NAC/Interim: 09/2010

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

MERCURY VAPOR (Hg^0)

(CAS Reg. No. 7439-97-6)

INTERIM

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels — AEGL-1, AEGL-2 and AEGL-3 — are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

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EXECUTIVE SUMMARY

Mercury vapor, Hg^0, (CAS Reg. No. 7439-97-6) is a colorless, odorless gas generated from elemental mercury or inorganic mercury compounds such as mercuric chloride. Under ambient conditions, mercury is a silver-white, liquid metal. Metallic mercury is non-flammable and only slightly volatile (vapor pressure of 0.002 mm).

Controlled inhalation studies in human volunteers that addressed metabolism used concentrations that ranged from 0.01 mg/m^3 for 7 hours to 0.40 mg/m^3 for 15 minutes. No complaints of ocular or respiratory tract irritation were reported in these studies. Review of past workplace exposure shows that concentrations of 0.4-2.0 mg/m^3 in industry result in mercury poisoning only after chronic exposure. Concentrations of 1.0-5.0 mg/m^3 were not unusual in mercury mining operations in the past (AIHA 2002). Additional human data were available from reconstructions of accidental exposures. An estimated airborne concentration of 16 mg/m^3 for a few hours was lethal to an infant; whereas, an estimated concentration of 15 mg/m^3 for 0.75 hours failed to induce symptoms of Hg poisoning in high-school-age students.

Animal studies addressed acute and repeat-dose toxicity, neurotoxicity, and developmental/reproductive toxicity. Death at high concentrations is due to damage to the lungs which results in respiratory failure. At lower concentrations, mercury vapor is neurotoxic. Absorbed mercury binds to various proteins, particularly thiol-containing proteins, resulting in nonspecific cell injury. Developmental studies that addressed neurotoxicity (primarily spontaneous activity and learning ability) yielded conflicting results. Sufficiently high mercury exposures can induce developmental toxicity at maternally toxic concentrations. Data were inadequate to determine the carcinogenic potential of mercury vapor.

Mercury vapor has no odor. At low concentrations, there are no sensory or irritant warning properties. Therefore, AEGL-1 values are not recommended.

Although maternal exposures were for 2 hours/day for 10 days, a single 2-hour exposure of pregnant Long-Evens rats to 4 mg/m^3 mercury vapor (Morgan et al. 2002) was used as the point of departure for the AEGL-2. This value is a NOAEL for developmental effects. Developmental effects including increased resorption, decreased litter size and decreased neonatal weight were observed at the next higher concentration of 8 mg/m^3. Uncertainty factors for the AEGL-2 were based on a weight of evidence of approach. The following factors were considered in deriving an interspecies uncertainty factor: the 4 mg/m^3 value was a NOAEL for developmental effects (below the definition of the AEGL-2), the exposures were repeated for 10 days, rodents have a higher respiratory rate and cardiac output compared with humans (resulting in faster uptake), and human monitoring studies show some effects at concentrations of 0.4 to 2 mg/m^3 only with chronic exposure (AIHA 2002). The following factors were considered in ascribing an intraspecies uncertainty factor: the population of fetuses is considered a sensitive if not the most sensitive population, the protective action of the placenta in sequestering mercury [the mean concentration of mercury in the brain of dams exposed to 4 mg/m^3 for 10 days was 60-fold higher than in the fetal brain (Morgan et al. 2002)], and incidences of miscarriages and stillbirths were unaffected in women chronically exposed to mercury vapor (median air concentration, 0.09 mg/m^3; range, 0.025-0.60 mg/m^3), although congenital anomalies were

statistically non-significantly increased (Elghany et al. 1997). Based on these factors, interspecies and intraspecies uncertainty factors of 1 and 3 were applied. Application of larger uncertainty factors, for example 10 or 30 (resulting in 2-hour values of 0.4 or 0.13 mg/m^3), results in values that are inconsistent with the available human data, including the chronic exposure of pregnant women in the study of Elghany et al. (1997). In the absence of time-scaling information, the resulting 2-hour value of 1.33 mg/m^3 was time-scaled using default n values of 3 and 1 for shorter and longer exposure durations, respectively (NRC 2001).

The AEGL-3 values were based on a single 1-hour exposure of male Wistar rats to 26.7 mg/m^3; no deaths occurred during the 15-day post-exposure period (Livardjani et al. 1991). No clinical signs were observed, but lungs showed edema and necrosis. Extending the exposure period for another hour (at approximately the same concentration) resulted in 62.5% mortality. This 1-hour highest non-lethal value of 26.7 mg/m^3 meets the definition of the AEGL-3. The 26.7 mg/m^3 value was adjusted by a total uncertainty factor of 3 (an interspecies uncertainty factor of 1 and an intraspecies uncertainty factor of 3) based on a weight of evidence approach. Larger uncertainty factors result in values incompatible with the overall data. Reversible behavioral changes were observed in male and female Wistar rats inhaling 17.2 mg/m^3 for 2 hours/day for 22 exposures (Beliles et al. 1968). The uncertainty factor of 3 is considered sufficient to protect susceptible populations. Values derived using an intraspecies uncertainty factor of 3 are supported by the non-lethal concentrations estimated in accidental exposures [up to 15 mg/m^3 for 0.75 hours [Shelnitz et al. 1988; AIHA 2002)] and measured in occupational settings [0.4-2.0 mg/m^3 (AIHA 2002)]. The resulting 1-hour value of 8.9 mg/m^3 was time-scaled using default n values of 3 and 1 for shorter and longer exposure durations, respectively (NRC 2001). Because the 8-hour time-scaled value of 1.1 mg/m^3 appears low in comparison to accidental non-lethal exposures and is lower than some chronic occupational exposures, the 8-hour value was set equal to the 4-hour value.

The calculated values are listed in the table below.

S 1. Summary of AEGL Values for Mercury Vapor

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL–1[a] (Nondisabling)	Not Recommended	Not Recommended	Not Recommended	Not Recommended	Not Recommended	No odor or warning properties
AEGL–2 (Disabling)	3.1 mg/m^3 (0.38 ppm)	2.1 mg/m^3 (0.26 ppm)	1.7 mg/m^3 (0.21 ppm)	0.67 mg/m^3 (0.08 ppm)	0.33 mg/m^3 (0.04 ppm)	No fetal effects: 4 mg/m^3, 2 hours/day, 10 d – rat (Morgan et al. 2002)
AEGL–3 (Lethal)	16 mg/m^3 (2.0 ppm)	11 mg/m^3 (1.3 ppm)	8.9 mg/m^3 (1.1 ppm)	2.2 mg/m^3 (0.27 ppm)	2.2 mg/m^3 (0.27 ppm)	Highest non-lethal value, 26.7 mg/m^3 for 1 h - rat (Livardjani et al. 1991)

[a] Mercury vapor is odorless. AEGL-1 values are not recommended because mercury vapor has no odor or warning properties at concentrations that may cause health effects.

1. INTRODUCTION

Mercury vapor (CAS Reg. No. 7439-97-6) is a colorless and odorless gas generated from elemental mercury or inorganic mercury compounds. The metallic form of mercury and the

vapor exist in the zero oxidation state (Hg °). At ambient conditions, mercury is a silver-white, liquid metal. It is non-flammable and only slightly volatile (vapor pressure of 0.002 mm). Mercury is practically insoluble in water, but is soluble in many organic solvents (O'Neil et al. 2001; AIHA 2002). Additional chemical and physical properties are summarized in Table 1.

Due to its unique chemical and physical properties such as uniform volume expansion over its entire liquid range, mercury has many uses. It is used in the chloralkali industry as a cathode in the electrolysis of brine and in making a variety of scientific instruments and electrical control devices, as an amalgam tooth filling, and in mining for the extraction of gold (Goyer and Clarkson 2001). Dental amalgam contains 50% mercury. In the past, liquid elemental mercury was a common component of thermometers, barometers, and other laboratory measuring devices. The largest commercial use of mercury in the U.S. (35%) is for electrolytic production of chlorine and caustic soda in mercury cells. In 1995, U.S. consumption was 463 metric tons (ATSDR 1999). The use of mercury in batteries, pigments, explosives, and as a catalyst for production of various plastics has been discontinued in the U.S. (U.S. EPA 1992).

Mercury is a naturally occurring element in the earth's crust. Mercury is mined from cinnebar ore. World wide, cinnebar is mined by open-pit and underground mining; cinnebar is no longer mined in the U.S. The primary method of mercury extraction from ore is by heating in a retort or furnace. Leaching, electrolysis, and electro-oxidation methods have also been used. Primary mercury production has decreased due to mercury recovery and recycling. Use has also declined due to legal restrictions; in the U.S., mercurial compounds are no longer used as biocides in protective coatings and in seed treatment. In 2003, world mine production from the four major producing countries was 1300-1400 tons (DeVito and Brooks, 2005).

TABLE 1. Chemical and Physical Properties

Parameter	Value	Reference
Synonyms	Metallic mercury vapor; elemental mercury vapor; quicksilver (solid form)	AIHA 2002
Chemical formula	Hg	O'Neil et al. 2001
Molecular weight	200.59	O'Neil et al. 2001
CAS Reg. No.	7439-97-6	AIHA 2002
Physical state	Liquid metal; colorless vapor generated from elemental liquid mercury or inorganic compounds of mercury	AIHA 2002
Solubility in water	0.28 μmoles/L (insoluble)	O'Neil et al. 2001
Vapor pressure (25 °C)	2×10^{-3} (mm Hg)	O'Neil et al. 2001
Vapor density (air =1)	6.9	AIHA 2002
Saturation concentration in air	13 mg/m^3 (1.6 ppm) at 20°C 16 mg/m^3 (2.0 ppm) at 22°C 30 mg/m^3 3.7 ppm at 30°C 111 mg/m^3 (13.5 ppm) at 50°C	AIHA 2002
Liquid density (water =1)	13.5 g/cm^3 at 25 °C	O'Neil et al. 2001
Melting point	-38.9°C	O'Neil et al. 2001
Boiling point	356.7°C	O'Neil et al. 2001

Flammability limits	Not flammable	AIHA 2002
Conversion factors*	1 ppm = 8.20 mg/m^3 1 mg/m^3 = 0.122 ppm	AIHA 2002

*In this document, values reported in ppm have been converted to mg/m^3 for consistency.

2. HUMAN TOXICITY DATA

Mercury vapor is odorless (ATSDR 1999).

Mercury vapor emitted from amalgam dental fillings is the major source of mercury exposure of the general public. Mercury excretion correlates with the number of "faces" of the amalgam fillings. Other sources of mercury include natural degassing of the earth's crust, food, and occupational exposure. Diet represents about 1.66 nmol/day compared with fillings, 15-85 nmol/day. Quantities emitted from the earth's surface are believed to be equal to those from industrial applications (WHO 2003; Goyer and Clarkson 2001).

Exposure of humans to extremely high concentrations of mercury vapor may produce an acute, corrosive bronchitis and interstitial pneumonitis (Goyer and Clarkson 2001). At sublethal concentrations, symptoms include tremor or increased excitability. Chronic exposure can result in a variety of neuromotor effects including tremor, ataxia, weakness and erethism, characterized by withdrawal, depression, sensory and sleep disturbances, and emotional lability (Newland et al. 1996). Increased excitability, tremors, and gingivitis have been associated historically with inhalation of mercury vapor and exposure to mercury nitrate in the fur, felt, and hat industries. Acrodynia (pink disease) has been reported in infants exposed via contaminated clothes and carpeting (ACGIH 1996). Mercury was once a common additive in teething powders and other baby products, and sensitive infants developed skin rash.

Studies on the toxicity of mercury vapor have been reviewed by Friberg and Vostal (1972), U.S. EPA (1995), ACGIH (1996), ATSDR (1999), AIHA (2002), and WHO (2003).

2.1. Acute Exposures

2.1.1. Lethality

Concentrations lethal to humans have been reconstructed from accidental exposures (Table 2). These accidents resulted from heating of metallic mercury. Death in all cases was attributed to respiratory failure. Three reports that included fatalities were summarized by AIHA (2002) as follows. Eight employees were accidentally exposed during recovery of tons of warm mercury spilled from a ruptured generator (Tennant et al. 1961). The exposure duration was 3-5 hours and the atmospheric concentrations were estimated at 18-30 mg/m^3 (2.2-3.7 ppm) based on mercury in autopsy samples as well as the concentration of mercury in saturated air in a warm room. All eight employees became ill, and one died. In the second report, torches were used in a confined space to cut mercury-contaminated pipes (Eto et al. 1999; Kurisaki et al. 1999; Asano et al. 2000). All 27 employees became ill and three died. The duration of exposure was 2-3 hours for the three fatalities and the concentration was estimated at 43 mg/m^3 (5.2 ppm) based on a simulation of the accident. The simulation was consistent with mercury found in autopsy tissues. In one other case, liquid mercury was accidentally spilled on a hot stove. All three exposed

individuals became ill; the only fatality was an infant (Campbell 1948). According to the study author, different medical intervention would have been applied if the exposure to mercury had been reported when the infant was admitted to hospital.

2.1.2. Nonlethal Toxicity

Data on acute exposures are available only from reconstruction of accidents and metabolism studies (See Section 4.1 for metabolism studies). AIHA (2002) described two instances in which exposures to estimated concentrations of 13 mg/m^3 (1.6 ppm) for 3-5 hours or 16 mg/m^3 (2 ppm) for <8 hours produced cough, dyspnea, and chest tightness (Seaton and Bishop 1978; McFarland and Reigel 1978). In a third report, high-school-age students exposed to an estimated 15 mg/m^3 (1.8 ppm) for 0.75 hours failed to exhibit signs of acute Hg^0 poisoning (Shelnitz et al. 1988). Exposure of the students was verified by long-term measurements of urinary mercury. Two additional reports of gold ore processing in a home resulted in illness, but no fatalities. The estimated concentration was 16 mg/m^3 and the duration was estimated at a few hours.

TABLE 2. Estimated Human Exposures - Reconstructions of Accidental Exposures[a]

Exposure Situation (Reference)	Estimated Exposure Time	Estimated Concentration	Number Exposed (Number ill,[b] fatalities)
Recovery of tons of mercury from ruptured generator (Tennant et al. 1961)	3-5 h	18-30 mg/m^3 (2.2-3.7 ppm)	8 (8, 1)
Torches used in confined space to cut contaminated pipes (Eto et al. 1999; Kurisaki et al. 1999; Asano et al. 2000))	2-3 h	43 mg/m^3 (5.2 ppm)[c]	27 (27, 3)
Liquid mercury poured on stove[d] (Campbell 1948)	"few h"	16 mg/m^3 (2 ppm)	3 (3, 1 [infant])
Home gold ore processing[d] (Haddad and Stenberg 1963)	"few h"	16 mg/m^3 (2 ppm)	2 (2, 0)
Home gold ore processing[d] (Hallee 1969)	"few h"	16 mg/m^3 (2 ppm)	5 (5, 0)
Workers exposed to vaporized mercury in airflow[e] (Seaton and Bishop 1978)	3-5 h	13 mg/m^3 (1.6 ppm)	4 (4, 0)
Broken thermostat on hot oven in small building (McFarland and Reigel 1978)	<8 h	44.3 mg/m^3 (5.4 ppm)[c]	9 (6, 0)
Mercuric oxide heated in unventilated school laboratory[d] (Shelnitz et al. 1988)	0.75 h	15 mg/m^3 (1.8 ppm)	23 (0, 0)

[a] Data taken from AIHA 2002.
[b] Symptoms summarized in text.
[c] AIHA (2002) reported an estimated concentration of 16 mg/m^3 (see footnote d).
[d] The minimum of the computed air concentration (mass of vaporized mercury divided by volume of enclosed area) and the theoretical air saturation concentration for mercury vapor (16 mg/m^3) at the known or assumed air temperature of 22ºC.

[e] Mercury vaporized (estimated at 100 mL) at 90 °C, blown into a pressure chamber at 500 ft^3/min, temperature of walls 260 °C, then into chamber (7.2 x 2.4 x 1.8 m) containing workers at 20ºC. Twenty hours later, 2 mg/m^3 measured by Drager tube.

Milne et al (1970) reported that four workmen became ill for up to a month after exposure to mercury while repairing a mercury-contaminated tank. Individual exposures depended on task performed, and ranged from 2.5 to 5 hours. A simulation of the accident while repairing a similar tank showed mercury concentrations of 1.1 to 2.9 mg/m^3 in the breathing zone of the workmen. During the actual exposure, a nearby small steam heating pipe was inadvertently left turned on, likely increasing the mercury concentrations in the tank.

2.2. Occupational Monitoring

Personal sampling of two workers during maintenance operations at a chloralkali plant showed TWAs of metallic mercury vapor of 0.152 mg/m^3 (0.019 ppm) and 0.131 mg/m^3 (0.016 ppm) (Barregard et al. 1992). Total exposure times were 20 and 23 hours, respectively, over two days. On the third day both subjects were exposed to an average concentration of 0.190 mg/m^3 (0.023 ppm) for 8 hours. Stationary sampling in the room showed a TWA of 0.060 mg/m^3 (0.007 ppm). For an additional 7 workers, concentrations in work rooms were between 0.010 and 0.400 mg/m^3 (0.001 and 0.049 ppm). Two of the workers (not clearly stated which ones) had used respiratory equipment during 15% of the working hours. Symptoms were not addressed, but maintenance operations appeared to be routine.

IARC (1993) summarized occupational exposure to mercury in various industries and occupations. Mean air concentrations ranged up to 0.20 mg/m^3 (0.024 ppm). IARC pointed out that these general air samples are usually lower than personal samples. Biological monitoring (blood and urine samples) reflected the exposure concentrations. A review of occupational monitoring studies by WHO (2003) suggests that an increased prevalence of subclinical symptoms such as slight objective changes in short-term memory or tremor may occur with long-term exposure to mercury vapor at levels $\geq$20 $\mu g/m^3$ (0.0024 ppm).

AIHA (2002) summarized past workplace exposures. Concentrations in the range of 0.4-2 mg/m^3 (0.05-0.25 ppm) in industries have resulted in chronic mercury poisoning. Air concentrations of 1.0-5.0 mg/m^3 (0.12-0.61 ppm) were not unusual in mercury mining operations in the past.

2.3. Neurotoxicity

Effects of mercury vapor on the central nervous system have been well documented (Goyer and Clarkson 2001). As noted, high, acute, non-fatal concentrations produce tremor and increased excitability and can induce pneumonitis. At lower concentrations, symptoms may be non-specific. Specific concentrations at which these symptoms occur were not provided.

2.4. Developmental/Reproductive Toxicity

Studies addressing the effect of mercury vapor on human reproduction and development were summarized by ACGIH (1996), ATSDR (1999), and AIHA (2002). No numeric acute-duration exposure data were available. Retrospective studies on human fertility were evenly divided between those showing an effect and those showing no effect. Developmental data were similarly inconclusive. Exposure concentrations were not provided in most studies. A 28-year study of pregnancies in 57 women chronically exposed to inorganic mercury vapor (median air concentration, 0.09 mg/m^3; range, 0.025-0.60 mg/m^3) did not reveal a significant difference from 27 controls regarding miscarriages or stillbirths (Elghany et al. 1997). The overall fetal death rate was similar to that of New York state and national levels for the same period. Although statistically non-significant, the incidence of congenital anomalies including clubfoot and extrophy of the bladder was higher in Hg-exposed workers than in unexposed workers (4.2% vs 0%). But, there was no apparent concentration-response relationship for the congenital anomalies (concentrations of 0.025 to 0.23 mg/m^3); however, the study authors noted the small size of their study population and suggested that additional studies, either a larger, retrospective or prospective epidemiological study, be conducted. Health habits of the pregnant women were not assessed. Inorganic mercury concentrations were monitored using a portable, ultraviolet absorption mercury vapor meter. Samples were taken in the area of the workers faces.

According to AIHA (2002), case studies of accidental exposures suggest that infants and toddlers are at greater risk than older children and adults of developing severe and progressive lung injury. Many of these studies did not cite concentrations. In some cases, infants may have experienced higher exposure while crawling on the floor. Campbell (1948) reports that an infant that died from mercury poisoning was close to a hot stove on which mercury was vaporized. Symptoms of fatigue, nausea, and abdominal cramps were reported in two adults in the household.

The concentration of total mercury in brain and kidney of 18-19 terminated fetuses and 14-15 deceased infants was analyzed by Lutz et al. (1996). The mean concentrations of mercury in the brain of fetuses and infants were 5 and 6 μg/kg (ng/g) wet weight (range, ≤2-23 μg/kg). The mean concentrations in the kidney of fetuses and infants were 9 μg/kg (range, ≤5-34 μg/kg) and 12 μg/kg (range, 3-37 μg/kg), respectively (data summarized in Table 7). There was a tendency of increasing concentration of mercury in the fetal kidney but not in the brain with increasing number of amalgam fillings in the mothers. The mercury in the tissue samples was not speciated, and, based on results of other studies, the authors indicate that most of the mercury in the brain may be methyl mercury. These mean values for mercury in the human brain are similar to that found by Fredriksson et al. (1996) for rats exposed *in utero* to 1.8 mg/m^3 during PND 2-3.

2.5. Genotoxicity

Evidence for the genotoxicity of mercury vapor is limited. Cytogenetic monitoring studies of occupationally-exposed workers produced mixed results, but the overall findings in studies with appropriate control groups found no convincing evidence that mercury adversely affects the number or structure of chromosomes in human somatic cells (ATSDR 1999; U.S. EPA 1995).

2.6. Carcinogenicity

Chronic toxicity/carcinogenicity studies were summarized by ACGIH (1996) and the U.S. EPA (1995). ACGIH used an A4 classification - *not classifiable as a human carcinogen* - for inorganic forms of mercury including metallic mercury. The U.S. EPA in their Integrated Risk Information System (IRIS) considered the evidence for both animal and human carcinogenicity inadequate and assigned a classification of *D - not classifiable as to human carcinogenicity*. The U.S. EPA identified a LOAEL for systemic effects of 0.025 mg/m^3 (0.003 ppm) for chronic (8-hours/day) exposures. The critical effects were hand tremor, increases in memory disturbance, and slight subjective and objective evidence of autonomic dysfunction. A NOAEL was not identified.

2.7. Summary

Data on human exposure to mercury vapor are limited to accidental exposures and occupational monitoring. Concentrations from the reconstructed accidental exposures were based on symptoms, estimated releases, room size, urinary mercury excretion, and, in cases of death, tissue concentrations at autopsy. Estimated exposures of 3-5 hours to 18-30 mg/m^3 (2.2-3.7 ppm) and 2-3 hours at 43 mg/m^3 (5.2 ppm) killed some workers (AIHA 2002). Exposures to concentrations of 13-16 mg/m^3 (1.6-2 ppm) for several hours caused cough, shortness of breath, and chest tightness (Seaton and Bishop 1978; McFarland and Reigel 1978; AIHA 2002). One case report of exposure to 15 mg/m^3 (1.8 ppm) for 0.75 hours found no overt symptoms (Shelnitz et al. 1988). An estimated concentration of 16 mg/m^3 was not lethal to adults, but one infant died following exposure of a "few hours."

Occupational studies indicate that exposure to mercury vapor concentrations of 0.4-2 mg/m^3 (0.05-0.25 ppm) may induce symptoms of mercury intoxication but only after repeated exposure over several weeks or longer. Signs of Hg poisoning have not been reported for exposure to these concentrations for hours or days (AIHA 2002).

Human developmental studies indicate a potential for an increase in fetal anomalies as a result of mercury vapor exposure, but the limited studies to date have not shown a statistically significant relationship. Additionally, the American Industrial Hygiene Association reported that the young child may be at greater risk for developing severe and progressive lung injury (AIHA 2002). Mercury vapor does not appear to be genotoxic. Studies are too limited to allow a conclusion concerning its carcinogenic potential.

3. ANIMAL TOXICITY DATA

3.1. Acute Studies

Acute studies with both lethal and non-lethal endpoints are summarized in Table 3.

3.1.1. Rats

Groups of 32 male Wistar rats inhaled (whole-body) analytically-determined concentrations of 26.7 mg/m^3 (3.25 ppm) for one hour or 27.0 mg/m^3 (3.29 ppm) for two hours

(Livardjani et al. 1991). Sacrifices took place from 1 to 15 days postexposure. No rats exposed to 26.7 mg/m^3 for one hour died and no clinical signs were evident. Animals inhaling 27.0 mg/m^3 for two hours showed dyspnea and 20 died within 5 days of exposure. Microscopic examination of the lung tissue revealed alveolar edema, hyaline membranes, and occasional fibrosis.

3.1.2. Mice

Groups of 16 C57Bl6 wild-type and metallothionein-null mice inhaled 0 or 5.5-6.7 mg/m^3 (0.67-0.82 ppm) of mercury vapor for 3 hours, and the mice were killed at 1, 24, 72, or 168 hours post-exposure (Yoshida et al. 1999a). Metallothionein was induced in the lungs, kidneys, and brain. Liver and kidney function, as determined by glutamate oxaloacetate transaminase and glutamate pyruvate transaminase activity, blood urea nitrogen, and serum creatinine, were all within normal limits.

Twenty-four male ICR mice inhaled an analytically-determined concentration of 9.8 mg/m^3 (1.2 ppm) mercury vapor for 1 hour; groups of six animals were sacrificed at 1, 24, 48, and 120 hours after exposure (Shimojo et al. 1996). Protein in broncho-alveolar lavage fluid (BALF) was used as a marker of lung injury. Protein in BALF increased with time: 169% of the control value at both 1 and 24 hours and 441% of the control value at 48 hours. At 48 hours after exposure, BALF contained large amounts of hemoglobin, indicating pulmonary hemorrhage. Superoxide dismutase, an antioxidant enzyme, increased following exposure, but returned to a near control level by 120 hours postexposure. Mortality was not addressed.

3.1.3. Rabbits

Rabbits were exposed to mercury vapor at an average analytically-determined concentration of 28.7 mg/m^3 (3.5 ppm) for 1 to 30 hours (Ashe et al. 1953). Fourteen rabbits were used, with one or two at each exposure duration. The longer exposure durations were conducted intermittently, over periods of several days. Surviving animals were sacrificed on the 6th day after exposure ended. Two rabbits exposed for one hour showed mild to moderate damage to the brain, kidney, heart, and lung (not further described). A two-hour exposure (2 rabbits) resulted in marked cellular degeneration of the kidney and brain. Exposure for ≥4 hours resulted in moderate to marked cellular degeneration of the heart, liver, and lungs and severe damage to the kidney and brain. Severe damage was characterized as nearly complete destruction with widespread necrosis. One rabbit inhaling Hg^0 for 6 hours/day for 5 days (total of 30 hours) died near the end of exposure.

TABLE 3. Summary of Acute Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Time	Effect	Reference
Rat	26.7 mg/m^3 (3.25)	1 h	No deaths; mild lung lesions; no breathing difficulties	Livardjani et al. 1991
	27.0 mg/m^3 (3.29)	2 h	Death of 20/32; severe lung lesions; dyspnea	
Mouse	5.5-6.7 mg/m^3 (0.67-0.82)	3 h	Normal liver and kidney function	Yoshida et al. 1999a
Mouse	9.8 mg/m^3 (1.2)	1 h	Increased protein content of broncho-alveolar lavage fluid	Shimojo et al. 1996
Rabbit	28.7 mg/m^3 (3.5)	1 h	Mild organ damage	Ashe et al. 1953
		$\geq$4 h	severe organ damage	

3.2. Repeat-Dose Studies

Recent repeat-dose studies are summarized in Table 4. Older studies are described in the following text, but, because of design flaws and outdated analytical methodology, are not included in Table 4. Data from repeat-exposure studies that addressed neurotoxicity are summarized in Table 4, but are discussed in Section 3.3. Studies in Table 4 are arranged first by species and then by increasing concentration. Data from repeat-exposure studies that addressed pregnancy outcome are included in Table 5 and are discussed in Section 3.4.

Two dogs exposed 8 hours/day for 40 days to 1.89 mg/m^3 (0.23 ppm) showed no clinical signs (Fraser et al. 1934). Six dogs exposed 8 hours/day to 15.29 to 20.06 mg/m^3 (1.86-2.44 ppm) died within 1-3 days and two of six dogs exposed daily for 8 hours to 12.55 mg/m^3 (1.53 ppm) died within 2-3 days. The remaining dogs developed shortness of breath, weakness, vomiting, and diarrhea. Although well-conducted for the time, this study suffers from outdated analytical methodology and the reported exposure concentrations are not reliable.

Groups of 25 female Long-Evans rats were exposed nose-only to 4 mg/m^3 (0.49 ppm) 2 hours/day for up to 10 days (Brambila et al. 2002). Groups of 5 treated and 5 control rats were sacrificed on days 1, 5, 10, 17, and 37. Microscopic examination of kidneys failed to reveal tissue damage in the kidney (the only organ examined). No clinical effects were described and no deaths were mentioned at sacrifice on day 37.

No clinical signs other than slight body weight loss (data not provided) were observed in male and female brown Norway rats (groups of 7) exposed to a measured concentration of 1 mg/m^3 (0.12 ppm) of mercury vapor for 24 hours/day, 7 days/week, for 5 weeks or 6 hours/day, 3 days/week for 5 weeks (Warfvinge et al. 1992). One rat in the continuous exposure group died of kidney damage after 4 weeks of exposure. Neurological examinations were not performed. The mercury exposure induced an autoimmune disease (not otherwise described) (Hua et al. 1992).

No deaths occurred in a group of female Wistar rats exposed to 1 mg/m^3 (0.12 ppm), 24 hours/day for 28 days (Gage 1961). After 10 days of continuous exposure, a steady-state was achieved in that elimination of mercury in the urine was equal to absorption.

TABLE 4. Summary of Repeat-Dose Inhalation Data in Laboratory Animals

Species	Concentration (ppm)	Exposure Duration	Effect	Reference
Rat, male Wistar	0.48 mg/m^3 (0.06)	5 h/d, 4-5 d/wk, 8 wk	"Irritable" behavior during weeks 6-8; microscopic changes in nervous system	Schionning et al. 1998; Sorensen et al. 2000
Rat, Norway	1 mg/m^3 (0.12)	24 h/d, 7 d/wk, 5 wks	One death (of 7 rats) after 5 weeks of exposure	Warfvinge et al. 1992
Rat, female, Wistar	1 mg/m^3 (0.12)	24 h/d, 28 d	All rats survived; weight loss; lethargy by the 7th day; slight tremors when handled at termination	Gage 1961
Rat, male, (strain unidentified)	3.0 mg/m^3 (0.37)	3 h/d, 5 d/wk, 12-42 weeks	Reversible tremors at 18 weeks; except for kidney changes, normal histopathology at sacrifice	Kishi et al. 1978
Rat, female, Long-Evans	4 mg/m^3 (0.49)	2 h/d, 10 d	No deaths, no kidney damage	Brambila et al. 2000
Rat, male and female Wistar	17.2 mg/m^3	2 h/d, 5 d/wk, 30 days	Reversible behavioral changes (increase in escape response and response time latency at 15 days; decrease in avoidance response	Beliles et al. 1968
Mouse, C57Bl6	0.06 mg/m^3 (0.007)	8 h/d, 23 wk	Neurobehavioral effects (increased activity)	Yoshida et al. 2004
Mouse, C57Bl6	0.1 mg/m^3 (0.12) 4.1 mg/m^3 (0.50)	1 h/d, 3 d/wk, two wk, followed by 30 min/d, 3 d/w, 11 wk	No toxic signs and no deaths	Yasutake et al. 2004
Mouse, C57Bl6	6.6-7.5 mg/m^3 (0.80-0.91)	4 h/d, 3 d	No deaths, no lung lesions	Yoshida et al. 1999b
Rabbit, male	4.0 mg/m^3 (0.49)	6 h/d, 4 d/wk, 13 wk	Slight tremors and clonus at 13 weeks	Fukuda 1971

No deaths occurred and no signs of toxicity were evident in wild-type or metallothionein-null mice exposed to 0.1 mg/m^3 (0.1 ppm) for 1 hour/day, 3 days/week for two weeks, followed by exposure to 4.1 mg/m^3 for 30 minutes/day, 3 days/week for 11 weeks (Yasutake et al. 2004). Metallothionein was induced/increased in the brains of wild-type mice. Mercury could be detected histochemically in the brains of both strains of mice, but no pathological change was observed. When tested at 12 and 23 weeks, increased activity and decreased passive avoidance were observed in female OLA129/C57BL6 mice following exposure to 0.06 mg/m^3 for 8 hours/day for 23 weeks (Yoshida et al. 2004). These effects were greater in metallothionein-null mice.

Groups of 14 C57Bl6 wild-type and metallothionein-null mice inhaled 0 or 6.6-7.5 mg/m^3 of mercury vapor for 4 hours/day for 3 consecutive days (Yoshida et al. 1999b). Seven mice from each group were sacrificed 24 hours after the first exposure. Clinical signs were not

described. No wild-type mice died over the 3-day period. Two and eight metallothionein-null mice died within 24 hours after 2 and 3 days of exposure, respectively. Pulmonary histology showed congestion, atelectasis, and mild to moderate hemorrhage in the alveoli of both wild-type and metallothionein-null mice. The lesions were more severe in the metallothionein-null mice and, for both groups, became more pronounced as exposure duration increased. With increasing exposure duration, metallothionein increased in the lungs of wild-type mice, but not in the lungs of metallothionein-null mice.

A group of 16 rabbits inhaled 6.0 mg/m^3 (0.73 ppm) mercury vapor for 7 hours/day, 5 days/week (Ashe et al. 1953). Exposures continued for up to 12 weeks. None of the rabbits died. A rabbit exposed for one week showed mild to moderate damage of the kidney, liver, brain, heart, and lung. In most cases, damage to the kidney and brain became more severe with longer exposures and was described as ranging from marked cellular degeneration with some necrosis to nearly complete destruction with widespread necrosis.

3.3. Neurotoxicity

Neurotoxicity studies are discussed below. Developmental neurotoxicity studies are summarized in Section 3.4 and Table 5.

Adult male Wistar rats inhaled 0.48 mg/m^3 of metallic mercury for 5 hours/day, 4 or 5 days/week over an 8-week period (Schionning et al. 1998; Sorensen et al. 2000). During the last 2-3 weeks of exposure, the treated rats became “irritable” and food and water intake were decreased. Analysis of changes in the nerve tissue was by microscopic “stereological” observations. The peripheral nervous system was little affected. The mean cross section of myelin associated with nerve fibers in the dorsal nerve roots was significantly reduced (by 20%) and there was a tendency towards a reduction in axon area of myelinated nerve fibers in the dorsal nerve roots and in the total numbers and mean volume of some cell types. The central nervous system (cerebellum) showed reductions in numbers of Purkinje and granule cells and volume of the granular cell layer.

Reversible behavioral changes were observed in male and female Wistar-derived rats exposed to 17.2 mg/m^3 (2.1 ppm) mercury vapor for 2 hours/day, 5 days/week for 18-22 exposures over 30 days (Beliles et al. 1968) and 14 male Wistar rats exposed to 3.0 mg/m^3 (0.37 ppm) mercury vapor for 3 hours/day, 5 days/week for 12 to 42 weeks (Kishi et al. 1978). In the first study, six female albino rats were used in avoidance escape studies (five controls) and seven pairs of male rats were used in reflexive fighting studies (five control pairs). Mercury exposure produced an increase in escape response latency and a decrease in avoidance responding when tested during the exposure. For female rats, the increase in escape response began about day 15 of exposure. Male rats showed an increased spontaneous fighting response late in the exposure. During the last 5 days of exposure, female rats in the avoidance escape study showed a fine tremor and some weight loss. The behavioral changes were reversed during a 60-day recovery period. At autopsy following exposure, two of three female rats that exhibited behavior changes had histological changes in the medulla oblongata of the central nervous system, consisting of perivascular cuffing by lymphocytes. These lesions were less severe in rats sacrificed after the recovery period. No lesions were observed in the lung, liver, or kidney. Male rats also showed

infiltration of lymphocytes in the central nervous system. The concentration of mercury was measured with a vapor analyzer.

In the second study (Kishi et al. 1978), male rats (two groups of seven, strain unspecified) exposed to 3.0 mg/m^3 (0.37 ppm) mercury vapor for 3 hours/day, 5 days/week for 12 to 42 weeks exhibited behavioral changes and gained less weight than a control group. When tested during the weeks of exposure, rats showed a decline in avoidance response and an increase in escape latency. The time to onset of these effects varied from 12 to 39 weeks. Tremors were first observed during the 18th week of exposure. All rats recovered to a normal rate of responding and normal latency within 12 weeks after termination of exposure. Rats sacrificed at the end of exposure showed slight degenerative changes in the tubular epithelium of the kidney, but no changes in the lung, liver, or brain. Tissues of rats sacrificed after recovery were normal.

Slight tremors and clonus were observed in two of six male rabbits that inhaled an analytically determined average concentration of 4.0 mg/m^3 (0.49 ppm) mercury vapor for 6 hours/day, 4 days/week for 13 successive weeks (Fukuda 1971). These signs were observed at the end of the weeks of exposure.

3.4. Developmental/Reproductive Toxicity

Reproductive and developmental toxicity studies including developmental neurotoxicity studies and fetal and neonatal tissue concentrations of mercury are summarized in Table 5.

Mercury vapor penetrates the maternal placental and blood-brain barrier of the developing fetus. Mercury associated with metallothionein accumulates in the placenta. Following in utero exposure, mercury concentrations in fetal organs are lower than those of respective maternal organs (Khayat and Dencker 1982; Yoshida et al. 1986; Brambila et al. 2002).

Pregnant squirrel monkeys were exposed to either 0.5 or 1.0 mg/m^3 (0.06 or 0.12 ppm) of mercury vapor for either 4 or 7 hours/day (Newland et al. 1996). Exposures were conducted for 5 days/week between weeks 3 and 22 of gestation, for a total number of exposure days ranging from 63-79 (gestation period of 154 days). None of the six tested offspring was prenatally exposed over exactly the same period of gestation. Offspring were selected from "uneventful" pregnancies. The offspring were 0.8 to 4 years of age when evaluated in a lever-press test. Exposure-related increases in performance variability and longer lever-press duration were reported, with one offspring displaying "erratic" behavior, but results were extremely variable among and between the controls and exposed groups.

Soderstrom et al (1995) exposed groups of eight pregnant Sprague-Dawley rats to 1.5 mg/m^3 for 1 or 3 hours/day, either early in pregnancy (gestation day [GD] 6-11) or late in pregnancy (GD 13-18). There was no effect on body weight of the dams or neonates, and clinical signs and development of the offspring observed at postnatal day 2-3 were normal. A group of offspring were sacrificed on PND 2-3 for examination of mercury in different areas of the brain. Additional groups were sacrificed on PNDs 21 and 60, and areas of the brain were analyzed for nerve growth factor and its low- and high-affinity receptors (mRNA coding for nerve growth factor) as well as choline acetyltransferase activity. On day 2-3 postexposure, mercury

concentrations in brain of the neonate control and 1-hour and 3-hour exposure groups were 1, 4, and 11 ng/g wet weight, respectively (it is assumed this is for both early and late pregnancy exposures). Following the higher exposure during early pregnancy, nerve growth factor was increased in the hippocampus area of the brain and decreased in the basal forebrain and septal area on PND 21. mRNA was reduced in the basal forebrain. The authors suggested neuronal damage and disturbed trophic regulation during development.

TABLE 5. Reproductive, Developmental, and Developmental Neurotoxicity Studies in Laboratory Animals

Species	Concentration/ Duration/Age	Effect	Reference
Reproductive			
Rat	(1) Pre-breeding: 1, 2, or 4 mg/m^3 2 h/d, 11 consecutive days; (2) 1 or 2 mg/m^3 8 days prior to and 8 days after breeding	(1) Estrous cycle and hormone level changes secondary to general toxicity at 4 mg/m^3; (2) No significant effect on pregnancy rate or pregnancy maintenance	Davis et al. 2001
Developmental/Neurotoxicity			
Monkey	0.5, 1.0 mg/m^3, 4 or 7 h/d between gestation wk 3 and 22	Exposure-related, but variable performance in lever-press test in adulthood	Newland et al. 1996
Rat	1.5 mg/m^3, 1 or 3 h/d GD 6-11 or 13-18	No clinical signs; no developmental effects; nerve growth factor increased or decreased in different areas of the brain	Söderstrom et al. 1995
Rat	1.8 mg/m^3, 1 or 3 h/d GD 11-14 or 17-20	No clinical signs and no effect on maturation endpoints of offspring. Neurotoxicity tests indicated reduced ability to adapt; hypoactivity at 3 months and hyperactivity at 14 months, but no effect 11 months later; no effect on swim maze test	Danielsson et al. 1993
Rat	1.8 mg/m^3, 1.5 h/d, GD 14-19	No effect on clinical signs or developmental markers of offspring; hyperactivity in spontaneous motor activity and latencies in some maze tests at 4-5 months of age; mercury concentration in brain at 2-3 days postpartum: 5±2 µg/kg wet weight	Frederiksson et al. 1996
Rat	1, 2, 4, or 8 mg/m^3, 2 h/d, GD 6-15	Concentration-related increases in fetal tissue concentrations of mercury after 5 and 10 days; maternal and fetotoxicity at 8 mg/m^3 (dams became moribund by PND 1); decreased weight gain (7%) in the dams in the 4 mg/m^3 group	Morgan et al. 2002; Brambila et al. 2002
Rat	4 mg/m^3, 2 h/d, GD 6-15	No effect on responses of peripheral nerves, somatosensory (cortical and cerebellar), auditory or visual modalities when tested on PNDs 140-168	Herr et al. 2004
Rat	0.05 mg/m^3, 1 or 4 h, neonatal days 11-17	No clinical signs; changes in motor activity and learning in one test, tested at 2-6 months of age	Fredriksson et al. 1992

GD = gestation day.

Groups of 12 pregnant Sprague-Dawley rats inhaled 0 or 1.8 mg/m^3 (0.22 ppm) mercury vapor for 1 hour (defined as the low-dose group) or 3 hours (high-dose group) during GD 11-14 and 17-20 (Danielsson et al. 1993). These concentrations were not maternally toxic. On days 2-3 postpartum, three offspring from each group were sacrificed and the brain, liver, and kidney were analyzed for mercury. There were statistically significant dose-related elevated amounts of mercury in all organs analyzed except for brain in the low-dose group.

Additional groups of offspring in this study (Danielsson et al. 1993) were examined for maturation endpoints as well as activity and learning. There were no differences in body weight, maturation variables, or clinical signs between exposed and control offspring. Treated offspring were hypoactive for spontaneous motor activity when tested at 3 months of age but hyperactive at 14 months. In a radial arm maze learning test (for a food reward), prenatally exposed rats showed retarded acquisition of spatial learning. However, there were no differences between control and exposed groups in learning ability in a swim maze. In a test of habituation to a novel environment, prenatally exposed rats showed a reduced ability to adapt. When tested at 11 months after the initial tests, there were no differences in activity among the control and exposed groups of offspring.

Fredriksson et al. (1996) exposed 12 pregnant Sprague-Dawley rats to 1.8 mg/m^3 (0.22 ppm) mercury vapor for 1.5 hours/day during GD 14-19. Additional groups were administered methyl mercury by gavage (2 mg/kg/day over GD 6-9) or both methyl mercury and mercury vapor at the described doses. Compared to a control group, treated offspring (all groups) showed no differences in clinical parameters or developmental markers. Surface righting reflex and negative geotaxis were unaffected within a few days after birth. When tested at 4-5 months of age, offspring treated with mercury vapor alone showed hyperactivity in spontaneous motor activity (locomotion, rearing, and total activity) and longer latencies in swim and radial arm maze tests. Results in some tests were conflicting as latency was shown in the swim maze on the second test day of two consecutive days of testing but not on the first day. Exposure to methylmercury did not alter these functions, but coexposure to methylmercury and mercury vapor increased the mercury vapor-induced deficits.

Pregnant Long-Evans rats were exposed nose-only to analytically-determined concentrations of 0, 1, 2, 4, or 8 mg/m^3 of mercury vapor for 2 hours/day from GD 6 through 15 (Morgan et al. 2002). Initial groups consisted of 25 rats, with sacrifices on GD 6, 10, and 15 and 1 week after the last exposure. Maternal toxicity, described as concentration-related decreases in weight gain and mild nephrotoxicity (increased urinary protein and alkaline phosphatase, but not glucose), were observed in rats exposed to 4 and 8 mg/m^3. Dams exposed to 8 mg/m^3 exhibited mild tremor and unsteady gait (day of onset not stated), and were euthanized in moribund condition on postnatal day (PND) 1. There was no histopathological evidence of toxicity in maternal lung, liver, or kidney of any rats exposed to 1, 2, 4, or 8 mg/m^3 at GD 6 or 15, or PND 1. Metallothionein and glutathione *S*-transferase activity levels were increased in the kidney, lung, and brain of maternal animals (measured only in the 4 mg/m^3 group), but not in the tissues of neonates. [Glutathione transferase activity was higher in pregnant rats than in a group of concurrent control non-pregnant rats (Brambila et al. 2002)]. Developmental effects were

confined to the 8 mg/m^3 group and consisted of increased resorption, decreased litter size, and decreased PND 1 neonatal weight. Neonatal organ weights were not affected by exposure. Mercury levels in brain, liver, and kidney of neonatal rats increased with increasing number of exposure days and increasing exposure concentration. At the end of the 10-day exposure, concentrations were highest in the fetal liver followed by the kidney and brain. In transplacentally-exposed neonates of dams exposed to 4 mg/m^3, mercury accumulation in the kidney was approximately 1000-fold less than in the kidney of dams. The authors stated that adverse effects of mercury on developmental outcome occurred only at a concentration that caused maternal toxicity.

The effect of mercury vapor exposure on neuronal function of the above gestationally-exposed rats was reported by Herr et al. (2004). The study was limited to effects on offspring of pregnant Long Evans rats exposed nose-only to 0 or 4 mg/m^3 for 2 hours/day on GD 6 through 15. The authors stated that this is approximately a maximal tolerated dose for the dams. Offspring (one female and one male per dam) were tested between postnatal days 140-168 using a battery of sensory evoked potentials. Peripheral nerve action potential, nerve conduction velocity, somatosensory evoked responses (cortical and cerebellar), brainstem auditory evoked responses, pattern evoked potential, and flash evoked potential were quantified. None of the evoked responses were significantly altered. On PND 1, fetal brains contained approximately 20 ng/g total mercury (controls, approximately 1 ng/g).

Fredriksson et al. (1992) exposed groups of 10 neonatal Sprague-Dawley rats to an analytically-determined concentration of 0.05 mg/m^3 (0.006 ppm) for 1 hour (low exposure) or 4 hours (high exposure) daily from days 11-17 of age. This period of time is considered a period of rapid brain growth in rats. Rats were tested for behavioral changes at 2-6 months of age. Tests included spontaneous motor activity (locomotion, rearing, and total activity) and learning (radial arm maze and swim maze). No clinical signs were observed during the exposure days and there was no weight change. Tested motor activity was variable between ages (two and four months) and over the one-hour observation time (broken into three 20-minute sessions). At two months of age, rats exposed to the low dose showed no difference in motor activity compared with controls; whereas, the rats exposed to the high dose showed an increase in locomotion and total activity and a decrease in rearing. At four months of age, the low-dose rats showed increased locomotion and total activity and decreased rearing; the high-dose rats showed a marked hypoactivity in all three motor activity tests. In the radial-arm maze, tested over 2 days at 6 months of age, rats showed a concentration-dependent impairment in learning. Learning improved over the two-day test for the control and low-exposure groups, but not for the high-exposure group. There was no difference among control and treated groups in the swim maze test.

Female reproductive toxicity was studied by Davis et al. (2001) by exposing female Sprague-Dawley rats, nose-only, to 0, 1, 2, or 4 mg/m^3 mercury vapor for 2 hours/day for 11 consecutive days. A two-hour exposure to 4 mg/m^3 for 11 days resulted in a 22% weight decrease relative to controls (weight decreases following 1, 4, and 7 days were 1, 4, and 8%, respectively). Estrous cycles were slightly prolonged in the 2 and 4 mg/m^3 dose groups, and serum estradiol and progesterone levels were significantly decreased and increased, respectively, in the 4 mg/m^3 group compared to controls. These effects were attributed to body weight loss

and general toxicity. In an evaluation of pregnancy outcome, female rats were exposed to 1 or 2 mg/m^3 of mercury vapor, 2 hours/day for 8 days prior to breeding or 8 days after breeding. There was no effect on pregnancy rate or numbers of implantation sites.

3.5. Genotoxicity

Genotoxicity studies were reviewed by ATSDR (1999). Most of the studies addressed the genotoxicity of organic mercury compounds. Studies with inorganic mercury were usually performed with mercuric chloride. Mercuric chloride was not mutagenic in the *Salmonella typhimurium* plate incorporation assay (strains TA98, TA102, TA1535, and TA1537). However, mercuric chloride can damage DNA in rat and mouse embryo fibroblasts. A dose-related increase in chromosome aberrations was observed in the bone marrow of mice administered mercuric chloride orally at doses up to 4.4 mg/kg, but not in mice injected intraperitoneally at similar doses. *In vitro*, mercuric chloride increased chromosome aberrations in Chinese hamster ovary cells. From these studies, ATSDR concluded that, although the data are mixed, inorganic mercury compounds have some genotoxic or clastogenic potential.

3.6. Chronic Toxicity/Carcinogenicity

Ashe et al. (1953) reported that there was no histopathological evidence of respiratory damage in 24 rats exposed to 0.1 mg/m^3 of mercury vapor for 7 hours/day, 5 days/week for 72 weeks. The U.S. EPA considers the evidence for both animal and human carcinogenicity inadequate (U.S. EPA 1995). Their classification is *D - not classifiable as to human carcinogenicity.*

3.7. Summary

Recently conducted studies show that a 1-hour exposure of mice to 9.8 mg/m^3 mercury vapor resulted in lung damage (Shimojo et al. 1996); whereas, a 2-hour exposure of pregnant rats to 8 mg/m^3 was a NOAEL for lesions of the lung, liver, and kidney when examined immediately after exposure (Morgan et al. 2002). The 2-hour exposure to 8 mg/m^3 resulted in a decreased weight gain compared with controls and mild nephrotoxicity as indicated by urinary enzymes. A one-hour exposure of rats to approximately 26.7 mg/m^3 resulted in lung lesions, but no deaths; a 2-hour exposure to 27 mg/m^3 resulted in death of 20 of 32 rats (Livardjani et al. 1991). There were no lesions of the lung, liver, or kidney in non-pregnant and pregnant female rats exposed to 4 mg/m^3 for 2 hours/day for 1 or 10 days (Brambila et al. 2002; Morgan et al. 2002). Kidney lesions were not found in neonates exposed *in utero* to 4 mg/m^3. Developmental effects were observed only in association with maternal toxicity, following repeated exposure to 8 mg/m^3.

Reversible behavioral changes were observed in male and female Wistar-derived rats exposed to 17.2 mg/m^3 (2.1 ppm) for 2 hours/day, 5 days/week for 22 exposures over 30 days (Beliles et al. 1968) and 14 male rats (strain unspecified) exposed to 3.0 mg/m^3 (0.37 ppm) for 3 hours/day, 5 days/week for 12 to 42 weeks (Kishi et al. 1978). Following a recovery period, lesions were observed in the central nervous system in some rats in the first study and in the kidney in the second study.

Developmental neurotoxicity tests with rats involving 6-8 daily 1-4-hour exposures at concentrations as low as 0.05 mg/m^3 (0.006 ppm) were associated with altered spontaneous motor activity and decrements in learning tasks (Fredriksson et al. 1992; 1996; Danielsson et al. 1993). The study with squirrel monkeys (Newland et al. 1996) clearly shows effects but does not provide sufficient information about the shape that a dose-response relationship might assume, and it did not identify a no-effect level.

Genotoxicity studies, usually conducted with mercuric chloride, demonstrated mixed results; none of the studies used the inhalation method of administration. According to ATSDR (1999), inorganic mercury compounds may have some genotoxic or clastogenic potential. No recent chronic toxicity/carcinogenicity studies have been conducted with laboratory animals.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

A review of animal and human studies indicates that 70-80% of inhaled mercury is absorbed into the lungs, primarily in the alveolar-interstitial region (Leggett et al. 2001; AIHA 2002). Deposition in the lungs is controlled by the rate of breathing (Hayes and Rothstein 1962). As an uncharged monatomic gas, mercury is highly diffusible and lipid soluble. The lipophilic vapor is readily absorbed into the bloodstream; from there it diffuses to all tissues in the body (Goyer and Clarkson 2001). In erythrocytes it is rapidly oxidized by cytosolic catalase-hydrogen peroxide to mercuric mercury (Hg^{+2}). Mercuric mercury is highly reactive and rapidly combines with intracellular ligands such as sulfhydryls, potentially disrupting enzymes and proteins essential to normal organ function. It may also form complexes with glutathione which are then secreted in the bile. The presence of mercury in the body induces thiol-containing proteins, the metallothioneins. Induction of metallothioneins (regulated by at least two genes, MT-1 and MT-II) is believed to be a protective mechanism. Metallothioneins are induced in the kidney and placenta of rat dams exposed during gestation (Brambila et al. 2002; Morgan et al. 2002) and in fetal rat brain following *in utero* exposure (Aschner et al. 1997).

A small amount of elemental mercury may be transported to tissues including the brain where biotransformation takes place. Elemental mercury traverses the blood-brain barrier more readily than mercuric ions. Mercury is absorbed by all tissues, but the primary organs of deposition are the brain and kidneys (Goyer and Clarkson 2001). Deposition in tissues is linearly related to exposure time and atmospheric concentration. Clearance half-times of inhaled mercury by human subjects range from 1.7 days for the lungs to 64 days for the kidney region (Hursh et al. 1976). Mercury absorbed by human skin was estimated to be 2.2% of that absorbed by the lung (Hursh et al. 1989). Excretion is in the urine and feces; only a small portion is excreted in the expired air.

The biokinetics of inhaled mercury vapor (Hg^0) have been studied in human subjects. These studies are summarized in Table 6 and blood concentrations are summarized in Table 7. Exposure concentrations and durations ranged from 0.10 mg/m^3 (0.007 ppm) for 7 hours (Teisinger and Fiserova-Bergerova 1965) to 0.40 mg/m^3 (0.049 ppm) for 15 minutes (Sandborgh-Englund et al. 1998). No adverse effects were reported in these studies. The most recent, well-conducted study in which known extraneous sources of mercury were minimized is described.

Additionally, a monitoring study is included in Table 7. Blood mercury in control subjects is generally below 50 ng/mL and urine mercury is generally below 25 µg/L (Goldwater 1972).

TABLE 6. Human Metabolism Studies

Concentration (Subjects)	Exposure Duration	Observation	Reference
0.050-0.35 mg/m^3 (3 male, 1 female subjects)	5 min[a]	70-85% absorption	Nielsen Kudsk 1965
0.06-0.11 mg/m^3 (5 male subjects)[b]	14-24 min	74% retention; 7% expired; tissue half-lives; lung, 1.7 days, head, 21 days	Hursh et al. 1976; Cherian et al. 1978
0.06-0.40 mg/m^3 (5 male subjects; 3 ingested 65 mL ethanol)[b]	11-21 min	73% retention; lower Hg retention (55%) following ingestion of ethanol	Hursh et al. 1980
0.4 mg/m^3 (9 males, females; light physical exercise at 50 W)[c]	15 min	rapid absorption; 67% retention; 7.5-12% loss by expiration in 3 days; blood plasma half-life of 10 days	Sandborgh-Englund et al. 1998
0.10 mg/m^3 (4 subjects); 0.20 mg/m^3 (1 subject)[c]	7 h	76% retention; urinary excretion (µg/24 hours) approximated non-exposed values	Teisinger and Fiserova-Bergerova 1965
0.01-0.106 mg/m^3; mean 0.04 mg/m^3 (10 workers)	8 h, 5 d	blood Hg concentration of 2.0 µg/dl; urinary Hg concentration of 50 µg/g creatinine	Roels et al. 1987

[a] Exhaled air was collected for 5 minutes; it is assumed the exposures were also for 5 minutes.
[b] Subjects inhaled through a mouthpiece.
[C] Nasal inspiration and oral expiration.

Sandborgh-Englund et al. (1998) described the absorption, blood levels, and excretion of mercury vapor after a single exposure in humans. Nine healthy volunteers, two males and seven females, ages 19-53, inhaled 0.4 mg/m^3 (analytically determined range of 0.365 to 0.430 mg/m^3) of mercury vapor through a reverse valve mouthpiece for 15 minutes. None of the subjects had amalgam fillings, and fish had been excluded from the diet for the previous month. The subjects exercised on a bicycle ergometer at 50 W. The median retention was 69% of the inhaled dose (range 57-73%). During the following three days, 7.5-12% of the absorbed dose was lost by exhalation, with a median half-life of mercury in expired breath of two days. Absorption by blood and plasma was rapid, followed by a bi-exponential decline in both media. Substantial inter-individual variation was observed in the area under the concentration-time curves for blood and plasma. About 1% of the absorbed dose was excreted via the urine during the first 3 days after exposure, and an estimated 8-40% was excreted during 30 days. Total mercury in blood (plasma and erythrocytes combined) increased from a baseline value of 6.0 nmol/L (range 4.0-7.6 nmol/L) to a maximum concentration of 7.4 nmol/L (median net value; 25-75 percentile of 6.6-8.9 nmol/L). Blood samples were taken from 15 minutes up to 8 hours after the beginning of the exposure. The maximum blood concentration was reached 5 hours after the beginning of exposure. Baseline blood samples were composed of primarily methyl mercury.

Jonsson et al. (1999) used the data of Sandborgh-Englund et al. (1998) to model the kinetics of mercury vapor in humans. A four-compartment model, including two depot compartments to account for retention in lungs and kidneys, respectively, gave the best fit to the data. The median half-time in the respiratory depot compartment was estimated at 1.8 days; the median half-life in the excretion depot was estimated at 63 days.

Barregard et al. (1996) observed two phases of elimination in workers following an initial high unquantified exposure to Hg vapor. Workers were also exposed to inorganic Hg compounds and lead. Monitoring followed 2-10 days of exposure, 7 hours/day, after which signs and symptoms of Hg intoxication appeared. The half-life of the fast phase was 2-16 days and the half-life of the slow phase was more than a month. The authors attributed the fast phase to exceedence of the capacity of the Hg binding sites in the kidney.

Roels et al. (1987) monitored workers at an alkaline battery manufacturing plant. Monitoring was performed daily with personal samplers for 8-hour periods for 5 days. Atmospheric concentrations ranged from 0.010 to 0.106 mg/m^3 (overall mean 0.040 mg/m^3). Blood mercury concentrations taken at the end of the work shift averaged 2.0 µg/dl (20 µg/L) and urine samples collected the following morning averaged 50 µg/g creatinine (values estimated from graphs).

Falnoga et al. (1994) followed the uptake of mercury in tissues and organs of male adult Wistar rats placed in the working area of a mercury mine for 38 days. Average air concentrations were 0.57 (0.50-0.70) mg/m^3. Blood samples, taken at 4, 8, and 18 hours into the exposure, were 209, 256, and 479 ng/g, respectively (approximately 0.21, 0.26, and 0.48 µg/mL, respectively); the control value was 11.6 ng/g. Blood concentrations leveled off at 1 to 1.5 days into the exposure (647-776 ng/g), but were higher on the 38th day of exposure (880 ng/g). Following exposure of rats to a slightly higher concentration, 1.1 (0.55-1.72) mg/m^3 for 17 days, elimination from organs and tissues was complete in 46 days. The authors described uptake into the blood as irreversible zero order kinetics and elimination from the blood by irreversible first order kinetics. The authors stated that several rats died during the exposure to 1.1 mg/m^3, but gave neither the number of rats nor day of death.

Neonatal rats were exposed to mercury vapor, 0.05 mg/m^3 for 1 or 4 hours/day, from days 11 to 17 of age; sacrifice took place on day 25 (Fredriksson et al. 1992). Mercury concentrations (mg/kg) in tissues of the control, 1-hour, and 4-hour exposure groups were: brain, 0.002, 0.002, and 0.002; liver, 0.017, 0.084, and 1.247; and kidney, 0.063, 0.219, and 6.734, respectively. These concentrations were measured approximately one week after exposure. Nursing infants may be exposed via consumption of contaminated breast milk from nursing mothers exposed via the occupational or diet sources (ATSDR 1999).

Adult Wistar rats of either sex inhaled 0.5, 1.0, or 2.0 mg/m^3 for 1, 2, or 3 hours (nine exposure groups) (Halbach and Fichtner 1993). Tissue concentrations, determined immediately after exposure, increased linearly with exposure time or with Hg concentration in air. For example, following inhalation of 0.5 mg/m^3 for 1, 2, or 3 hours, brain concentrations were 7, 12, and 15 µg/kg, respectively. Following inhalation of 0.5, 1, or 2 mg/m^3 for one hour, brain concentrations were 7, 12, and 18 µg/kg, respectively. Concentrations were highest in the lung.

Although the transport of mercuric ions is limited at the placental barrier by the presence of high-affinity binding sites (Dencker et al. 1983), dissolved mercury vapor easily penetrates the placental barrier and accumulates in fetal tissues. Mercury was elevated in tissues of fetuses of exposed pregnant rats and monkeys, although the magnitude of accumulation was less than that seen in the maternal brain (Fredriksson et al. 1992; Danielsson et al. 1993; Warfvinge et al. 1994; Newland et al. 1996; Morgan et al. 2002; see Section 3.4. for study descriptions). Examples of fetal uptake in animal models are listed in Table 7.

TABLE 7. Tissue Concentrations of Mercury[a]

Concentration (Subjects)	Exposure Duration	Observation/Tissue Concentration	Reference
Human Monitoring Studies			
0.01-0.106 mg/m^3; mean 0.04 mg/m^3 (10 workers – occupational exposure)	8 h, 5 d	20 μg/L (blood) 50 μg/g creatinine (urinary Hg)	Roels et al. 1987
Background (military population with dental amalgams)	Chronic	2.55 μ/L (blood, total mercury) 0.54 μg/L (blood inorganic mercury) 3.09 μg/L (urine, total mercury) 2.88 μg/L (urine, inorganic mercury)	Kingman et al. 1998
Background Exposure: 0.40 mg/m^3 (9 healthy volunteers)[b]	– 15 min	0.19 μg/L (blood, inorganic mercury) 1.20 μg/L (blood, total mercury) 1.48 μg/L (blood, total mercury)	Sandborgh-Englund et al. 1998
Background Fetuses Infants (<3 months)	–	Total mercury: Brain: 5 ng/g; kidney: 9 ng/g Brain: 6 ng/g; kidney: 12 ng/g	Lutz et al. 1996
Rodents			
Rat: 4 mg/m^3 Non-pregnant Pregnant Neonates	 10 d, 2 h/d GD 6-15 PND 21	Kidney (total mercury): 60 μg/g (control: 0.009 μg/g) 86 μg/g (control: 0.019 μg/g) 0.089 μg/g (control: 0.018 μg/g)	Brambila et al. 2002
Rat: 4 mg/m^3 Dam Fetus	10 d, 2 h/d	Brain: Control: 0.002 μg/g GD 15: 3 μg/g Control: 0.001 μg/g GD 15: 0.05 μg/g	Morgan et al. 2002
Rat: 0.05 mg/m^3	days 11-17 of age 1 or 4 h/d; sacrificed day 25	Brain: Control: 0.002 μg/g 1 h/d: 0.017 μg/g 4 h/d: 0.063 μg/g	Fredriksson et al. 1992
Rat: 1.8 mg/m^3 in utero	GD 14-19, 1.5 h/d	Brain: 5 ng/g (measured PND 2-3)	Fredriksson et al. 1996
Guinea pig: 0.2-0.3 mg/m^3 Dam Neonate	2 h/d, 4 days	Brain: Control: 29 ng/g Exposed: 95 ng/g Control: 19 ng/g Exposed: 17 ng/g	Yoshida et al. 1986

[a] Concentrations are wet weight.
[b] Mercury measured five hours after exposure (background subtracted); no dental amalgams, fish excluded from diet.
GD = gestation day; PND = post-natal day.

In the study of Morgan et al. (2002), metallothionein and mercury concentrations in selected tissues of the dam and fetus were provided following inhalation of 4 mg/m^3, 2 hours/day, on GD 6-15. On GD 10, metallothionein concentrations were highest in the placenta of the dam followed by the kidney, liver, and lung. Due to small size, fetal tissue could not be

weighed separate from the placenta prior to GD 10 and brain tissue could not be separated from the fetus prior to GD 15. On GD 15, the mean mercury concentration in the developing brain of the fetus was 49 ng/g (approximately 0.05 µg/g). The mean mercury concentration in the brain of dams was approximately 3 µg/g, and that of the placenta was 2.4 µg/g. The concentration in the fetal brain was a factor of approximately 60 lower than that of the dam brain. On PND 21, the concentration in the kidney of neonates exposed *in utero* to 4 mg/m^3 was 0.089 µg/g, whereas the concentration in the kidney of the control neonate was 0.018 µg/g.

Yoshida et al. (2002) studied the role of metallothionein in maternal-to-fetal distribution of mercury in pregnant C57Bl6 mice. Following inhalation of 5.5-6.7 mg/m^3 for 3 hours during late gestation, elevated mercury concentration in the placenta was associated with metallothionein. The authors suggested that metallothionein plays a defensive role in preventing maternal-to-fetal mercury transfer. In non-exposed and mercury-vapor exposed mice, metallothionein levels were highest in the liver followed by the placenta. Metallothionein concentrations were statistically significantly higher in the lung and kidney of exposed dams compared with the control group. Mercury concentrations were elevated in the fetuses (whole body) of exposed dams by a factor of 9-10 compared to fetuses of control dams.

During late gestation, pregnant Hartley strain guinea pigs were exposed to 0.2-0.3 mg/m^3 for 2 hours/day for 4-11 days (Yoshida et al. 1986). Dams and offspring were sacrificed immediately after birth. After 4 days of exposure, mercury in brain of offspring was not increased over control levels; however, concentrations were increased in lung, liver, and kidney. After ≥5 days of exposure, mercury was increased in all offspring tissues.

Between GD 65 and 76, Hartley strain guinea pigs inhaled 8-10 mg/m^3 for 150 minutes (Yoshida et al. 1990). Some dams were sacrificed at 2 hours after exposure and tissue levels of dams and fetuses were analyzed for mercury. Additional dams were allowed to give birth and offspring, fostered to unexposed dams, were sacrificed at 5 or 10 days after exposure. Fetal brain concentrations of mercury were not elevated compared to controls. The highest mercury concentration was in the liver, largely bound to metallothionein. At 5 to 10 days after exposure, neonate brain concentrations were elevated 3- to 5-fold compared with current controls. On days 5 and 10, the highest mercury concentrations were found in the kidney, followed by liver, lung, and brain. The authors suggested that mercury, initially bound to metallothionein in the liver was redistributed during the neonatal period. In the fetal liver, about 50% of the mercury is bound to metallothionein (Yoshida et al. 1987).

4.2. Mechanism of Toxicity

At high levels of exposure, respiratory failure, cardiac arrest, and cerebral edema ensue (Goyer and Clarkson 2001; WHO 2003). These consequences have been attributed to the divalent (Hg^{+2}) mercury which binds to a variety of enzymes and intracellular proteins including those of microsomes and mitochondria, producing nonspecific cell injury or cell death (Goyer and Clarkson 2001). The affinity of mercury for ligands containing sulfhydryl (SH or thiol) groups results in a glutathione complex which is excreted in the bile. The central nervous system is probably the most sensitive target for elemental mercury vapor exposure. Within the kidney, the primary toxic effect is on the epithelial cells of the proximal tubules (ATSDR 1999).

4.3. Structure-Activity Relationships

No data were located relevant to structure-activity relationships.

4.4. Other Relevant Information

4.4.1. Species Variability

No relevant data on species variability were located. The absorption, distribution, and excretion of mercury in humans and animals have similar aspects (ATSDR 1999). The rate of inhalation of xenobiotics including that of mercury vapor is related to the ventilation rate and the inhaled concentration (Hayes and Rothstein 1962; Medinsky and Valentine 2001). Relative to body weight, rodents have a much higher respiratory rate and cardiac output than humans [the respiratory rate of the mouse may be up to 10 times that of the human (Witschi and Last 2001; Kale et al. 2002)]. Respiratory rate and cardiac output are the two primary determinants of systemic uptake of volatile gases following inhalation exposure. As a result of the greater respiratory rate and cardiac output, rodents generally receive a greater overall dose than humans at equivalent exposure concentrations.

Few data were available to compare concentrations of mercury in human and rodent tissues. Mercury in brain of 19 human fetuses and 14 infants of less than three months of age at autopsy averaged 5 and 6 ng/g wet weight, respectively (ranges, 2-9 and ≤2-23 ng/g, respectively) (Lutz et al. 1996). Autopsy results of human infants at birth showed total mercury concentrations in the cerebral cortex of <1 to 20 ng/g wet weight of tissue (Drasch et al. 1994). The variability among human young is most likely due to differing diets and number of dental amalgam surfaces in the mothers. Mercury in control fetal guinea pigs and 5- and 10-day old guinea pigs averaged 13±2, 9±1, and 7±1 ng/g wet weight, respectively (Yoshida et al. 1990). Following *in utero* exposure to 10 mg/m^3 of mercury for 150 minutes, brain concentrations in guinea pigs of the respective age groups were 14±5, 27±1, and 32-33 ng/g wet weight. Fetal levels were measured two hours post-exposure. The mean concentrations of mercury in GD 15 fetuses of rat dams exposed to 4 mg/m^3 mercury vapor for 10 days was 49 ng/g. Values could not be provided following a single exposure, but this study as well as other studies show tissue accumulation with repeat exposure.

Exposure of rats during fetal development comprises a subchronic exposure. Ten days of exposure for 2 hours/day for a total of 20 hours over a 20 day gestation period (Morgan et al. 2002) comprises 4% of the rat gestational period; whereas, the same exposure scenario comprises 0.3% of the human gestation period of 270 days.

4.4.2. Susceptible Populations

Based on a reconstructed accidental inhalation exposure and results of accidental food poisoning, infants and children are considered the most susceptible members of the population (ATSDR 1999; AIHA 2002). Mercury (Hg^o) rapidly passes the blood-brain barrier and reaches the fetal brain (Danielsson et al. 1993; Fredriksson et al. 1996). A neurotoxicity study with neonatal rats involved repeat exposures (Fredriksson et al. 1992). Exposure to 0.05 mg/m^3

(0.006 ppm) mercury vapor for 4 hours/day for 7 days resulted in changes in activity and learning in some neurotoxicity tests but not in others.

Increased mercury uptake of neonates compared with dams may indicate increased sensitivity. Yoshida et al. (1989) exposed Hartley strain guinea pig dams and 12-hour-old neonates to 8-10 mg/m^3 of mercury vapor for 2 hours. Animals were sacrificed immediately after the exposure. Catalase activity was determined in blood and liver, and mercury and metallothionein concentrations were measured in selected tissues. Compared with the respective control and exposed groups of dams, catalase activity was lower in neonate blood and liver by factors of 2 (blood) and 5 (liver) in the control group and by factors of 1.3 (blood) and 4 (liver) in the exposed group. Mercury in plasma of neonates was two to three times higher than concentrations in maternal plasma, but the concentrations in erythrocytes were similar. Except for kidney, mercury concentrations in organs of neonates were higher than that of dams, with brain values of neonates being 12-28% higher. For both control and exposed groups, metallothionein concentration in the liver was higher in the neonates than in the dams.

In contrast to neonates, fetal tissues of rats accumulate less mercury than the tissues of mercury-treated dams (Fredriksson et al. 1992; Danielsson et al. 1993; Warfvinge et al. 1994; Newland et al. 1996; Morgan et al. 2002). Following 10 days of exposure to 4 mg/m^3, (GD 15) total mercury in brains of dams and fetal rats were 3300 and 49 ng/g of tissue, respectively (Morgan et al. 2002).

Following exposure of nine healthy male and female volunteers to 0.40 mg/m^3 for 15 minutes, the maximum blood concentration of mercury did not vary greatly (median, 7.4 nmol/L; range, 5.9-13.0 nmol/L) (Sandborgh-Englund et al. 1998). The time to maximum blood concentration varied considerably.

Based on simulations of accidental exposure, a concentration of 16 mg/m^3 was fatal to an infant (Campbell 1948), whereas concentrations of 18-43 mg/m^3 were fatal to 4 of 35 adults (Tennant et al. 1961; Asano et al. 2000).

4.4.3. Concentration-Exposure Duration Relationship

Studies with animal models show that tissue mercury concentration increases with exposure concentration and exposure duration (Morgan et al. 2002; Yoshida et al. 1986). However, no data were available to describe a concentration-response relationship. Exponential scaling (ten Berge et al. 1986) was used to derive exposure duration-specific values. It has been shown that the concentration-exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent n ranges from 0.8 to 3.5. In the absence of chemical-specific data, an n value of 3 was applied to extrapolate to shorter time periods, and an n value of 1 was applied to extrapolate to longer time periods to provide AEGL values that would be protective of human health (NRC 2001).

4.4.4. Concurrent Exposure Issues

Amalgam dental fillings as well as food such as fish constitute major sources of chronic mercury exposure in humans. Mercury vapor from amalgam dental fillings is a potentially significant source of exposure to elemental mercury as estimates of daily intake from amalgam restorations range from 3 to 17 μg mercury/day, with the majority of individuals exposed to 5 μg mercury/day. Mercury in whole blood ranges from 2 μg/L in the absence of fish consumption to 8 μg/L when 2-4 fish meals/week are eaten. The mercury intake from fish is primarily in the form of methyl mercury (Brune et al. 1991; Barregard 1993; Sandborgh-Englund et al. 1998; ATSDR 1999; WHO 2003).

Catalase inhibitors such as ethanol inhibit the oxidation of elemental mercury to divalent mercury, thus reducing mercury retention. Human subjects that ingested 65 mL of ethanol prior to exposure to mercury vapor had reduced mercury retention, an increase in the rapid phase of vapor loss by expiration, increased mercury storage in the liver, a marked reduction in mercury uptake by the red blood cells, and the abolition of prompt storage of mercury by the lung. Similar results were seen with mice and rats (Hursh et al. 1980).

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Exposure to mercury vapor at low concentrations does not induce irritation or other warning signs. There is no odor.

Controlled human exposures during metabolism studies used low concentrations and short exposure durations. No adverse effects were reported following exposure of healthy adults to 0.10 mg/m^3 for seven hours (Teisinger and Fiserova-Bergerova 1965) or 0.40 mg/m^3 for up to 15 minutes, the latter exposure accompanied by light physical exercise (Sandborgh-Englund et al. 1998).

Under conditions of a reconstructed accidental exposure, high-school-age students exposed to an estimated 15 mg/m^3 for 0.75 hours did not become ill (Shelnitz et al. 1988).

5.2. Summary of Animal Data Relevant to AEGL-1

Acute studies with animal models used concentrations that induced effects greater than those defined by an AEGL-1. Repeat-dose studies, including neurotoxicity studies, resulted in organ lesions; the time of appearance of these lesions could not be ascertained.

5.3. Derivation of AEGL-1 Values

Mercury vapor is odorless and produces no irritation or early warning signs. Accidental human exposures (Section 2.1) show that even lethal exposures may be tolerated for several hours without apparent warning signs. Because there are no signs of notable discomfort or irritation at low concentrations, and studies that document asymptomatic, non-sensory effects

that meet the definition of an AEGL-1 are not available, AEGL-1 values are not recommended (Table 8).

TABLE 8. AEGL-1 Values for Mercury Vapor

10-min	30-min	1-h	4-h	8-h
Not Recommended	Not Recommended	Not Recommended	Not Recommended	Not Recommended

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

As noted in Section 4.1, no adverse effects were reported following controlled exposures of healthy adults to 0.10 mg/m^3 mercury vapor for seven hours (Teisinger and Fiserova-Bergerova 1965) or 0.40 mg/m^3 for up to 15 minutes (Sandborgh-Englund et al. 1998). The latter exposure was accompanied by light physical exercise.

In their summary of occupational monitoring studies, the AIHA (2002) notes that exposure to mercury vapor concentrations of 0.4-2 mg/m^3 (0.05-0.25 ppm) "may result in symptoms of mercury intoxication after exposures of weeks or longer. Adverse effects have not been reported for exposure to these concentrations of hours or days." Similarly, chronic exposure to low concentrations during pregnancy (0.025-0.6 mg/m^3) have failed to show an increase in miscarriages or stillbirths, but congenital anomalies were non-significantly increased (Elghany et al. 1997). The increase was not concentration related.

Concentrations during accidental exposures are generally estimated. Students exposed to an estimated 15 mg/m^3 (1.8 ppm) in an unventilated high-school lab for approximately 0.75 hours did not become ill (Shelnitz et al. 1988). Based on simulations of accidental exposure, a concentration of 16 mg/m^3 for a "few hours" was fatal to an infant (Campbell 1948), whereas concentrations of 18-43 mg/m^3 for several hours were fatal to 4 of 35 adults (Tennant et al. 1961; Asano et al. 2000).

6.2. Summary of Animal Data Relevant to AEGL-2

Pregnant Long-Evans rats exhibited no lesions of the lungs, liver, or kidney after 1, 5, or 10 two-hour daily exposures to 4 mg/m^3 mercury vapor, although dams became moribund following 10 days of exposure to 8 mg/m^3 (Brambila et al. 2002; Morgan et al. 2002). Developmental effects consisting of increased resorptions and decreased litter size were confined to the 8 mg/m^3 exposure group. No effects on pregnancy or offspring were reported in the group exposed to 4 mg/m^3. Following 10 days of exposure to 4 mg/m^3, the mean mercury concentration in the brain of the developing fetus was lower by 60-fold than that in the brain of the dam (0.05 µg/g vs 3 µg/g). A slight weight loss in the dams following inhalation of 4 mg/m^3 for 10 days was attributed to the repeat nature of the exposure. Pregnancies were uneventful in squirrel monkeys exposed to 0.5 or 1.0 mg/m^3 for approximately half of their gestation period, but offspring tested at 0.8 to 4 years of age showed variable behavioral deficits.

A 1-hour exposure of mice to 9.8 mg/m^3 greatly increased the protein content of broncho-alveolar lavage fluid; hemoglobin was present in the fluid at 48 hours, suggesting lung damage (Shimojo et al. 1996). No deaths were reported within 5 days post-exposure. Liver and kidney function were normal in mice that inhaled 5.5-6.7 mg/m^3 for 3 hours as determined by sacrifices up to 7 days later (Yoshida et al. 1999a). Rats exposed to 26.7 mg/m^3 for 1 hour showed no breathing difficulties, but exhibited lung lesions (Livardjani et al. 1991). No deaths occurred after the 1-hour exposure; but extension of the exposure for another hour resulted in 62.5% mortality.

In repeat-dose studies, reversible neurotoxicity was observed in rats exposed to 17.2 mg/m^3 mercury vapor for 2 hours/day, 5 days/week for 22 exposures (Beliles et al. 1968) or 3.0 mg/m^3 for 3 hours/day, 5 days/week for 12 to 42 weeks (Kishi et al. 1978). Rats were held for up to 12 weeks after cessation of exposure; only minor effects were reported. Developmental studies with repeated exposures showed variable results and may not be relevant to a single exposure, as mercury accumulates in the brain with each successive exposure.

6.3. Derivation of AEGL-2 Values

Although maternal exposures were for 2 hours/day for 10 days, a single 2-hour exposure of pregnant Long-Evens rats to 4 mg/m^3 mercury vapor (Morgan et al. 2002) was used as the point of departure for the AEGL-2. This value is a NOAEL for developmental effects. Developmental effects including increased resorption, decreased litter size and decreased neonatal weight were observed at the next highest concentration of 8 mg/m^3. Uncertainty factors for the AEGL-2 are based on a weight of evidence of approach. The following factors were considered in deriving an interspecies uncertainty factor: the 4 mg/m^3 value was a NOAEL for developmental effects (below the definition of the AEGL-2), the exposures were repeated for 10 days, rodents have a higher respiratory rate and cardiac output compared with humans (resulting in faster uptake), and human monitoring studies show some effects at concentrations of 0.4 to 2 mg/m^3 only with chronic exposure (AIHA 2002). The following factors were considered in deriving an intraspecies uncertainty factor: the population of fetuses is considered a sensitive if not the most sensitive population, the protective action of the placenta in sequestering mercury [the mean concentration of mercury in the brain of dams exposed to 4 mg/m^3 for 10 days was 60-fold higher than in the fetal brain (Morgan et al. 2002)], and incidences of miscarriages and stillbirths were unaffected in women chronically exposed to 0.025 to 0.6 mg/m^3, although anomalies were statistically non-significantly increased (Elghany et al. 1997). Based on these factors, interspecies and intraspecies uncertainty factors of 1 and 3 were applied. Application of larger uncertainty factors, for example 10 or 30 (resulting in 2-hour values of 0.4 or 0.13 mg/m^3), results in values that are inconsistent with the available human data, including the chronic exposure of pregnant women in the study of Elghany et al. (1997). In the absence of time-scaling information, the resulting 2-hour value of 1.33 mg/m^3 was time-scaled using default n values of 3 and 1 for shorter and longer exposure durations, respectively (NRC 2001). Time-scaling calculations are in Appendix A and values are listed in Table 9 below. A category plot of AEGL values in relation to toxicity data is shown in Appendix B.

TABLE 9. AEGL-2 Values for Mercury Vapor				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
3.1 mg/m^3 (0.38 ppm)	2.1 mg/m^3 (0.26 ppm)	1.7 mg/m^3 (0.21 ppm)	0.67 mg/m^3 (0.08 ppm)	0.33 mg/m^3 (0.04 ppm)

The AEGL-2 values are supported by the data of Yoshida et al. (1986). Following inhalation of 0.2-0.3 mg/m^3, 2 hours/day for 4 days, by guinea pig dams, mercury concentrations were elevated in the dam brain by a factor of 3.3 (95 vs 29 ng/g) whereas the concentration in the neonate brain was similar to that of the control (19 and 17 ng/g, respectively).

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

Human data are limited to reconstructions of accidental exposures. One such study indicates that students exposed to an estimated 15 mg/m^3 in an unventilated high-school lab for approximately 0.75 hours did not become ill (Shelnitz et al. 1988). Longer exposures to similar concentrations resulted in illness, and exposure to higher concentrations for several hours resulted in some fatalities (see Table 2).

7.2. Summary of Animal Data Relevant to AEGL-3

Male Wistar rats inhaling 26.7 mg/m^3 mercury vapor for one hour and observed for up to 15 days exhibited no clinical signs, but exhibited lung edema and necrosis (Livardjani et al. 1991). Extending the exposure period for another hour (at approximately the same concentration) resulted in 62.5% mortality. Although the study is old, rabbits exposed to 31.3 mg/m^3 for 1 hour and held for 6 days showed no mortality, but mild to moderate undefined changes in the lung, kidney, brain, and heart were observed (Ashe et al. 1953).

Reversible behavioral changes were observed in male and female Wistar-derived rats exposed to 17.2 mg/m^3 (2.1 ppm) for 2 hours/day, 5 days/week for 22 exposures over 30 days (Beliles et al. 1968) and 14 male rats (strain unspecified) exposed to 3.0 mg/m^3 (0.37 ppm) for 3 hours/day, 5 days/week for 12 to 42 weeks (Kishi et al. 1978). Following a recovery period, lesions were observed in the central nervous system in some rats in the first study and in the kidney in the second study.

7.3. Derivation of AEGL-3 Values

The 1-hour non-lethal exposure of rats to 26.7 mg/m^3 (Livardjani et al. 1991) was used as the point of departure for development of AEGL-3 values. The 26.7 mg/m^3 value was adjusted by a total uncertainty factor of 3 (an interspecies uncertainty factor of 1 and an intraspecies uncertainty factor of 3) based on a weight of evidence approach. Larger uncertainty factors result in values incompatible with the overall data. Reversible behavioral changes were observed in male and female Wistar rats inhaling 17.2 mg/m^3 for 2 hours/day for 22 exposures (Beliles et al. 1968). The uncertainty factor of 3 is considered sufficient to protect susceptible populations. Values derived using an intraspecies uncertainty factor of 3 are supported by the non-lethal

concentrations estimated in accidental exposures [up to 15 mg/m^3 for 0.75 hours [Shelnitz et al. 1988; AIHA 2002)] and measured in occupational settings [0.4-2.0 mg/m^3 (AIHA 2002)]. The resulting 1-hour value of 8.9 mg/m^3 was time-scaled using default n values of 3 and 1 for shorter and longer exposure durations, respectively. Because the 8-hour time-scaled value of 1.1 mg/m^3 appears low in comparison to accidental non-lethal exposures and is lower than some chronic occupational exposures, the 8-hour value was set equal to the 4-hour value. Time-scaling calculations are in Appendix A and values are listed in Table 10 below. A category plot of AEGL values in relation to the animal toxicity and human metabolism data is found in Appendix B.

TABLE 10. AEGL-3 Values for Mercury Vapor

10-min	30-min	1-h	4-h	8-h
16 mg/m^3 (2.0 ppm)	11 mg/m^3 (1.3 ppm)	8.9 mg/m^3 (1.1 ppm)	2.2 mg/m^3 (0.27 ppm)	2.2 mg/m^3 (0.27 ppm)

The derived values are supported by concentrations estimated during accidental non-lethal exposures. Concentrations of 15 mg/m^3 for 0.75 hours and 16 mg/m^3 for a "few hours" were not lethal to older children and adults (although one infant death was recorded) (AIHA 2002). The derived values are also supported by the study of Beliles et al. (1968) in which reversible behavioral changes were observed in male and female Wistar-derived rats exposed to 17.2 mg/m^3 mercury vapor for 2 hours/day, 5 days/week for 22 exposures over 30 days. A histological change in the medulla oblongata comprised of perivascular cuffing by lymphocytes was partially reversible following a recovery period. This lesion may be attributed to the repeat exposure protocol. No lesions were observed in other tissues.

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

AEGL values are summarized in Table 11. Because mercury vapor has no odor or warning properties, AEGL-1 values were not recommended.

The point of departure for the AEGL-2 was a single 2-hour exposure of pregnant rats to 4 mg/m^3 mercury vapor (Morgan et al. 2002). The exposure to 4 mg/m^3 was a NOAEL for developmental effects in rats. The 4 mg/m^3 value was adjusted by a total uncertainty factor of 3 (an interspecies uncertainty factor of 1 and an intraspecies uncertainty factor of 3) based on a weight of evidence approach and the incompatibility of the derived values with monitoring data if a larger uncertainty factor is used. Based on mercury uptake by the sensitive developing brain of the fetus, compared with uptake by the brain of the dam, an intraspecies uncertainty factor of 3 was considered sufficient to protect susceptible populations. In the absence of time-scaling information, the resulting 2-hour value of 1.33 mg/m^3 was time-scaled using default n values of 3 and 1 for shorter and longer exposure durations, respectively.

The point of departure for AEGL-3 values was the 1-hour exposure of rats to 26.7 mg/m^3 (Livardjani et al. 1991). A 2-hour exposure at this approximate concentration resulted in significant mortality. The 26.7 mg/m^3 value was adjusted by a total uncertainty factor of 3 (an interspecies uncertainty factor of 1 and an intraspecies uncertainty factor of 3) based on (1) faster

uptake in rodents compared with humans and (2) the incompatibility with monitoring and accidental exposure data if a larger uncertainty factor is used. The uncertainty factor of 3 is considered sufficient to protect susceptible populations. The resulting 1-hour value of 8.9 mg/m^3 was time-scaled using default n values of 3 and 1 for shorter and longer exposure durations, respectively.

TABLE 11. Summary of AEGL Values for Mercury Vapor

Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1[a] (Nondisabling)	Not Recommended	Not Recommended	Not Recommended	Not Recommended	Not Recommended
AEGL-2 (Disabling)	3.1 mg/m^3 (0.38 ppm)	2.1 mg/m^3 (0.26 ppm)	1.7 mg/m^3 (0.21 ppm)	0.67 mg/m^3 (0.08 ppm)	0.33mg/m^3 (0.04 ppm)
AEGL-3 (Lethal)	16 mg/m^3 (2.0 ppm)	11 mg/m^3 (1.3 ppm)	8.9 mg/m^3 (1.1 ppm)	2.2 mg/m^3 (0.27 ppm)	2.2 mg/m^3 (0.27 ppm)

[a] Mercury vapor is odorless. AEGL-1 values are not recommended because mercury vapor has no odor or warning properties at concentrations that may cause extensive tissue damage.

8.2. Comparison with Other Standards and Guidelines

Standards and guidelines for exposure to mercury vapor are summarized in Table 12. The AIHA (2002) did not develop an Emergency Response Planning Guideline-1 (ERPG-1) because mercury vapor is odorless and produces no irritation or other early warning signs. The ERPG-2 was based on a combination of animal studies (Fraser et al. 1934; Kishi et al. 1978; Livardjani et al. 1991) and nine occupational studies. The occupational exposures involved vapor concentrations of 0.05-0.25 ppm (0.41-2.1 mg/m^3) which resulted in symptoms in some workers after exposures of weeks or longer, but not after periods of hours or days. The ERPG-3 was also based on a combination of controlled laboratory studies with animals and fairly consistent findings from accidental human exposures.

The 1-hour Spacecraft Maximum Allowable Concentration (SMAC) is 0.01 ppm (0.08 mg/m^3), and the 24-hour value is 0.002 ppm (0.02 mg/m^3) (NRC 1996). The lung was considered the target organ for acute exposure. The 1-hour value was based on an estimated LOAEL of 2 mg/m^3 for 5 hours from reconstruction of accidental exposure of 13 workers. Uncertainty factors of 10 and the square route of 13 divided by 10 were applied; the latter number was applied to account for the small number of subjects.

The ACGIH (1996) TLV-TWA of 0.025 mg/m^3 was based on a combination of factors including a Biological Exposure Index urine mercury level of 35 μg Hg/g creatinine collected prior to an 8-hour work shift. The BEI applies only to exposure to elemental and inorganic forms of mercury and not to organic mercury exposures. The monitoring data of Roels et al. (1987) suggests that 50 μg Hg/g creatinine is the biological threshold for neurological damage in workers.

The NIOSH REL and the OSHA PEL are both 0.05 mg/m^3, and the ceiling values established by NIOSH and OSHA are both 0.1 mg/m^3. The NIOSH IDLH is 10 mg/m^3. The

IDLH is based on acute inhalation toxicity data in animals in the study of Ashe et al. (1953). All NIOSH and OSHA values have a skin notation. The German MAK is 0.1 mg/m^3 and the Dutch MAC is 0.05 mg/m^3.

The National Academy of Sciences (NRC 1984) developed Emergency and Continuous Exposure Limits (EEGLs) for Selected Airborne Contaminants. Their 24-hour EEGL of 0.2 mg/m^3 was based on the data of Milne et al. (1970). In that study, four workmen became ill after exposure to an estimated 1.1 to 4.0 mg/m^3 for 2.5 to 5 hours. A shorter-term guideline was not established.

TABLE 12. Extant Standards and Guidelines for Mercury Vapor

Guideline	Exposure Duration				
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	Not Recommended	Not Recommended	Not Recommended	Not Recommended	Not Recommended
AEGL-2	3.1 mg/m^3	2.1 mg/m^3	1.7 mg/m^3	0.67 mg/m^3	0.33 mg/m^3
AEGL-3	16 mg/m^3	11 mg/m^3	8.9 mg/m^3	2.2 mg/m^3	2.2 mg/m^3
ERPG-1 (AIHA)[a]			Not appropriate		
ERPG-2 (AIHA)			0.25 ppm (2.0 mg/m^3)		
ERPG-3 (AIHA)			0.5 ppm (4.1 mg/m^3)		
SMAC (NRC)[b]			0.01 ppm (0.08 mg/m^3)		
TWA (OSHA)[c]					0.1 mg/m^3
IDLH (NIOSH)[d]		10 mg/m^3			
REL-TWA, ceiling (NIOSH)[e]					0.05 mg/m^3, 0.1 mg/m^3
TLV-TWA (ACGIH)[f]					0.025 mg/m^3
MAK (Germany)[g]					0.1 mg/m^3 II(8)
MAC (The Netherlands)[h]					0.05 mg/m^3

[a]**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association** (AIHA 2002)
The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without perceiving a clearly defined objectionable odor.
The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.
The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.

[b]**SMAC (Spacecraft Maximum Allowable Concentration, National Research Council)** (NRC 1996)
SMACs are intended to provide guidance on chemical exposures during normal operations of spacecraft as well as emergency situations. The one-hour SMAC is a concentration of airborne substance that will not compromise the performance of specific tasks by astronauts during emergency conditions or cause serious or permanent toxic effects. Such exposures may cause reversible effects such as skin or eye irritation, but they are not expected to impair judgment or interfere with proper responses to emergencies.

[c]**OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average)** (NIOSH 2005) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week.

[d]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH 2005) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[e]**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH 2005) is defined analogous to the ACGIH-TLV-TWA.

[f]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 1996) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[g]**MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft [German Research Association] 2005) is defined analogous to the ACGIH-TLV-TWA. For mercury, category II(8) indicates an excursion factor of 2, 8 times during the shift.

[h]**MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration])** (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands 2000) is defined analogous to the ACGIH-TLV-TWA. The 15-minute peak is 0.5 mg/m^3.

8.3. Data Adequacy and Research Needs

There are no human data with measured concentrations and symptoms that meet the definitions of the AEGLs. Human metabolism studies used relatively low and presumably safe concentrations. The metabolism studies in conjunction with estimated concentrations from non-fatal human accidental exposures were considered in the development of AEGL values. An AEGL-1 was not recommended because mercury is odorless and without irritation at concentrations that may be harmful. The AEGL-2 and AEGL-3 values were based on several rodent studies that used suitable concentrations and exposure durations. The sensitive developing fetus was considered in development of AEGL-2 values.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1 Values

Because mercury vapor has no odor or warning properties, AEGL-1 values are not recommended.

Derivation of AEGL-2 Values

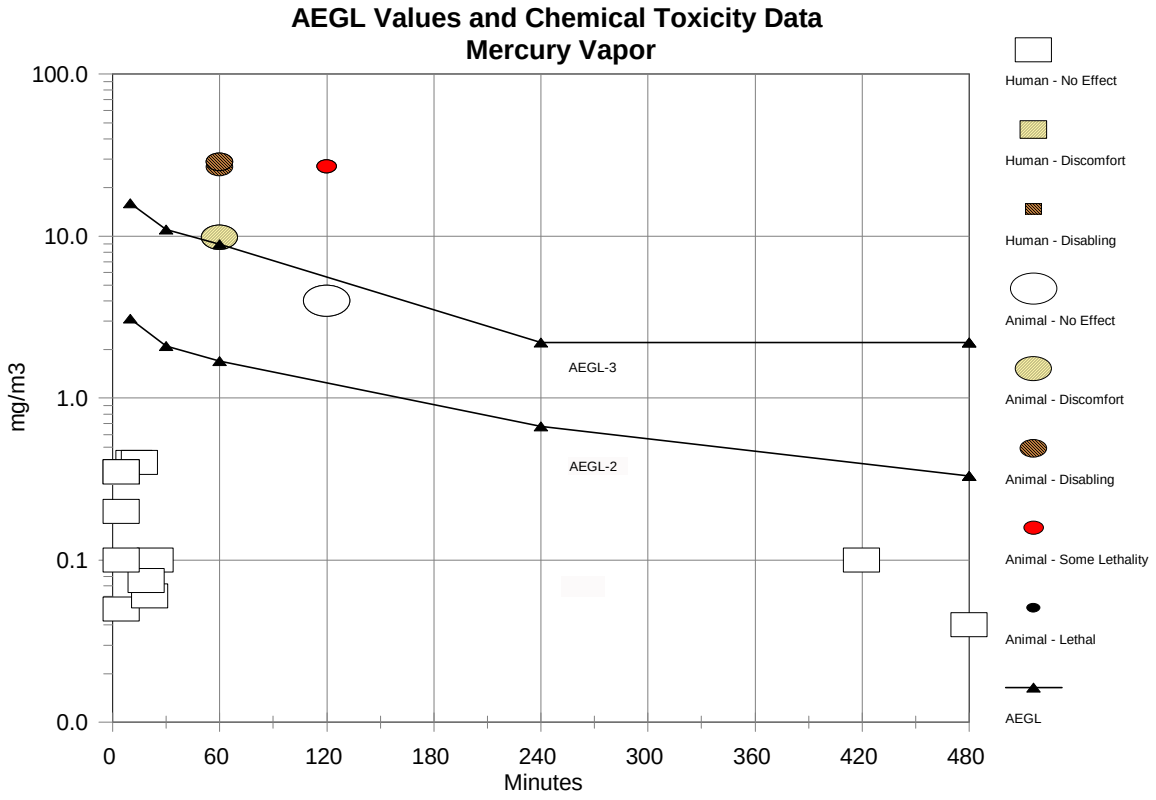
Key Study:	Morgan et al. 2002
Toxicity endpoint:	A 2-hour/day, 10-day exposure to 4 mg/m^3 mercury vapor was a NOAEL for increased resorptions and fetal death in pregnant rats. The next higher concentration, 8 mg/m^3, resulted in fetotoxicity.
Time scaling:	$C^n \times t = k$ where n = 3 and 1 for shorter and longer exposure periods, respectively (ten Berge et al. 1986; NRC 2001).
Uncertainty factors:	Total of 3 (weight of evidence approach) Interspecies: 1, based on the following factors: the 4 mg/m^3 value was a NOAEL for developmental effects (below the definition of the AEGL-2), the exposures were repeated for 10 days, rodents have a higher respiratory rate and cardiac output compared with humans (resulting in faster uptake), and human monitoring studies show some effects at concentrations of 0.4 to 2 mg/m^3 only with chronic exposure. Intraspecies: 3, based on the following factors: the population of fetuses is considered a sensitive if not the most sensitive population, the protective action of the placenta in sequestering mercury (Morgan et al. 2002), and incidences of miscarriages and stillbirths were unaffected in women chronically exposed to 0.025 to 0.6 mg/m^3, although anomalies were statistically non-significantly increased.
Calculations:	$C/3 = (4\ mg/m^3)/3 = 1.33\ mg/m^3$ $C^3 \times t = k$ $(1.33)^3 \times 120\ minutes = (282.32\ mg/m^3)^3 \bullet minutes$ $C^1 \times t = k$ $1.33 \times 120\ minutes = 159.6\ mg/m^3 \bullet minutes$
10-minute AEGL-2:	$C^3 \times 10\ minutes = 282.32\ (mg/m^3)^3 \bullet minutes$ $C = 3.1\ mg/m^3$
30-minute AEGL-2:	$C^3 \times 30\ minutes = 282.32\ (mg/m^3)^3 \bullet minutes$ $C = 2.1\ mg/m^3$
1-hour AEGL-2:	$C^3 \times 60\ minutes = 282.32\ (mg/m^3)^3 \bullet minutes$ $C = 1.7\ mg/m^3$
4-hour AEGL-2:	$C^1 \times 240\ minutes = 159.6\ mg/m^3 \bullet minutes$ $C = 0.67\ mg/m^3$
8-hour AEGL-2:	$C^1 \times 480\ minutes – 159.6\ mg/m^3 \bullet minutes$ $C = 0.33\ mg/m^3$

Derivation of AEGL-3 Values

Key Study:	Livardjani et al. 1991
Toxicity endpoint:	Highest 1-hour non-lethal exposure of rats: 26.7 mg/m^3
Time scaling:	$C^n \times t = k$ where n = 3 and 1 for shorter and longer exposure periods, respectively (ten Berge et al. 1986; NRC 2001).
Uncertainty factors:	Total of 3 (an interspecies uncertainty factor of 1 and an intraspecies uncertainty factor of 3), based on (1) faster uptake in rodents compared with humans and (2) the incompatibility of derived values with monitoring data and accidental exposure data if a larger uncertainty factor is used. The intraspecies uncertainty factor of 3 is considered sufficient to protect susceptible populations.
Calculations:	$C/3 = (26.7\ mg/m^3)/3 = 8.9\ mg/m^3$ $C^3 \times t = k$ $(8.9\ mg/m^3)^3 \times 60\ minutes = (42298.14\ mg/m^3)^3 \bullet minutes$ $C^1 \times t = k$ $8.9\ mg/m^3 \times 60\ minutes = 534\ mg/m^3 \bullet minutes$
10-minute AEGL-3:	$C^3 \times 10\ minutes = 42298.14\ (mg/m^3)^3 \bullet minutes$ $C = 16\ mg/m^3$
30-minute AEGL-3:	$C^3 \times 30\ minutes = 42298.14\ (mg/m^3)^3 \bullet minutes$ $C = 11\ mg/m^3$
1-hour AEGL-3:	$C/3 = 8.9\ mg/m^3$
4-hour AEGL-3:	$C^1 \times 240\ minutes = 534\ mg/m^3 \bullet minutes$ $C = 2.2\ mg/m^3$
8-hour AEGL-3:	$C^1 \times 480\ minutes - 534\ mg/m^3 \bullet minutes$ $C = 1.1\ mg/m^3$ (see below)

Because of inconsistency with some monitoring data and estimated non-fatal concentrations, the 8-hour AEGL-3 value of 1.1 mg/m^3 was set equal to the 4-hour value (2.2 mg/m^3).

APPENDIX B: Category Graph of AEGL Values and Toxicity Data



Data:

Category: 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal					
Source	**Species**	**mg/m^3**	**Minutes**	**Category**	**Comments**
NAC/AEGL-1		NR	10	AEGL	
NAC/AEGL-1		NR	30	AEGL	
NAC/AEGL-1		NR	60	AEGL	
NAC/AEGL-1		NR	240	AEGL	
NAC/AEGL-1		NR	480	AEGL	
NAC/AEGL-2		3.1	10	AEGL	
NAC/AEGL-2		2.1	30	AEGL	
NAC/AEGL-2		1.7	60	AEGL	
NAC/AEGL-2		0.67	240	AEGL	
NAC/AEGL-2		0.33	480	AEGL	
NAC/AEGL-3		16	10	AEGL	
NAC/AEGL-3		11	30	AEGL	
NAC/AEGL-3		8.9	60	AEGL	
NAC/AEGL-3		2.2	240	AEGL	
NAC/AEGL-3		2.2	480	AEGL	
Nielsen-Kudsk 1965	human	0.05 0.10 0.20 0.35	5 5 5 5	0 0 0 0	metabolism study
Hursh et al. 1976	human	0.11 0.06	24 19	0 0	metabolism study
Hursh et al. 1980	human	0.06 0.40	21 12	0 0	metabolism study
Sandborgh-Englund et al. 1998	human	0.40	15	0	metabolism study
Teisinger and Fiserova-Bergerova 1965	human	0.10	420	0	metabolism study
Roels et al. 1987	human	0.04	480	0	occupational monitoring
Morgan et al. 2002	rat	4.0	120	0	no fetotoxicity
Livardjani et al. 1991	rat	26.7 27.0	60 120	2 SL	no deaths; mild lung lesions 62.5% mortality
Shimojo et al. 1996	mouse	9.8	60	1	increased protein – broncho-alveolar fluid
Ashe et al. 1953	rabbit	28.7	60	2	mild organ damage

APPENDIX C: Derivation Summary
MERCURY VAPOR (CAS Reg. No. 7439-97-6)

AEGL-1 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
Not Recommended[a]	**Not Recommended**	**Not Recommended**	**Not Recommended**	**Not Recommended**

[a] AEGL-1 values are not recommended because mercury vapor has no odor or warning properties at concentrations that may cause extensive tissue damage.

AEGL-2 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
3.1 mg/m^3	**2.1 mg/m^3**	**1.7 mg/m^3**	**0.67 mg/m^3**	**0.33mg/m^3**
Key Reference: Morgan, D.L., S.M. Chanda, H.C. Price, R. Fernando, J. Liu, E. Brambila, R.W. O'Connor, R.P. Beliles, and S. Barone, Jr. 2002. Disposition of inhaled mercury vapor in pregnant rats: maternal toxicity and effects on developmental outcome. Toxicol. Sci. 66:261-273.				
Test Species/Strain/Number: Rat (pregnant)/Long-Evans/25 (serial sacrifice)				
Exposure Route/Concentrations/Durations: Inhalation/0, 1, 2, 4, 8 mg/m^3 for 2 hours/day over GD 6-15				
Effects: No fetotoxicity observed after 2 hour/day, 10-day exposure to 4 mg/m^3. Developmental effects including resorptions, decreased litter size and decreased PND 1 weight at 8 mg/m^3.				
Endpoint/Concentration/Rationale: 2-hour exposure to 4 mg/m^3 was a NOAEL for the definition of the AEGL-2, i.e., irreversible effects to the fetus.				
Uncertainty Factors/Rationale: Total uncertainty factor: 3 (based on weight of evidence approach) Interspecies: 1, based on the following factors: the 4 mg/m^3 value was a NOAEL for developmental effects (below the definition of the AEGL-2), the exposures were repeated for 10 days, rodents have a higher respiratory rate and cardiac output compared with humans (resulting in faster uptake), and human monitoring studies show some effects at concentrations of 0.4 to 2 mg/m^3 only with chronic exposure (AIHA 2002). Intraspecies: 3, based on the following factors: the population of fetuses is considered a sensitive if not the most sensitive population, the protective action of the placenta in sequestering mercury (Morgan et al. 2002), and incidences of miscarriages and stillbirths were unaffected in women chronically exposed to 0.025 to 0.6 mg/m^3, although congenital anomalies were statistically non-significantly increased (Elghany et al. 1997).				
Modifying Factor: None applied				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: $C^n \times t = k$ where n is 3 and 1 for shorter and longer exposure durations, respectively (ten Berge et al. 1986; NRC 2001).				
Data Adequacy: The values are supported by occupational monitoring of pregnant women. A study of pregnancies in women chronically exposed to mercury vapor (median air concentration, 0.09 mg/m^3; range, 0.025-0.599 mg/m^3) did not reveal a significant difference from controls regarding miscarriages and stillbirths, although congenital anomalies were statistically non-significantly increased (Elghany et al. 1997).				

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AEGL-3 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
16 mg/m^3	**11 mg/m^3**	**8.9 mg/m^3**	**2.2 mg/m^3**	**2.2 mg/m^3**
Key Reference: Livardjani, F. M. Ledig, P. Kopp, M. Dahlet, M. Leroy, and A. Jaeger. 1991. Lung and blood superoxide dismutase activity in mercury vapor exposed rats: effect of *N*-acetylcysteine treatment. Toxicology 66:289-295.				
Test Species/Strain/Number: Rat/Wistar/32				
Exposure Route/Concentrations/Durations: Inhalation/0, 26.7 mg/m^3 for 1 hour, 27.0 mg/m^3 for 2 hours				
Effects: 1-hour exposure to 26.7 mg/m^3: no deaths over 15-day observation period; lung lesions 2-hour exposure to 27.0 mg/m^3: death of 20/32 rats				
Endpoint/Concentration/Rationale: NOAEL for lethality: 26.7 mg/m^3 for 1 hour meets the definition of the AEGL-3				
Uncertainty Factors/Rationale: Total uncertainty factor: 3 (an interspecies uncertainty factor of 1 and an intraspecies uncertainty factor of 3), based on (1) faster uptake in rodents compared with humans, and (2) incompatibility of derived values with monitoring and accidental exposure data if larger uncertainty factors are used.				
Modifying Factor: None applied				
Animal to Human Dosimetric Adjustment: Not applicable				
Time Scaling: $C^n \times t = k$ where n is 3 and 1 for shorter and longer exposure durations, respectively (ten Berge et al. 1986; NRC 2001). The 8-hour value was set equal to the 4-hour value.				
Data Adequacy: Although the data base is not large and data on humans consist of clinical studies and estimated concentrations and exposure durations from accidental exposures, a repeat-dose study with the rat (Beliles et al. 1968) supports the values. In that study, male and female Wistar-derived rats exposed to 17.2 mg/m^3 for 2 hours/day 5 days/week for 22 exposures showed behavioral changes that were reversible following a recovery period. Organ lesions consisted of lymphocytic perivascular cuffing of the medulla oblongata.				

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