Mercury, elemental; CASRN 7439-97-6

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Mercury, elemental

File First On-Line 09/07/1988

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	yes	06/01/1995
Carcinogenicity Assessment (II.)	yes	05/01/1995

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Mercury, elemental
CASRN — 7439-97-6

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Mercury, elemental
CASRN — 7439-97-6
Last Revised — 06/01/1995

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Hand tremor, increases in memory disturbance; slight subjective and objective evidence of autonomic dysfunction **Human occupational inhalation studies** **Fawer et al., 1983; Piikivi and Tolonen, 1989; Piikivi and Hanninen, 1989; Piikivi, 1989;**	NOAEL: None LOAEL: 0.025 mg/cu.m (converted to LOAEL [ADJ] of 0.009 mg/cu.m)	30	1	3E-4 mg/cu.m

Critical Effect	Exposures*	UF	MF	RfC
Ngim et al., 1992; Liang et al., 1993				

*Conversion Factors and Assumptions: This is an extrarespiratory effect of a vapor (gas). The LOAEL is based on an 8-hour TWA occupational exposure. MVho = 10 cu.m/day, MVh = 20 cu.m/day. LOAEL(HEC) = LOAEL(ADJ) = 0.025 mg/cu.m x>MVho/MVh x 5 days/7 days = 0.009 mg/cu.m. Air concentrations (TWA) were measured in the Fawer et al. (1983), Ngim et al. (1992), and Liang et al. (1993) studies. Air concentrations were extrapolated from blood levels based on the conversion factor of Roels et al. (1987) as described in the Additional Comments section for the studies of Piikivi and Tolonen (1989), Piikivi and Hanninen (1989), and Piikivi (1989).

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Fawer, R.F., U. DeRibaupierre, M.P. Guillemin, M. Berode and M. Lobe. 1983.Measurement of hand tremor induced by industrial exposure to metallic mercury. J. Ind. Med. 40: 204-208.

Piikivi, L. and U. Tolonen. 1989. EEG findings in chlor-alkali workers subjected to low long term exposure to mercury vapor. Br. J. Ind. Med. 46: 370-375.

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

Piikivi, L. 1989. Cardiovascular reflexes and low long-term exposure to mercury vapor. Int. Arch. Occup. Environ. Health. 61: 391-395.

Ngim, C.H., S.C. Foo, K.W. Boey and J. Jeyaratnam. 1992. Chronic neurobehavioral effects of elemental mercury in dentists. Br. J. Ind. Med. 49: 782-790.

Liang, Y-X., R-K. Sun, Y. Sun, Z-Q. Chen and L-H. Li. 1993. Psychological effects of low exposure to mercury vapor: Application of a computer-administered neurobehavioral evaluation system. Environ. Res. 60: 320-327.

Fawer et al. (1983) used a sensitive objective electronic measure of intention tremor (tremors that occur at the initiation of voluntary movements) in 26 male workers (mean age of 44 years) exposed to low levels of mercury vapor in various occupations: fluorescent tube manufacture

(n=7), chloralkali plants (n=12), and acetaldehyde production (n=7). Controls (n=25; mean age of 44.6 years) came from the same factories but were not exposed occupationally. Personal air samples (two per subject) were used to characterize an average exposure concentration of 0.026 mg/cu.m. It should be noted that it is likely that the levels of mercury in the air varied during the period of exposure and historical data indicate that previous exposures may have been higher. Exposure measurements for the control cohort were not performed. The average duration of exposure was 15.3 years. The measures of tremor were significantly increased in the exposed compared to control cohorts, and were shown to correspond to exposure and not to chronologic age. These findings are consistent with neurophysiological impairments that might result from accumulation of mercury in the cerebellum and basal ganglia. Thus, the TWA of 0.026 mg/cu.m was designated a LOAEL. Using the TWA and adjusting for occupational ventilation rates and workweek, the resultant LOAEL(HEC) is 0.009 mg/cu.m.

Piikivi and Tolonen (1989) used EEGs to study the effects of long-term exposure to mercury vapor in 41 chloralkali workers exposed for a mean of 15.6 +/- 8.9 years as compared with matched referent controls. They found that the exposed workers, who had mean blood Hg levels of 12 ug/L and mean urine Hg levels of 20 ug/L, tended to have an increased number of EEG abnormalities when analyzed by visual inspection only. When the EEGs were analyzed by computer, however, the exposed workers were found to have significantly slower and attenuated brain activity as compared with the referents. These changes were observed in 15% of the exposed workers. The frequency of these changes correlated with cortical Hg content (measured in other studies); the changes were most prominent in the occipital cortex less prominent in the parietal cortex, and almost absent in the frontal cortex. The authors extrapolated an exposure level associated with these EEG changes of 0.025 mg/cu.m from blood levels based on the conversion factor calculated by Roels et al. (1987).

Piikivi and Hanninen (1989) studied the subjective symptoms and psychological performances on a computer-administered test battery in 60 chloralkali workers exposed to mercury vapor for a mean of 13.7 +/- 5.5 years as compared with matched referent controls. The exposed workers had mean blood Hg levels of 10 ug/L and mean urine Hg levels of 17 ug/L. A statistically significant increase in subjective measures of memory disturbance and sleep disorders was found in the exposed workers. The exposed workers also reported more anger, fatigue and confusion. No objective disturbances in perceptual motor, memory or learning abilities were found in the exposed workers. The authors extrapolated an exposure level associated with these subjective measures of memory disturbance of 0.025 mg/cu.m from blood levels based on the conversion factor calculated by Roels et al. (1987).

Both subjective and objective symptoms of autonomic dysfunction were investigated in 41 chloralkali workers exposed to mercury vapor for a mean of 15.6 +/- 8.9 years as compared with matched referent controls (Piikivi, 1989). The quantitative non-invasive test battery consisted of

measurements of pulse rate variation in normal and deep breathing, in the Valsalva maneuver and in vertical tilt, as well as blood pressure responses during standing and isometric work. The exposed workers had mean blood levels of 11.6 ug/L and mean urine levels of 19.3 ug/L. The exposed workers complained of more subjective symptoms of autonomic dysfunction than the controls, but the only statistically significant difference was an increased reporting of palpitations in the exposed workers. The quantitative tests revealed a slight decrease in pulse rate variations, indicative of autonomic reflex dysfunction, in the exposed workers. The authors extrapolated an exposure level associated with these subjective and objective measures of autonomic dysfunction of 0.030 mg/cu.m from blood levels based on the conversion factor calculated by Roels et al. (1987).

Two more recent studies in other working populations corroborate the neurobehavioral toxicity of low-level mercury exposures observed in the Fawer et al. (1983), Piikivi and Tolonen (1989), Piikivi and Hanninen (1989), and Piikivi (1989) studies.

Ngim et al. (1992) assessed neurobehavioral performance in a cross-sectional study of 98 dentists (38 female, 60 male; mean age 32, range 24-49 years) exposed to TWA concentrations of 0.014 mg/cu.m (range 0.0007 to 0.042 mg/cu.m) versus 54 controls (27 female, 27 male; mean age 34, range 23-50 years) with no history of occupational exposure to mercury. Air concentrations were measured with personal sampling badges over typical working hours (8-10 hours) and converted to an 8-hour TWA. No details on the number of exposure samples or exposure histories were provided. Blood samples from the exposed cohort were also taken and the data supported the correspondence calculated by Roels et al. (1987). Based on extrapolation of the average blood mercury concentration (9.8 ug/L), the average exposure concentration would be estimated at 0.023 mg/cu.m. The average duration of practice of the exposed dentists was 5.5 years. Exposure measurements of the control cohort were not performed. The exposed and control groups were adequately matched for age, amount of fish consumption, and number of amalgam dental fillings. The performance of the dentists was significantly worse than controls on a number of neurobehavioural tests measuring motor speed (finger tapping), visual scanning, visumotor coordination and concentration, visual memory, and visuomotor coordination speed. These neurobehavioral effects are consistent with central and peripheral neurotoxicity and the TWA is considered a LOAEL. Using the TWA and adjusting for occupational ventilation rates and the reported 6-day workweek, the resultant LOAEL(HEC) is 0.006 mg/cu.m.

Liang et al. (1993) investigated workers in a fluorescent lamp factory with a computer-administered neurobehavioral evaluation system and a mood inventory profile. The exposed cohort (mean age 34.2 years) consisted of 19 females and 69 males exposed to mercury vapor for at least 2 years prior to the study. Exposure was monitored with area samplers and ranged from 0.008 to 0.085 mg/cu.m across worksites. No details on how the exposure profiles to account for time spent in different worksites were constructed. The average exposure was estimated at 0.033

mg/cu.m. (range 0.005 to 0.19 mg/cu.m). The average duration was of working was 15.8 years for the exposed cohort. Urinary excretion was also monitored and reported to average 0.025 mg/L. The control cohort (mean age 35.1 years) consisted of 24 females and 46 males recruited from an embroidery factory. The controls were matched for age, education, smoking and drinking habits. Exposure measurements for the control cohort were not performed. The exposed cohort performed significantly worse than the control on tests of finger tapping, mental arithmetic, two-digit searches, switching attention, and visual reaction time. The effect on performance persisted after the confounding factor of chronological age was controlled. Based on these neurobehavioral effects, the TWA of 0.033 mg/cu.m is designated as LOAEL. Using the TWA and adjusting for occupational ventilation rates and workweek, the resultant LOAEL(HEC) is 0.012 mg/cu.m.

The above studies were taken together as evidence for a LOAEL based on neurobehavioral effects of low-level mercury exposures. The LOAEL(HEC) levels calculated on measured air concentration levels of the Ngim et al. (1992) and the Liang et al. (1993) studies bracket that calculated based on the air concentrations measured by Fawer et al. (1983) as a median HEC level. Extrapolations of blood levels, used as biological monitoring that accounts for variability in exposure levels, also converge at 0.025 mg/cu.m as a TWA which results in the same HEC level. Thus, the TWA level of 0.025 mg/cu.m was used to represent the exposure for the synthesis of the studies described above. Using this TWA and taking occupational ventilation rates and workweek into account results in a LOAEL(HEC) of 0.009 mg/cu.m.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — An uncertainty factor of 10 was used for the protection of sensitive human subpopulations (including concern for acrodynia - see Additional Comments section) together with the use of a LOAEL. An uncertainty factor of 3 was used for lack of database, particularly developmental and reproductive studies.

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

Probably the most widely recognized form of hypersensitivity to mercury poisoning is the uncommon syndrome known as acrodynia, also called erythredema polyneuropathy or pink disease (Warkany and Hubbard, 1953). Infantile acrodynia was first described in 1828, but adult cases have also since been reported. While acrodynia has generally been associated with short-term exposures and with urine levels of 50 ug/L or more, there are some cases in the literature in which mercury exposure was known to have occurred, but no significant (above background) levels in urine were reported. There could be many reasons for this, but the most likely is that

urine levels are not a simple measure of body burden or of target tissue (i.e., brain levels); however, they are the best means available for assessing the extent of exposure. It was felt that the RfC level estimated for mercury vapor based on neurotoxicity of chronic exposure in workers is adequate to protect children from risk of acrodynia because such exposures of long duration would be expected to raise urine levels by only 0.12 ug/L against a background level of up to 20 ug/L (i.e., such exposures would not add significantly to the background level of mercury in those exposed).

Roels et al. (1987) investigated the relationships between the concentrations of metallic mercury in air and levels monitored in blood or urine in workers exposed during manufacturing of dry alkaline batteries. Breathing zone personal samples were used to characterize airborne mercury vapors. Total mercury in blood and urine samples were analyzed using atomic absorption. The investigation controlled for several key factors including the use of reliable personal air monitoring, quality control for blood and urine analyses, standardization of the urinary mercury concentration for creatinine concentration, and stability of exposure conditions (examined subjects were exposed to mercury vapor for at least 1 year). Strong correlations were found between the daily intensity of exposure to mercury vapor and the end of workshift levels in blood ($r=0.86$; $n=40$) or urine ($r=0.81$; $n=34$). These relationships indicated a conversion factor of 1:4.5 (air:blood) and 1:1.22 (air:urine as ug/g creatinine). These factors were used to extrapolate blood or urine levels associated with effects in the reported studies to airborne mercury levels.

Sensory and motor nerve conduction velocities were studied in 18 workers from a mercury cell chlorine plant (Levine et al., 1982). Time-integrated urine Hg levels were used as an indicator of mercury exposure. Using linearized regression analysis, the authors found that motor and sensory nerve conduction velocity changes (i.e., prolonged distal latencies correlated with the time-integrated urinary Hg levels in asymptomatic exposed workers) occurred when urinary Hg levels exceeded 25 ug/L. This study demonstrates that mercury exposure can be associated with preclinical evidence of peripheral neurotoxicity.

Singer et al. (1987) studied nerve conduction velocity of the median motor, median sensor and sural nerves in 16 workers exposed to various inorganic mercury compounds (e.g., mercuric oxides, mercurial chlorides, and phenyl mercuric acid) for an average of 7.3 +/- 7.1 years as compared with an unexposed control group using t-tests. They found a slowing of nerve conduction velocity in motor, but not sensory, nerves that correlated with increased blood and urine Hg levels and an increased number of neurologic symptoms. The mean mercury levels in the exposed workers were 1.4 and 10 ug/L for blood and urine, respectively. These urine levels are 2-fold less than those associated with peripheral neurotoxicity in other studies (e.g., Levine et al., 1982). There was considerable variability in the data presented by Singer et al. (1987), however, and the statistical analyses (t-test) were not as rigorous as those employed by Levine et al. (1982) (linearized regression analysis). Furthermore, the subjects in the Levine et al. (1982)

study were asymptomatic at higher urinary levels than those reported to be associated with subjective neurological complaints in the workers studied by Singer et al. (1987). Therefore, these results are not considered to be as reliable as those reported by Levine et al. (1982).

Miller et al. (1975) investigated several subclinical parameters of neurological dysfunction in 142 workers exposed to inorganic mercury in either the chloralkali industry or a factory for the manufacture of magnetic materials. They reported a significant increase in average forearm tremor frequency in workers whose urinary Hg concentrations exceeded 50 ug/L as compared with unexposed controls. Also observed were eyelid fasciculation, hyperactive deep-tendon reflexes and dermatographia, but there was no correlation between the incidence of these findings and urinary Hg levels.

Roels et al. (1985) examined 131 male and 54 female workers occupationally exposed to mercury vapor for an average duration of 4.8 years. Urinary mercury (52 and 37 ug/g creatinine for males and females, respectively) and blood mercury levels (14 and 9 ug/L for males and females, respectively) were recorded, but atmospheric mercury concentration was not provided. Symptoms indicative of CNS disorders were reported but not related to mercury exposure. Minor renal tubular effects were detected in mercury-exposed males and females and attributed to current exposure intensity rather (urinary Hg >50 ug/g creatinine) than exposure duration. Male subjects with urinary mercury levels of >50 ug/g creatinine exhibited preclinical signs of hand tremor. It was noted that females did not exhibit this effect and that their urinary mercury never reached the level of 50 ug/g creatinine. A companion study (Roels et al., 1987) related air mercury (Hg-air)levels to blood mercury (Hg-blood) and urinary mercury (Hg-U) values in 10 workers in a chloralkali battery plant. Duration of exposure was not specified. A high correlation was reported for Hg-air and Hg-U for preshift exposure ($r=0.70$, $p<0.001$) and post-shift ($r=0.81$, $p<0.001$) measurements. Based on these data and the results of their earlier (1985) study, the investigators suggested that some mercury-induced effects may occur when Hg-U levels exceed 50 ug/g creatinine, and that this value corresponds to a mercury TWA of about 40 ug/cu.m.

A survey of 567 workers at 21 chloralkali plants was conducted to ascertain the effects of mercury vapor inhalation (Smith et al., 1970). Mercury levels ranged from <0.01 to 0.27 mg/cu.m and chlorine concentrations ranged from 0.1 to 0.3 ppm at most of the working stations of these plants. Worker exposure to mercury levels (TWA) varied, with 10.2% of the workers being exposed to <0.01 mg/cu.m, 48.7% exposed to 0.01 to 0.05 mg/cu.m, 25.6% exposed to 0.06 to 0.10 mg/cu.m and 4.8% exposed to 0.24 to 0.27 mg/cu.m (approximately 85% were exposed to Hg levels less than or equal to 0.1 mg/cu.m). The duration of employment for the examined workers ranged from one year (13.3%) to >10 years (31%), with 55.7% of the workers being employed for 2 or 9 years. A group of 600 workers not exposed to chlorine served as a control group for assessment of chlorine effects, and a group of 382 workers not exposed to either chlorine or mercury vapor served as the reference control group. A strong positive

correlation ($p<0.001$) was found between the mercury TWAs and the reporting of subjective neuropsychiatric symptoms (nervousness, insomnia), occurrence of objective tremors, and weight and appetite loss. A positive correlation ($p<0.001$) was also found between mercury exposure levels and urinary and blood mercury levels of test subjects. No adverse alterations in cardiorespiratory, gastrointestinal, renal or hepatic functions were attributed to the mercury vapor exposure. Additionally, biochemical (hematologic data, enzyme activities) and clinical measurements (EKG, chest X-rays) were no different between the mercury-exposed and non-exposed workers. No significant signs or symptoms were noted for individuals exposed to mercury vapor concentrations less than or equal to 0.1 mg/cu.m. This study provides data indicative of a NOAEL of 0.1 mg Hg/cu.m and a LOAEL of 0.18 mg Hg/cu.m. In a followup study conducted by Bunn et al. (1986), however, no significant differences in the frequency of objective or subjective findings such as weight loss and appetite loss were observed in workers exposed to mercury at levels that ranged between 50 and 100 ug/L. The study by Bunn et al. (1986) was limited, however, by the lack of information provided regarding several methodological questions such as quality assurance measures and control of possible confounding variables.

The mercury levels reported to be associated with preclinical and symptomatic neurological dysfunction are generally lower than those found to affect kidney function, as discussed below.

Piikivi and Ruokonen (1989) found no evidence of glomerular or tubular damage in 60 chloralkali workers exposed to mercury vapor for an average of 13.7 +/- 5.5 years as compared with their matched referent controls. Renal function was assessed by measuring urinary albumin and N-acetyl-beta-glucosaminidase (NAG) activity. The mean blood Hg level in the exposed workers was 14 ug/L and the mean urinary level was 17 ug/L. The authors extrapolated the NOAEL for kidney effects based on these results of 0.025 mg/cu.m from blood levels using the conversion factor calculated by Roels et al. (1987).

Stewart et al. (1977) studied urinary protein excretion in 21 laboratory workers exposed to 10-50 ug/cu.m of mercury. Their urinary level of mercury was about 35 ug/L. Increased proteinuria was found in the exposed workers as compared with unexposed controls. When preventive measure were instituted to limit exposure to mercury, proteinuria was no longer observed in the exposed technicians.

Lauwerys et al. (1983) found no change in several indices of renal function (e.g., proteinuria, albuminuria, urinary excretion of retinol-binding protein, aminoaciduria, creatinine in serum, beta-2-microglobulin in serum) in 62 workers exposed to mercury vapor for an average of 5.5 years. The mean urinary Hg excretion in the exposed workers was 56 ug/g creatinine, which corresponds to an exposure level of about 46 ug/cu.m according to a conversion factor of 1:1.22 (air:urine [ug/g creatinine]) (Roels et al., 1987). Despite the lack of observed renal effects, 8

workers were found to have an increased in serum anti-laminin antibodies, which can be indicative of immunological effects. In a followup study conducted by Bernard et al. (1987), however, there was no evidence of increased serum anti-laminin antibodies in 58 workers exposed to mercury vapor for an average of 7.9 years. These workers had a mean urinary Hg excretion of 72 ug/g creatinine, which corresponds to an exposure levels of about 0.059 mg/cu.m.

Stonard et al. (1983) studied renal function in 100 chloralkali workers exposed to inorganic mercury vapor for an average of 8 years. No changes in the following urinary parameters of renal function were observed at mean urinary Hg excretion rates of 67 ug/g creatinine: total protein, albumin, alpha-1-acid glycoprotein, beta-2-microglobulin, NAG, and gamma-glutamyl transferase. When urinary Hg excretion exceeded 100 ug/g creatinine, a small increase in the prevalence of higher activities of NAG and gamma-glutamyl transferase was observed.

The mercury levels reported to be associated with preclinical and symptomatic neurological dysfunction and kidney effects are lower than those found to pulmonary function, as discussed below.

McFarland and Reigel (1978) described the cases of 6 workers who were acutely exposed (4-8 hours) to calculated metallic mercury vapor levels of 1.1 to 44 mg/cu.m. These men exhibited a combination of chest pains, dyspnea, cough, hemoptysis, impairment of pulmonary function (reduced vital capacity), diffuse pulmonary infiltrates and evidence of interstitial pneumonitis. Although the respiratory symptoms resolved, all six cases exhibited chronic neurological dysfunction, presumably as a result of the acute, high-level exposure to mercury vapor.

Lilis et al. (1985) described the case of a 31-year-old male who was acutely exposed to high levels of mercury vapor in a gold-extracting facility. Upon admission to the hospital, the patient exhibited dyspnea, chest pain with deep inspiration, irregular infiltrates in the lungs and reduced pulmonary function (forced vital capacity [FVC]). The level of mercury to which he was exposed is not known, but a 24-hour urine collection contained 1900 ug Hg/L. Although the patient improved gradually over the next several days, 11 months after exposure he still showed signs of pulmonary function abnormalities (e.g., restriction and diffusion impairment).

Levin et al. (1988) described four cases of acute high-level mercury exposure during gold ore purification. The respiratory symptoms observed in these four cases ranged from minimal shortness of breath and cough to severe hypoxemia. The most severely affected patient exhibited mild interstitial lung disease both radiographically and on pulmonary function testing. One patient had a urinary Hg level of 245 ug/L upon hospital admission. The occurrence of long-term respiratory effects in these patients could not be evaluated since all but one refused follow-up treatment.

Ashe et al. (1953) reported that there was no histopathological evidence of respiratory damage in 24 rats exposed to 0.1 mg Hg/cu.m 7 hr/day, 5 days/week for 72 weeks. This is equivalent to a NOAEL[HEC] of 0.07 mg/cu.m.

Kishi et al. (1978) observed no histopathological changes in the lungs of rats exposed to 3 mg/cu.m of mercury vapor 3 hours/day, 5 days/week for 12-42 weeks.

Beliles et al. (1967) observed no histopathological changes in the lungs of pigeons exposed to 0.1 mg/cu.m of mercury vapor 6 hours/day, 5 days/week for 20 weeks.

Neurological signs and symptoms (i.e., tremors) were observed in 79 workers exposed to metallic mercury vapor whose urinary mercury levels exceeded 500 ug/L. Short-term memory deficits were reported in workers whose urine levels were less than 500 ug/L (Langolf et al., 1978).

Impaired performance in mechanical and visual memory tasks and psychomotor ability tests was reported by Forzi et al. (1978) in exposed workers whose urinary Hg levels exceeded 100 ug/L.

Decreased strength, decreased coordination, increased tremor, decreased sensation and increased prevalence of Babinski and snout reflexes were exhibited by 247 exposed workers whose urinary Hg levels exceeded 600 ug/L. Evidence of clinical neuropathy was observed at urinary Hg levels that exceeded 850 ug/L (Albers et al., 1988).

Preclinical psychomotor dysfunction was reported to occur at a higher incidence in 43 exposed workers (mean exposure duration of 5 years) whose mean urinary excretion of Hg was 50 ug/L. Workers in the same study whose mean urinary Hg excretion was 71 ug/L had a higher incidence of total proteinuria and albuminuria (Roels et al., 1982).

Postural and intention tremor was observed in 54 exposed workers (mean exposure duration of 7.7 years) whose mean urinary excretion of Hg was 63 ug/L (Roels et al., 1989).

Verbeck et al. (1986) observed an increase in tremor parameters with increasing urinary excretion of mercury in 21 workers exposed to mercury vapor for 0.5-19 years. The LOAEL for this effect was a mean urinary excretion of 35 ug/g creatinine.

Rosenman et al. (1986) evaluated routine clinical parameters (physical exams, blood chemistry, urinalysis), neuropsychological disorders, urinary NAG, motor nerve conduction velocities and occurrence of lenticular opacities in 42 workers of a chemical plant producing mercury compounds. A positive correlation ($p<0.05$ to $p<0.001$) was noted between urinary mercury

(levels ranged from 100-250 ug/L) and the number of neuropsychological symptoms, and NAG excretions and the decrease in motor nerve conduction velocities.

Evidence of renal dysfunction (e.g., increased plasma and urinary concentrations of beta-galactosidase, increased urinary excretion of high-molecular weight proteins and a slightly increased plasma beta-2-microglobulin concentration) was observed in 63 chloralkali workers. The incidence of these effects increased in workers whose urinary Hg excretion exceeded 50 ug/g creatinine (Buchet et al., 1980).

Increased urinary NAG levels were found in workers whose urinary Hg levels exceeded 50 ug/L (Langworth et al., 1992).

An increase in the concentration of urinary brush border proteins (BB-50) was observed in 20 workers whose mean urinary Hg excretion exceeded 50 ug/g creatinine (Mutti et al., 1985).

Foa et al. (1976) found that 15 out of 81 chloralkali workers exposed to 60-300 ug/cu.m mercury exhibited proteinuria.

An increased excretion of beta-glutamyl transpeptidase, indicative of renal dysfunction, was found in 509 infants dermally exposed to phenylmercury via contaminated diapers (Gotelli et al., 1985).

Berlin et al. (1969) exposed rats, rabbits and monkeys to 1 mg/cu.m of mercury vapor for 4 hours and measured the uptake and distribution of mercury in the brain as compared with animals injected intravenously with the same doses of mercury as mercuric salts. Mercury accumulated in the brain following inhalation exposure to metallic mercury vapor at levels that were 10 times higher than those observed following intravenous injection of the same dose of mercury as mercuric salts. These results demonstrate that mercury is taken up by the brain following inhalation of the vapor at higher levels than other forms of mercury and that this occurs in all species studied.

Limited animal studies concerning inhalation exposure to inorganic mercury are available. The results of a study conducted by Baranski and Szymczyk (1973) were reported in an English abstract. Adult female rats were exposed to metallic mercury vapor at 2.5 mg/cu.m for 3 weeks prior to fertilization and during gestation days 7-20. A decrease in the number of living fetuses was observed in the dams compared with unexposed controls, and all pups born to the exposed dams died by the sixth day after birth. However, no difference in the occurrence of developmental abnormalities was observed between exposed and control groups. The cause of death of the pups in the mercury-exposed group was unknown, although an unspecified percentage of the deaths was attributed by the authors to a failure of lactation in the dams. Death

of pups was also observed in another experiment where dams were only exposed prior to fertilization (to 2.5 mg/cu.m), which supports the conclusion that the high mortality in the first experiment was due at least in part to poor health of the mothers. Without further information, this study must be considered inconclusive regarding developmental effects.

The only other study addressing the developmental toxicology of mercury is the one reported in abstract form by Steffek et al. (1987) and, as such, is included as a supporting study. Sprague-Dawley rats (number not specified) were exposed by inhalation to mercury vapor at concentrations of 0.1, 0.5 or 1.0 mg/cu.m throughout the period of gestation (days 1-20) or during the period of organogenesis (days 10-15). The authors indicated the exposure protocols to be chronic and acute exposure, respectively. At either exposure protocol, the lowest mercury level produced no detectable adverse effect. At 0.5 mg/cu.m, an increase in the number of resorptions (5/41) was noted for the acute group, and two of 115 fetuses exhibited gross cranial defects in the chronic group. At 1.0 mg/cu.m, the number of resorptions was increased in acute (7/71) and chronic (19/38) groups and a decrease in maternal and fetal weights also was detected in the chronic exposure group. No statistical analysis for these data was provided. A LOAEL of 0.5 mg/cu.m is provided based on these data.

Mishinova et al. (1980) investigated the course of pregnancy and parturition in 349 women exposed via inhalation to metallic mercury vapors (unspecified concentrations) in the workplace as compared to 215 unexposed women. The authors concluded that the rates of pregnancy and labor complication were high among women exposed to mercury and that the effects depended on "the length of service and concentration of mercury vapors." Lack of sufficient details preclude the evaluation of dose-response relationships.

In a questionnaire that assessed the fertility of male workers exposed to mercury vapor, Lauwerys et al. (1985) found no statistically significant change in the observed number of children born to the exposed group compared with a matched control group. The urinary excretion of mercury in the exposed workers ranged from 5.1 to 272.1 ug/g creatinine.

Another study found that exposure to metallic mercury vapor caused prolongation of estrus cycles in animals. Baranski and Szymczyk (1973) reported that female rats exposed via inhalation to mercury vapor at an average of 2.5 mg/cu.m, 6 hours/day, 5 days/week for 21 days experienced longer estrus cycles than unexposed animals. In addition, estrus cycles during mercury exposure were longer than normal estrus cycles in the same animals prior to exposure. Although the initial phase of the cycle was protracted, complete inhibition of the cycle did not occur. During the second and third weeks of exposure, these rats developed signs of mercury poisoning including restlessness, seizures and trembling of the entire body. The authors speculated that the effects on the estrus cycle were caused by the action of mercury on the CNS (i.e., damage to the hypothalamic regions involved in the control of estrus cycling).

Renal toxicity has been reported following oral exposure to inorganic mercury salts in animals, with the Brown-Norway rat appearing to be uniquely sensitive to this effect. These mercury-induced renal effects in the Brown-Norway rat are the basis for the oral RfD for mercurial mercury. Several investigators have produced autoimmune glomerulonephritis by administering HgCl2 to Brown-Norway rats (Druet et al., 1978).

The current OSHA standard for mercury vapor is 0.05 mg/cu.m. NIOSH recommends a TWA Threshold Limit Value of 0.05 mg/cu.m for mercury vapor.

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Medium
RfC — Medium

Due to the use of a sufficient number of human subjects, the inclusion of appropriate control groups, the exposure duration, the significance level of the reported results and the fact that exposure levels in a number of the studies had to be extrapolated from blood mercury levels, confidence in the key studies is medium. The LOAEL values derived from these studies can be corroborated by other human epidemiologic studies. The adverse effects reported in these studies are in accord with the well-documented effects of mercury poisoning. The lack of human or multispecies reproductive/developmental studies precludes assigning a high confidence rating to the database and inadequate quantification of exposure levels. Based on these considerations, the RfC for mercury is assigned a confidence rating of medium.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — U.S. EPA, 1995

This IRIS Summary is included in The Mercury Study Report to Congress which was reviewed by OHEA and EPA's Mercury Work Group in November 1994. An Interagency Review by scientists from other federal agencies took place in January 1995. The report was also reviewed by a panel of non-federal external scientists in January 1995 who met in a public meeting on January 25-26. All reviewers comments have been carefully evaluated and considered in the revision and finalization of this IRIS Summary. A record of these comments is summarized in the IRIS documentation files.

Other EPA Documentation — None

Agency Work Group Review — 11/16/1989, 03/22/1990, 04/19/1990

Verification Date — 04/19/1990

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Mercury, elemental conducted in September 2002 identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Mercury, elemental
CASRN — 7439-97-6
Last Revised — 05/01/1995

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — D; not classifiable as to human carcinogenicity

Basis — Based on inadequate human and animal data. Epidemiologic studies failed to show a correlation between exposure to elemental mercury vapor and carcinogenicity; the findings in these studies were confounded by possible or known concurrent exposures to other chemicals, including human carcinogens, as well as lifestyle factors (e.g., smoking). Findings from genotoxicity tests are severely limited and provide equivocal evidence that mercury adversely affects the number or structure of chromosomes in human somatic cells.

II.A.2. Human Carcinogenicity Data

Inadequate. A number of epidemiological studies were conducted that examined mortality among elemental mercury vapor-exposed workers. Conflicting data regarding a correlation between mercury exposure and an increased incidence of cancer mortalities have been obtained. All of the studies have limitations that complicate interpretation of their results for associations between mercury exposure and induction of cancer; increased cancer rates were attributable to other concurrent exposures or lifestyle factors.

A retrospective cohort study examined mortality among 5663 white males who worked between 1953 and 1963 at a plant in Oak Ridge, Tennessee, where elemental mercury was used for lithium isotope separation (Cragle et al., 1984). The workers were divided into three cohorts: exposed workers who had been monitored on a quarterly basis for mercury levels in urine (n=2,133); workers exposed in the mercury process section for whom urinalysis monitoring data were not collected (n=270); and unexposed workers from other sections of the nuclear weapons production facility (n=3260). The study subjects worked at least 4 months during 1953-1958 (a period when mercury exposures were likely to be high); mortality data from death certificates were followed through the end of 1978. The mean age of the men at first employment at the facility was 33 years, and the average length of their employment was >16 years with a mean of 3.73 years of estimated mercury exposure. Air mercury levels were monitored beginning in 1955; during 1955 through the third quarter of 1956, air mercury levels were reportedly above 100 ug/cu.m in 30-80% of the samples. Thereafter, air mercury levels decreased to concentrations below 100 ug/cu.m. The mortality experience (i.e., the SMR) of each group was compared with the age-adjusted mortality experience of the U.S. white male population. Among exposed and monitored workers, no significant increases in mortality from cancer at any site were reported, even after the level or length of exposure was considered. A significantly lower mortality from all causes was observed. An excessive number of deaths was reportedly due to lung cancer in the exposed and monitored workers (42 observed, 31.36 expected), but also in the unexposed workers (71 observed, 52.93 expected). The SMR for each group was 1.34; the elevated incidence of lung cancer deaths was, therefore, attributed to some other factor at the plant and/or to lifestyle factors (e.g., smoking) common to both the exposed and unexposed

groups. Study limitations include small cohort sizes for cancer mortality, which limited the statistical stability of many comparisons.

Barregard et al. (1990) studied mortality and cancer morbidity between 1958 and 1984 in 1190 workers from eight Swedish chloralkali plants that used the mercury cell process in the production of chlorine. The men included in the study had been monitored for urinary or blood mercury for more than one year between 1946 and 1984. Vital status and cause of death were ascertained from the National Population Register and the National Bureau of Statistics. The cancer incidence of the cohort was obtained from the Swedish Cancer Register. The observed total mortality and cancer incidences were compared with those of the general Swedish male population. Comparisons were not made between exposed and unexposed workers. Mean urinary mercury levels indicated a decrease in exposure between the 1950s and 1970s; the mean urinary mercury level was 200 ug/L during the 1950s, 150 ug/L during the 1960s and 50 ug/L in the 1970s. Mortality from all causes was not significantly increased in exposed workers. A significant increase in deaths from lung tumors was observed in exposed workers 10 years or more after first exposure (rate ratio, 2.0; 95% CI, 1.0-3.8). Nine of the 10 observed cases of lung cancer occurred among workers (457 of the 1190) possibly exposed to asbestos as well as to mercury. No dose response was observed with respect to mercury exposure and lung tumors. This study is limited because no quantitation was provided on smoking status, and results were confounded by exposure to asbestos.

Ahlbom et al. (1986) examined the cancer mortality during 1961-1979 of cohorts of Swedish dentists and dental nurses aged 20-64 and employed in 1960 (3454 male dentists, 1125 female dentists, 4662 female dental nurses). Observed incidences were compared with those expected based on cancer incidence during 1961-1979 among all Swedes employed during 1960 and the proportion of all Swedes employed as dentists and dental nurses. Data were stratified by sex, age (5-year age groups) and county. The incidence of glioblastomas among the dentists and dental nurses combined was significantly increased compared to survival rates (SMR, 2.1; 95% CI, 1.3-3.4); the individual groups had apparently elevated SMRs (2.0-2.5), but the 95% confidence intervals of these groups included unity. By contrast, physicians and nurses had SMRs of only 1.3 and 1.2, respectively. Exposure to mercury could not be established as the causative factor because exposure to other chemicals and X-rays was not ruled out.

Amandus and Costello (1991) examined the association between silicosis and lung cancer mortality between 1959 and 1975 in 9912 white male metal miners employed in the United States between 1959 and 1961. Mercury exposures were not monitored. Exposures to specific metals among the silicotic and nonsilicotic groups were analyzed separately. Lung cancer mortality in both silicotic and nonsilicotic groups was compared with rates in white males in the U.S. population. Both silicotic (n=11) and nonsilicotic mercury miners (n=263) had significantly increased lung cancer mortality (SMR, 14.03; 95% CI, 2.89-40.99 for silicotics. SMR, 2.66; 95%

CI, 1.15-5.24 for nonsilicotics). The analysis did not focus on mercury miners, and confounders such as smoking and radon exposure were not analyzed with respect to mercury exposure. This study is also limited by the small sample size for non-silicotic mercury miners.

A case-control study of persons admitted to a hospital in Florence, Italy, with lung cancer between 1981-1983 was performed to evaluate occupational risk factors (Buiatti et al., 1985). Cases were matched with one or two controls (persons admitted to the hospital with diagnoses other than lung cancer or suicide) with respect to sex, age, date of admission and smoking status. Women who had "ever worked" as hat makers had a significantly increased risk of lung cancer. The duration of employment as a hat maker averaged 22.2 years, and latency averaged 47.8 years. Workers in the Italian hat industry were known to be occupationally exposed to mercury; however, the design of this study did not allow evaluation of the relationship between cumulative exposure and cancer incidence. In addition, interpretation of the results of this study is limited by the small sample size (only 6/376 cases reported this occupation) and by exposure of hat makers to other pollutants including arsenic, a known lung carcinogen.

Ellingsen et al. (1992) examined the total mortality and cancer incidence among 799 workers employed for more than 1 year in two Norwegian chloralkali plants. Mortality incidence between 1953 and 1988 and cancer incidence between 1953 and 1989 were examined. Mortality and cancer incidence were compared with that of the age-adjusted general male Norwegian population. No increase in total cancer incidence was reported, but lung cancer was significantly elevated in the workers (rate ratio, 1.66; 95% CI, 1.0-2.6). No causal relationship can be drawn from the study between mercury exposure and lung cancer because no correlation existed between cumulative mercury dose, years of employment or latency time. Also, the prevalence of smoking was 10 20% higher in the exposed workers, and many workers were also exposed to asbestos.

II.A.3. Animal Carcinogenicity Data

Inadequate. Druckrey et al. (1957) administered 0.1 mL of metallic mercury to 39 male and female rats (BD III and BD IV strains) via intraperitoneal injection. Among the rats surviving longer than 22 months, 5/12 developed peritoneal sarcomas. The increase in the incidence of sarcomas was observed only in those tissues that had been in direct contact with the mercury. Although severe kidney damage was reported in all treated animals, no renal tumors or tumors at any site other than the peritoneal cavity were observed.

II.A.4. Supporting Data for Carcinogenicity

Cytogenetic monitoring studies of workers occupationally exposed to mercury by inhalation provide very limited evidence that mercury adversely affects the number or structure of

chromosomes in human somatic cells. Popescu et al. (1979) compared four men exposed to elemental mercury vapor with an unexposed group and found a statistically significant increase in the incidence of chromosome aberrations in the WBCs from whole blood. Verschaeve et al. (1976) found an increase in aneuploidy after exposure to low concentrations of vapor, but results could not be repeated in later studies (Verschaeve et al., 1979). Mabille et al. (1984) did not find increases in structural chromosomal aberrations of lymphocytes of exposed workers. Similarly, Barregard et al. (1991) found no increase in the incidence or size of micronuclei and no correlation between micronuclei and blood or urinary mercury levels of chloralkali workers. A statistically significant correlation was observed between cumulative exposure to mercury and micronuclei induction in T lymphocytes in exposed workers, suggesting a genotoxic effect.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral

None.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

None.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source document -- U.S. EPA, 1995

This IRIS Summary is included in The Mercury Study Report to Congress which was reviewed by OHEA and EPA's Mercury Work Group in November 1994. An Interagency Review by scientists from other federal agencies took place in January 1995. The report was also reviewed by a panel of non-federal external scientists in January 1995 who met in a public meeting on January 25-26. All reviewers comments have been carefully evaluated and considered in the revision and finalization of this IRIS Summary. A record of these comments is summarized in the IRIS documentation files.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 01/13/1988, 03/03/1994

Verification Date — 03/03/1994

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Mercury, elemental, conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (fax), or hotline.iris@epa.gov (Internet address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Mercury, elemental
CASRN — 7439-97-6

VI.A. Oral RfD References

None.

VI.B. Inhalation RfC References

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VII. Revision History

Substance Name — Mercury, elemental
CASRN — 7439-97-6

Date	Section	Description
09/07/1988	II.	Carcinogen summary on-line
05/01/1995	All	Name changed from mercury (inorganic)
05/01/1995	II.	Carcinogen assessment replaced
06/01/1995	I.B.	Inhalation RfC summary on-line
12/03/2002	I.B.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Mercury, elemental
CASRN — 7439-97-6
Last Revised — 05/01/1995

- 7439-97-6
- hydragyrum
- Mercury
- Mercury, elemental
- Mercury, inorganic
- Mercury, metallic
- Mercury (organo) alkyl compounds
- Caswell No. 546
- COLLOIDAL MERCURY
- EPA Pesticide Chemical Code 052301

- KWIK [Dutch]
- Liquid Silver
- Mercure [French]
- Mercurio [Italian]
- Mercurio [Spanish]
- Mercury compounds
- Mercury vapor
- NCI-C60399
- Quecksilber [German]
- Quicksilver