level in kidney only increased 17% (90 to 105  $\mu\text{g}/\text{g}$  tissue) from low to high doses, while that of the brain increased 608% (0.71 to 5.03  $\mu\text{g}/\text{g}$ ). These neuropathological changes were observed at the same mercury doses as this group reported previously for kidney autoimmune disease (Hua et al., 1993). The brain is a more sensitive target for mercury toxicity in part due to its greater ability to concentrate the metal.

## 7. Developmental and Reproductive Toxicity

Occupational exposure to mercury vapor has been associated with reproductive problems in a number of epidemiological studies. In a study of 418 dental assistants, Rowland et al. (1994) reported that the fecundability of the women with high exposure to dental amalgams was 63% (95% CI 42-96%) of that reported for the dental assistants with no amalgam exposure. Similarly, in a Chinese study by Yang et al. (2002), there was a significantly higher prevalence of abdominal pain (OR 1.47, 95% CI 1.03: 2.11) and dysmenorrhea (OR 1.66, 95% CI 1.07; 2.59) among female factory workers exposed to ambient mercury vapor (0.001-0.200  $\text{mg}/\text{m}^3$ ) compared with factory workers without mercury exposure. In another study of female factory workers exposed to mercury vapors, the frequency of adverse birth outcomes, especially congenital anomalies, was higher among those exposed to mercury levels at or substantially lower than 0.6  $\text{mg}/\text{m}^3$  (Elghany et al., 1997).

The adverse effects of elemental mercury exposure have also been demonstrated in animal models. In rats, elemental mercury readily crosses the placental barrier and accumulates in the fetus following inhalation (Morgan et al., 2002). Pregnant rats exposed by inhalation to 1.8 mg/m<sup>3</sup> of metallic mercury for 1 hour or 3 hours/day during gestation (days 11 through 14 plus days 17 through 20) bore pups that displayed significant dose-dependent deficits in behavioral measurements 3-7 months after birth compared to unexposed controls (Danielsson et al., 1993). Behaviors measured included spontaneous motor activity, performance of a spatial learning task, and habituation to the automated test chamber. The pups also showed dose-dependent, increased mercury levels in their brains, livers, and kidneys 2-3 days after birth.

Morgan et al. (2002) exposed pregnant rats for 2 hr per day to 1, 2, 4, or 8 mg/m<sup>3</sup> mercury vapor during gestation days (GD) 6-15, and found a dose-dependent distribution of mercury to all maternal and fetal tissues. Adverse effects on resorptions, postnatal litter size and neonatal body weights were only observed at the highest mercury dose, which was also maternally toxic. It is of interest to note that following cessation of maternal exposure on GD 15, the mass of the fetal brain and its content of mercury both increased 10-fold. Thus the fetal brain continued to accumulate mercury eliminated from maternal tissues. This suggests that the period of fetal exposure is longer than that of maternal exposure, and may affect more neurodevelopmental stages than the timing of the maternal exposure would suggest.

Mercury and mercury compounds, including inorganic forms, are listed under California Proposition 65 (Cal/EPA, Safe Drinking Water and Toxic Enforcement Act of 1986) as developmental toxins. It should be noted that there is substantial evidence in humans of the developmental toxicity of methylmercury exposure. However, this REL summary is meant to be applied to elemental and inorganic mercury, and thus we are not describing methylmercury toxicity in depth in this document.

## 8. Derivation of Reference Exposure Levels

### 8.1 Mercury Acute Reference Exposure Level

<i>Study</i>	Danielsson et al., 1993
<i>Study population</i>	groups of 12 pregnant rats
<i>Exposure method</i>	inhalation of metallic mercury vapors
<i>Exposure continuity</i>	
<i>Exposure duration</i>	1 hour per day
<i>Critical effects</i>	CNS disturbances in offspring
<i>LOAEL</i>	1.8 mg/m <sup>3</sup>
<i>NOAEL</i>	not observed
<i>Benchmark concentration</i>	not derived
<i>Time-adjusted exposure</i>	
<i>Human Equivalent Concentration</i>	n/a
<i>LOAEL uncertainty factor (UF<sub>L</sub>)</i>	10 (default; severe effect, no NOAEL)
<i>Subchronic uncertainty factor (UFs)</i>	
<i>Interspecies uncertainty factor</i>	
<i>Toxicokinetic (UF<sub>A-k</sub>)</i>	√10 (default, animal study)
<i>Toxicodynamic (UF<sub>A-d</sub>)</i>	10 (greater human vs rat susceptibility)
<i>Intraspecies uncertainty factor</i>	
<i>Toxicokinetic (UF<sub>H-k</sub>)</i>	√10 (default: critical study in young)
<i>Toxicodynamic (UF<sub>H-d</sub>)</i>	√10 (default: critical study in young)
<i>Cumulative uncertainty factor</i>	3000
<i>Reference Exposure Level</i>	<b>0.6 µg Hg/m<sup>3</sup> (0.07 ppb Hg<sup>0</sup>)</b>

Acute Reference Exposure Levels are levels at which intermittent one-hour exposures are not expected to result in adverse health effects (see Section 5 of the Technical Support Document (TSD)).

In the absence of acute inhalation studies in humans, the study by Danielsson et al. (1993) was selected as the critical study since it used a sensitive endpoint, neurotoxicity, in a highly susceptible, developmental stage. Maternal rats were exposed by inhalation to 1.8 mg/m<sup>3</sup> of metallic mercury vapor for 1 hour/day or 3 hours/day during gestation. The offspring displayed significant dose-dependent deficits in behavior 3-7 months after birth compared to controls. The default uncertainty factor of 10 is applied for the use of a LOAEL for moderate to severe effects in the absence of a NOAEL.

A default interspecies uncertainty factor of √10 for toxicokinetic (UF<sub>A-k</sub>) variability was used, while a larger interspecies UF<sub>A-d</sub> of 10 for toxicodynamic differences was used to reflect the potentially greater developmental susceptibility of humans versus rats. This is based, in part, on Lewandowski et al. (2003) who used a comparative approach to analyze in vivo and in vitro data on the responses of neuronal cells of rats, mice, and humans to MeHg. Their analysis suggests that humans may be up to 10-fold more sensitive to MeHg than are rats. Application of

Lewandowski's analysis assumes that the human and rat responses to elemental mercury are comparable with those to MeHg. The study by Fredriksson et al. (1996) (above) supports this assumption for neurobehavioral effects. A greater susceptibility of humans to adverse neurobehavioral effects following early-life exposures compared with experimental animals has also been seen with other metals, especially lead. For example, Schwartz (1994) reported no evidence for a threshold for neurobehavioral effects in children with blood lead levels of 1 µg/dL compared with less than 15 µg/dL in primates (Gilbert and Rice, 1987) and less than 20 µg/dL in rats (Cory-Slechta et al., 1985).

Since the critical study involved early life exposures, the default intraspecies toxicodynamic uncertainty factor ( $UF_{H-d}$ ) of  $\sqrt{10}$  was employed to account for individual variability. The intraspecies toxicokinetic uncertainty factor of  $\sqrt{10}$  reflects the absence of data in young humans, but also the lack of reason to expect major age differences, at least in the short-term kinetics. The resulting acute REL was  $0.6 \mu\text{g}/\text{m}^3$  (0.07 ppb).

This REL is developed for metallic mercury vapor but would be expected to be protective for inhalation of mercury salts. Although mercury salts have no significant vapor pressure under normal atmospheric conditions, they are of concern as hazards if aerosolized or produced during combustion. Animals exposed to mercury vapor inhalation had ten-fold higher brain mercury levels than animals exposed to a similar amount of injected inorganic mercury (mercuric nitrate) (Berlin et al., 1969); however the relationship between kinetics of mercury vapor and mercuric salts has not been extensively studied and may be complex, and dependent on the route, level and timing of exposure.

## 8.2 Mercury 8-Hour Reference Exposure Level

<i>Study</i>	Piikivi and Hanninen (1989); Fawer et al. (1983); Piikivi and Tolonen (1989); Piikivi (1989); Ngim et al. (1992)
<i>Study population</i>	Humans (236)
<i>Exposure method</i>	Inhalation of workplace air
<i>Exposure continuity</i>	8 hours per day, 5 days/week
<i>Exposure duration</i>	13.7 to 15.6 years
<i>Critical effects</i>	Neurotoxicity as measured by: intention tremor; memory and sleep disturbances; decreased performance on neurobehavioral tests (finger tapping, visual scan, visuomotor coordination, visual memory); decreased EEG activity
<i>LOAEL</i>	25 $\mu\text{g}/\text{m}^3$ (3 ppb)
<i>NOAEL</i>	not observed
<i>Benchmark concentration</i>	not derived
<i>Time-adjusted exposure</i>	18 $\mu\text{g}/\text{m}^3$ for LOAEL group (25 x 5/7)
<i>LOAEL uncertainty factor (UF<sub>L</sub>)</i>	10 (default, severe effect, no NOAEL)
<i>Subchronic uncertainty factor (UF<sub>s</sub>)</i>	1
<i>Interspecies uncertainty factor</i>	
<i>Toxicokinetic (UF<sub>A-k</sub>)</i>	1 (default: human study)
<i>Toxicodynamic (UF<sub>A-d</sub>)</i>	1 (default: human study)
<i>Intraspecies uncertainty factor</i>	
<i>Toxicokinetic (UF<sub>H-k</sub>)</i>	$\sqrt{10}$ (default for inter-individual variability)
<i>Toxicodynamic (UF<sub>H-d</sub>)</i>	10 (greater susceptibility of children and their developing nervous systems)
<i>Cumulative uncertainty factor</i>	300
<i>Reference Exposure Level</i>	<b>0.06 <math>\mu\text{g Hg}/\text{m}^3</math> (0.007 ppb Hg<sup>0</sup>)</b>

The 8-hour Reference Exposure Level is a concentration at or below which adverse noncancer health effects would not be anticipated for repeated 8-hour exposures (see Section 6 of the Technical Support Document).

The half life of elimination of mercury in humans following a single inhalation exposure of 14-24 min. was 21 days from the head, 64 days from the kidney, and 58 days from the body as a whole (Hursh et al., 1976). Urinary elimination among workers occupationally exposed for several years had an elimination half life of 55 days (Sallsten et al., 1994). Thus, since mercury is only slowly eliminated, the intervals between daily 8-hr exposures, and between weeks are not long enough for the elimination of significant amounts of the metal and it will accumulate in the body with repeated exposure. In view of this bioaccumulative property of mercury exposure in humans, it was considered necessary to use the same study and derivation (in terms of exposure for seven vs only five days per week) for the 8-hour REL as for the chronic REL described below. However, the exposure duration adjustment used in this case reflects a repeated exposure of 8 hours per day with an activity-related air intake of 10 m<sup>3</sup> per day (i.e. half that assumed for a 24-hour period for the chronic REL). As a result, the time-adjusted exposure is twice that for the

chronic REL. This adjustment reflects the expectation that activity levels, and hence breathing rates, will be higher during the exposure period than during the remaining 16 hours. The increased breathing rate enhances mercury inhalation during the 8 hour exposure period.

The studies chosen for determination of the 8-hr REL examined neurotoxicity in humans as a sensitive endpoint following long-term exposures. They all point to a LOAEL of approximately  $25 \mu\text{g}/\text{m}^3$  (3 ppb) with a time-adjusted value of  $18 \mu\text{g}/\text{m}^3$  ( $25 \times 5/7$ ). In the absence of a NOAEL, we applied an uncertainty factor of 10, the default with neurotoxicity considered a moderate to potentially severe effect. The critical study was conducted in humans and was not a subchronic study so no interspecies or subchronic uncertainty factors were applied. To allow for interindividual variability and to specifically account for greater susceptibility among children, an overall intraspecies uncertainty factor of 30 was applied with a toxicokinetic factor (H-k) of  $\sqrt{10}$  to reflect interindividual variability, and a toxicodynamic factor of 10 that reflects the higher susceptibility of the developing nervous system. The cumulative uncertainty is 300, and the resultant 8-hour REL is thus  $0.06 \mu\text{g Hg}/\text{m}^3$  (0.007 ppb Hg °).

### 8.3 Mercury Chronic Reference Exposure Level

<i>Study</i>	Piikivi and Hanninen (1989); Fawer et al. (1983); Piikivi and Tolonen (1989); Piikivi (1989); Ngim et al. (1992)
<i>Study population</i>	Humans (236)
<i>Exposure method</i>	Inhalation of workplace air
<i>Exposure continuity</i>	8 hours per day (10 m <sup>3</sup> /workday), 5 days/week
<i>Exposure duration</i>	13.7 to 15.6 year
<i>Critical effects</i>	Neurotoxicity as measured by: intention tremor; memory and sleep disturbances; decreased performance on neurobehavioral tests (finger tapping, visual scan, visuomotor coordination, visual memory); decreased EEG activity
<i>LOAEL</i>	25 µg/m <sup>3</sup> (3 ppb)
<i>NOAEL</i>	not observed
<i>Benchmark concentration</i>	not derived
<i>Time-adjusted exposure</i>	9 µg/m <sup>3</sup> for LOAEL group (25 x 10/20 x 5/7)
<i>LOAEL uncertainty factor (UF<sub>L</sub>)</i>	10 (default, severe effect, no NOAEL)
<i>Subchronic uncertainty factor (UF<sub>s</sub>)</i>	1
<i>Interspecies uncertainty factor</i>	
<i>Toxicokinetic (UF<sub>A-k</sub>)</i>	1 (default: human study)
<i>Toxicodynamic (UF<sub>A-d</sub>)</i>	1 (default: human study)
<i>Intraspecies uncertainty factor</i>	
<i>Toxicokinetic (UF<sub>H-k</sub>)</i>	√10 (default for inter-individual variability)
<i>Toxicodynamic (UF<sub>H-d</sub>)</i>	10 (greater susceptibility of children and their developing nervous systems)
<i>Cumulative uncertainty factor</i>	300
<i>Reference Exposure Level</i>	<b>0.03 µg Hg/m<sup>3</sup> (0.004 ppb Hg<sup>0</sup>)</b>

The chronic Reference Exposure Level is a concentration at which adverse noncancer health effects would not be expected from chronic exposures (see Section 7 in the Technical Support Document).

To calculate the chronic REL, studies were chosen that examined a sensitive endpoint (neurotoxicity) in humans following long-term exposures. They all point to a LOAEL of approximately 0.025 mg/m<sup>3</sup> (3 ppb). When adjusted for worker ventilation and workweek exposure, the LOAEL becomes 9 µg/m<sup>3</sup> (25 µg/m<sup>3</sup> x 10 m<sup>3</sup>/20 m<sup>3</sup> x 5 d/7 d). In the absence of a NOAEL, we applied an uncertainty factor of 10, the default with neurotoxicity considered a moderate to potentially severe effect. The critical study was conducted in humans and was not a subchronic study so no interspecies or subchronic uncertainty factors were applied. To allow for interindividual variability and to specifically account for greater susceptibility among children, an overall intraspecies uncertainty factor of 30 was applied with a toxicokinetic factor (H-k) of √10 to reflect interindividual variability, and a toxicodynamic factor of 10 that reflects the higher susceptibility of the developing nervous system. The cumulative uncertainty is 300, and the resultant chronic REL is thus 0.03 µg Hg/ m<sup>3</sup> (0.004 ppb Hg °).

The U.S.EPA (1995) based its RfC of  $0.3 \mu\text{g}/\text{m}^3$  (0.04 ppb) on the same study but used an intraspecies uncertainty factor of 3, a LOAEL uncertainty factor of 3 and included a Modifying Factor (MF) of 3 for database deficiencies (lack of developmental and reproductive toxicity data). This modifying factor was not used by OEHHA since allowance was made via the  $\text{UF}_{\text{H-d}}$  for the known sensitivity of children to the neurodevelopmental impacts of mercury.

It is noteworthy that none of the above studies discussed in sufficient detail a dose-response relationship between mercury vapor inhalation and the toxic effects measured. Because none of the studies mention a level below which toxic effects were not seen (a NOAEL), the extrapolation from a LOAEL to a NOAEL should be regarded with caution. Secondly, one study (Ngim et al., 1992) demonstrated neurotoxic effects from mercury inhalation at an exposure level slightly above the other studies, but for a shorter duration. It is possible that mercury could cause neurotoxic effects after a shorter exposure period than that reported in the study used in derivation of the chronic REL.

As mentioned above, OEHHA (1999) has developed a PHG for inorganic mercury in drinking water of 0.0012 mg Hg/L (1.2 ppb) as a level of exposure expected to be without significant health risk from daily water consumption. This value was based on data from a 1993 study by the National Toxicology Program that supported a NOAEL of 0.16 mg Hg/kg-day for renal toxicity in rats with chronic oral exposure. Application of the cumulative uncertainty factor of 1,000 (10 for use of a subchronic study, and 10 each for inter- and intraspecies variability) used in the PHG derivation, gives an oral REL of  $0.16 \mu\text{g Hg}/\text{kg}\text{-day}$ . This value is several-fold higher than the chronic REL developed above for inhalation of elemental mercury, and reflects the greater ease with which elemental mercury (vs. inorganic mercury) penetrates membranes, especially when exposure is via inhalation versus the oral route.

#### **8.4 Mercury as a Toxic Air Contaminant that Disproportionately Impacts Children**

In view of the differential impacts on infants and children identified in Section 6.2.1, and the possibility of direct (inhalation) and indirect exposure (through a diet containing aquatic animals contaminated with methylmercury), OEHHA recommends that elemental mercury be identified as a toxic air contaminant (TAC) which disproportionately impacts children under Health and Safety Code, Section 39699.5.

## 9. References

- ACGIH (1986). Documentation of the Threshold Limit Values and Biological Exposure Indices. Cincinnati (OH): American Conference of Governmental Industrial Hygienists.
- Albers JW, Kallenbach LR, Fine LJ, Langolf GD, Wolfe RA, Donofrio PD, Alessi AG, Stolp-Smith KA and Bromberg MB (1988). Neurological abnormalities associated with remote occupational elemental mercury exposure. *Ann Neurol* 24(5): 651-9.
- Allen JW, Mutkus LA and Aschner M (2001). Mercuric chloride, but not methylmercury, inhibits glutamine synthetase activity in primary cultures of cortical astrocytes. *Brain Res* 891(1-2): 148-57.
- Asano S, Eto K, Kurisaki E, Gunji H, Hiraiwa K, Sato M, Sato H, Hasuike M, Hagiwara N and Wakasa H (2000). Acute inorganic mercury vapor inhalation poisoning. *Pathol Int* 50(3): 169-74.
- Ashe W, Largent E, Dutra F, Hubbard D and Blackstone M (1953). Behavior of mercury in the animal organism following inhalation. *Ind. Hyg. Occup. Med.* 17: 19-43.
- Ask K, Akesson A, Berglund M and Vahter M (2002). Inorganic mercury and methylmercury in placentas of Swedish women. *Environ Health Perspect* 110(5): 523-6.
- ATSDR. (1999). Toxicological Profile for Mercury. U.S. Department for Human Health Services. Atlanta, GA
- Barregard L, Hultberg B, Schutz A and Sallsten G (1988). Enzymuria in workers exposed to inorganic mercury. *Int Arch Occup Environ Health* 61(1-2): 65-9.
- Berlin M, Fazackerley J and Nordberg G (1969). The uptake of mercury in the brains of mammals exposed to mercury vapor and to mercuric salts. *Arch Environ Health* 18(5): 719-29.
- Bernard AM, Roels HR, Foidart JM and Lauwerys RL (1987). Search for anti-laminin antibodies in the serum of workers exposed to cadmium, mercury vapour or lead. *Int Arch Occup Environ Health* 59(3): 303-9.
- Campbell J (1948). Acute mercurial poisoning by inhalation of metallic vapour in an infant. *Can Med Assoc J* 58: 72-75.
- CARB (2005a). Annual Statewide Toxics Summary - mercury  
<http://www.arb.ca.gov/aqd/toxics/statepages/hgstate.html>. Sacramento, CA.
- CARB. (2005b). *California Toxics Inventory for 2004*. California Air Resources Board.  
<http://www.arb.ca.gov/toxics/cti/cti.htm>.
- Castoldi AF, Coccini T, Ceccatelli S and Manzo L (2001). Neurotoxicity and molecular effects of methylmercury. *Brain Res Bull* 55(2): 197-203.

- Choi BH (1989). The effects of methylmercury on the developing brain. *Prog Neurobiol* 32(6): 447-70.
- Cordier S, Grasmick C, Paquier-Passelaigue M, Mandereau L, Weber JP and Jouan M (1998). Mercury exposure in French Guiana: levels and determinants. *Arch Environ Health* 53(4): 299-303.
- Cory-Slechta DA, Weiss B and Cox C (1985). Performance and exposure indices of rats exposed to low concentrations of lead. *Toxicol Appl Pharmacol* 78(2): 291-9.
- Counter SA, Buchanan LH, Laurell G and Ortega F (1998). Blood mercury and auditory neurosensory responses in children and adults in the Nambija gold mining area of Ecuador. *Neurotoxicology* 19(2): 185-96.
- Danielsson BR, Fredriksson A, Dahlgren L, Gardlund AT, Olsson L, Dencker L and Archer T (1993). Behavioural effects of prenatal metallic mercury inhalation exposure in rats. *Neurotoxicol Teratol* 15(6): 391-6.
- Drexler H and Schaller KH (1998). The mercury concentration in breast milk resulting from amalgam fillings and dietary habits. *Environ Res* 77(2): 124-9.
- Elghany NA, Stopford W, Bunn WB and Fleming LE (1997). Occupational exposure to inorganic mercury vapour and reproductive outcomes. *Occup Med (Lond)* 47(6): 333-6.
- Fagala GE and Wigg CL (1992). Psychiatric manifestations of mercury poisoning. *J Am Acad Child Adolesc Psychiatry* 31(2): 306-11.
- Fawer RF, de Ribaupierre Y, Guillemin MP, Berode M and Lob M (1983). Measurement of hand tremor induced by industrial exposure to metallic mercury. *Br J Ind Med* 40(2): 204-8.
- Florentine MJ and Sanfilippo DJ, 2nd (1991). Elemental mercury poisoning. *Clin Pharm* 10(3): 213-21.
- Fredriksson A, Dencker L, Archer T and Danielsson BR (1996). Prenatal coexposure to metallic mercury vapour and methylmercury produce interactive behavioural changes in adult rats. *Neurotoxicol Teratol* 18(2): 129-34.
- George L, Scott FE, Cole D, Siracusa L, Buffett C, Hunter W and Zinkewich R (1996). The mercury emergency and Hamilton school children: a follow-up analysis. *Can J Public Health* 87(4): 224-6.
- Gilbert SG and Rice DC (1987). Low-level lifetime lead exposure produces behavioral toxicity (spatial discrimination reversal) in adult monkeys. *Toxicol Appl Pharmacol* 91(3): 484-90.
- Grandjean P, Weihe P and Nielsen JB (1994). Methylmercury: significance of intrauterine and postnatal exposures. *Clin Chem* 40(7 Pt 2): 1395-400.

Grandjean P, Weihe P, White RF, Debes F, Araki S, Yokoyama K, Murata K, Sorensen N, Dahl R and Jorgensen PJ (1997). Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicol Teratol* 19(6): 417-28.

Grandjean P, White RF, Nielsen A, Cleary D and de Oliveira Santos EC (1999). Methylmercury neurotoxicity in Amazonian children downstream from gold mining. *Environ Health Perspect* 107(7): 587-91.

Hacon S, Artaxo P, Gerab F, Yamasoe MA, Campos RC, Conti LF and De Lacerda LD (1995). Atmospheric mercury and trace elements in the region of Alta Floresta in the Amazon basin. *Water, Air, and Soil Pollution* 80(1-4): 273-283.

Harada M (1995). Minamata disease: methylmercury poisoning in Japan caused by environmental pollution. *Crit Rev Toxicol* 25(1): 1-24.

Hua J, Brun A and Berlin M (1995). Pathological changes in the Brown Norway rat cerebellum after mercury vapour exposure. *Toxicology* 104(1-3): 83-90.

Hua J, Pelletier L, Berlin M and Druet P (1993). Autoimmune glomerulonephritis induced by mercury vapour exposure in the Brown Norway rat. *Toxicology* 79(2): 119-29.

Hursh JB, Cherian MG, Clarkson TW, Vostal JJ and Mallie RV (1976). Clearance of mercury (HG-197, HG-203) vapor inhaled by human subjects. *Arch Environ Health* 31(6): 302-9.

Kanlun S and Gottlieb CA (1991). A clinical pathologic study of four adult cases of acute mercury inhalation toxicity. *Arch Pathol Lab Med* 115(1): 56-60.

Kishi R, Doi R, Fukuchi Y, Satoh H, Satoh T, Ono A, Moriwaka F, Tashiro K and Takahata N (1993). Subjective symptoms and neurobehavioral performances of ex-mercury miners at an average of 18 years after the cessation of chronic exposure to mercury vapor. Mercury Workers Study Group. *Environ Res* 62(2): 289-302.

Kjellstrom T, Kennedy P, Wallis S, Stewart A, Friberg L, Lind B, Wutherspoon T and Mantell C. (1989). Physical and mental development of children with prenatal exposure to mercury from fish. Stage 2: Interviews and psychological tests at age 6. Report 3642. National Swedish Environmental Protection Board. Solna, Sweden

Kjellstrom T, Kennedy S, Wallis S and Mantell C. (1986). Physical and mental development of children with prenatal exposure to mercury from fish. Stage I: Preliminary tests at age 4. Report #3080. National Swedish Environmental Protection Board. Solna, Sweden

Kostial K, Kello D, Jugo S, Rabar I and Maljkovic T (1978). Influence of age on metal metabolism and toxicity. *Environ Health Perspect* 25: 81-6.

Langolf GD, Chaffin DB, Henderson R and Whittle HP (1978). Evaluation of workers exposed to elemental mercury using quantitative tests of tremor and neuromuscular functions. *Am Ind Hyg Assoc J* 39(12): 976-84.

Leggett RW, Munro NB and Eckerman KF (2001). Proposed revision of the ICRP model for inhaled mercury vapor. *Health Phys* 81(4): 450-5.

Lerch M and Bircher AJ (2004). Systemically induced allergic exanthem from mercury. *Contact Dermatitis* 50(6): 349-53.

Levin M, Jacobs J and Polos PG (1988). Acute mercury poisoning and mercurial pneumonitis from gold ore purification. *Chest* 94(3): 554-6.

Lewandowski TA, Ponce RA, Charleston JS, Hong S and Faustman EM (2003). Effect of methylmercury on midbrain cell proliferation during organogenesis: potential cross-species differences and implications for risk assessment. *Toxicol Sci* 75(1): 124-33.

Liang YX, Sun RK, Sun Y, Chen ZQ and Li LH (1993). Psychological effects of low exposure to mercury vapor: application of a computer-administered neurobehavioral evaluation system. *Environ Res* 60(2): 320-7.

Livardjani F, Ledig M, Kopp P, Dahlet M, Leroy M and Jaeger A (1991). Lung and blood superoxide dismutase activity in mercury vapor exposed rats: effect of N-acetylcysteine treatment. *Toxicology* 66(3): 289-95.

Lowry LK, Rountree PP, Levin JL, Collins S and Anger WK (1999). The Texarkana mercury incident. *Tex Med* 95(10): 65-70.

Lund BO, Miller DM and Woods JS (1993). Studies on Hg(II)-induced H<sub>2</sub>O<sub>2</sub> formation and oxidative stress in vivo and in vitro in rat kidney mitochondria. *Biochem Pharmacol* 45(10): 2017-24.

Marsh DO, Myers GJ, Clarkson TW, Amin-Zaki L, Tikriti S and Majeed MA (1979). Fetal methylmercury poisoning: clinical and toxicological data on 29 cases. *Ann Neurol* 7(4): 348-53.

Matthes FT, Kirschner R, Yow MD and Brennan JC (1958). Acute poisoning associated with inhalation of mercury vapor; report of four cases. *Pediatrics* 22(4 Part 1): 675-88.

McFarland RB and Reigel H (1978). Chronic mercury poisoning from a single brief exposure. *J Occup Med* 20(8): 532-4.

McKeown-Eyssen GE, Ruedy J and Neims A (1983). Methyl mercury exposure in northern Quebec. II. Neurologic findings in children. *Am J Epidemiol* 118(4): 470-9.

Morgan DL, Chanda SM, Price HC, Fernando R, Liu J, Brambila E, O'Connor RW, Beliles RP and Barone S, Jr. (2002). Disposition of inhaled mercury vapor in pregnant rats: maternal toxicity and effects on developmental outcome. *Toxicol Sci* 66(2): 261-73.

Murata K, Weihe P, Renzoni A, Debes F, Vasconcelos R, Zino F, Araki S, Jorgensen PJ, White RF and Grandjean P (1999). Delayed evoked potentials in children exposed to methylmercury from seafood. *Neurotoxicol Teratol* 21(4): 343-8.

Nakayama H, Niki F, Shono M and Hada S (1983). Mercury exanthem. *Contact Dermatitis* 9(5): 411-7.

NAS. (2000). *Toxicological Effects of Methyl Mercury*. National Academy of Sciences. Washington D.C.

Netterstrom B, Guldager B and Heeboll J (1996). Acute mercury intoxication examined with coordination ability and tremor. *Neurotoxicol Teratol* 18(4): 505-9.

Ngim CH, Foo SC, Boey KW and Jeyaratnam J (1992). Chronic neurobehavioural effects of elemental mercury in dentists. *Br J Ind Med* 49(11): 782-90.

OEHHA. (1999). *Public Health Goal for Inorganic Mercury in Drinking Water*. Office of Environmental Health Hazard Assessment. California Environmental Protection Agency. Sacramento, CA

Pamphlett R and Coote P (1998). Entry of low doses of mercury vapor into the nervous system. *Neurotoxicology* 19(1): 39-47.

Piikivi L (1989). Cardiovascular reflexes and low long-term exposure to mercury vapour. *Int Arch Occup Environ Health* 61(6): 391-5.

Piikivi L and Hanninen H (1989). Subjective symptoms and psychological performance of chlorine-alkali workers. *Scand J Work Environ Health* 15(1): 69-74.

Piikivi L, Hanninen H, Martelin T and Mantere P (1984). Psychological performance and long-term exposure to mercury vapors. *Scand J Work Environ Health* 10(1): 35-41.

Piikivi L and Ruokonen A (1989). Renal function and long-term low mercury vapor exposure. *Arch Environ Health* 44(3): 146-9.

Piikivi L and Tolonen U (1989). EEG findings in chlor-alkali workers subjected to low long term exposure to mercury vapour. *Br J Ind Med* 46(6): 370-5.

Rodgers JS, Hocker JR, Hanas RJ, Nwosu EC and Hanas JS (2001). Mercuric ion inhibition of eukaryotic transcription factor binding to DNA. *Biochem Pharmacol* 61(12): 1543-50.

Roels H, Lauwerys R, Buchet JP, Bernard A, Barthels A, Oversteyns M and Gaussin J (1982). Comparison of renal function and psychomotor performance in workers exposed to elemental mercury. *Int Arch Occup Environ Health* 50(1): 77-93.

Rowland AS, Baird DD, Weinberg CR, Shore DL, Shy CM and Wilcox AJ (1994). The effect of occupational exposure to mercury vapour on the fertility of female dental assistants. *Occup Environ Med* 51(1): 28-34.

Rowley B and Monestier M (2005). Mechanisms of heavy metal-induced autoimmunity. *Mol Immunol* 42(7): 833-8.

Sallsten G, Barregard L and Schutz A (1994). Clearance half life of mercury in urine after the cessation of long term occupational exposure: influence of a chelating agent (DMPS) on excretion of mercury in urine. *Occup Environ Med* 51(5): 337-42.

Schwartz J (1994). Low-level lead exposure and children's IQ: a meta-analysis and search for a threshold. *Environ Res* 65(1): 42-55.

Sexton DJ, Powell KE, Liddle J, Smrek A, Smith JC and Clarkson TW (1978). A nonoccupational outbreak of inorganic mercury vapor poisoning. *Arch Environ Health* 33(4): 186-91.

Smith RG, Vorwald AJ, Patil LS and Mooney TF, Jr. (1970). Effects of exposure to mercury in the manufacture of chlorine. *Am Ind Hyg Assoc J* 31(6): 687-700.

Sundberg J, Jonsson S, Karlsson MO and Oskarsson A (1999). Lactational exposure and neonatal kinetics of methylmercury and inorganic mercury in mice. *Toxicol Appl Pharmacol* 154(2): 160-9.

Taug C, Sanfilippo DJ, Rowens B, Szejda J and Hesse JL (1992). Acute and chronic poisoning from residential exposures to elemental mercury--Michigan, 1989-1990. *J Toxicol Clin Toxicol* 30(1): 63-7.

Teisinger J and Fiserova-Bergerova V (1965). Pulmonary retention and excretion of mercury vapors in man. *Ind Med Surg* 34: 580-4.

Tjalve H and Henriksson J (1999). Uptake of metals in the brain via olfactory pathways. *Neurotoxicology* 20(2-3): 181-95.

Torres AD, Rai AN and Hardiek ML (2000). Mercury intoxication and arterial hypertension: report of two patients and review of the literature. *Pediatrics* 105(3): E34.

U.S.EPA. (2000). Reference Dose for Mercury. External Review Draft. NCEA-S-0930. National Center for Environmental Assessment.

USEPA. (1995). *Mercury, elemental Reference concentration for chronic inhalation exposure (RfC)* <http://www.epa.gov/iris/subst/0370.htm>.

USEPA. (1997). Mercury Study Report to Congress. Health Effects of Mercury and Mercury Compounds (Vol V.). Office of Air Quality Planning and Standards; Office of Research and Development.

Warfvinge K (2000). Mercury distribution in the neonatal and adult cerebellum after mercury vapor exposure of pregnant squirrel monkeys. *Environ Res* 83(2): 93-101.

Warfvinge K, Hansson H and Hultman P (1995). Systemic autoimmunity due to mercury vapor exposure in genetically susceptible mice: dose-response studies. *Toxicol Appl Pharmacol* 132(2): 299-309.

Yang JM, Chen QY and Jiang XZ (2002). Effects of metallic mercury on the perimenstrual symptoms and menstrual outcomes of exposed workers. *Am J Ind Med* 42(5): 403-9.

Yole M, Wickstrom M and Blakley B (2007). Cell death and cytotoxic effects in YAC-1 lymphoma cells following exposure to various forms of mercury. *Toxicology* 231(1): 40-57.

Yoshida M, Satoh M, Shimada A, Yasutake A, Sumi Y and Tohyama C (1999). Pulmonary toxicity caused by acute exposure to mercury vapor is enhanced in metallothionein-null mice. *Life Sci* 64(20): 1861-7.

Yoshida M, Watanabe C, Satoh M, Yasutake A, Sawada M, Ohtsuka Y, Akama Y and Tohyama C (2004). Susceptibility of metallothionein-null mice to the behavioral alterations caused by exposure to mercury vapor at human-relevant concentration. *Toxicol Sci* 80(1): 69-73.