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Effects of mercury vapor exposure on neuromotor function in Chinese miners and smelters

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Abstract
Objectives Current risk assessment of elemental mercury vapor is based on the tremor toxicity. To clarify the neuromotor effects of occupational exposure to mercury vapor, hand tremor and postural sway were measured in 27 miners and smelters (i.e., exposed workers) and 52 unexposed subjects.
Methods Urine samples were collected and total mercury and creatinine concentrations were determined. Data of the tremor and postural sway were analyzed using the fast Fourier transformation.
Results The geometric means of the urinary mercury level (UHg) were 228 (range 22.6–4,577) μg/g creatinine for the exposed workers and 2.6 (1.0–17.4) μg/g creatinine for the unexposed subjects. Total tremor intensity and frequency-specific tremor intensities at 1–6 and 10–14 Hz were significantly larger in the exposed workers than in the unexposed subjects ($P < 0.05$), but they were not significantly related to the UHg among the exposed workers ($P > 0.05$). In contrast, there were no significant differences in any postural sway parameters between the above two groups ($P > 0.05$), but the transversal sway with eyes open was positively related to the UHg among the exposed workers in using multiple regression analysis ($P < 0.05$).
Conclusions These findings suggest that postural sway, as well as hand tremor, may be affected by elemental mercury vapor exposure, but the former test seems to be less sensitive to mercury than the latter one.

Keywords Elemental mercury vapor · Neuromotor function · Tremor · Postural sway · Mining and smelting works · Risk assessment

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Introduction

The effect of occupational exposure to elemental mercury vapor on postural sway remains uncertain, although patients with Minamata disease (i.e., methylmercury poisoning) had neurological signs and symptoms such as intention tremor and unsteady gait, together with paresthesia, constriction of visual field, and impairment of hearing and speech (Kurland et al. 1959). By contrast, many researchers, except for one group (Boogaard et al. 1996), have reported that hand tremor is associated with mercury exposure (Albers et al. 1988; Echeverria et al. 1998; Fawer et al. 1983; Langolf et al. 1978; McCullough et al. 2001; Netterstrøm et al. 1996; Roels et al. 1982; Wood et al. 1973). Given the spectral analysis of hand tremor, the tremor frequencies affected by mercury vapor have been observed at 6.6–10 Hz (Biernat et al. 1999), at 8–12 Hz

(Verberk et al. 1986), and at 10–15 Hz (Chapman et al. 1990). Actually, since current risk assessment of mercury vapor is based on the tremor toxicity (Agency for Toxic Substances and Disease Registry 1999), other adverse effects on the nervous system may also be relevant. For the comprehensive understanding of elemental mercury neurotoxicity, accordingly, it is valuable to examine the postural sway, together with other neuromotor tests, in mercury-exposed workers.

The methodology of postural sway has been already established in adults and children (Araki et al. 1997, 2000; Iwata et al. 2006). Especially, many reports have been published regarding the effect of lead on postural sway and postural instability in lead workers has been suggested to be initiated at the blood lead concentration below the level of 20 μg/dl (Iwata et al. 2005a). On the contrary, since we can hardly find such reports on elemental mercury vapor, the postural sway test may be less sensitive to mercury than to lead even though miners exposed to elemental mercury vapor had high concentrations of mercury in the brain (Takahata et al. 1970). In this study, we measured both the hand tremor and postural sway, which are thought to be useful for the assessment of occupational and environmental neurotoxicants (Araki et al. 1997; Biernat et al. 1999; Iwata et al. 2005a, b, 2006; McCullough et al. 2001; Netterstrøm et al. 1996), in mercury-exposed workers (i.e., mine workers) to assess the neuromotor effects of elemental mercury vapor.

Materials and methods

There are some small-scale mercury mining sites in the southwestern region of China (Qiu et al. 2006). Smelting methods employed in such sites remain an old fashion style (He et al. 1984). At two places of the above sites among the mountains, male mercury-exposed workers were invited to participate in this study. The miners were working for digging the cinnabar, i.e., the ore containing mercury, in a mineshaft and carrying them to smelting place. The smelters were engaged in for the work to heat the cinnabar in order to release elemental mercury from the compound mercury sulfide. Also, male villagers residing at an agricultural area of the same province were invited as the referent group (i.e., unexposed subjects), who were farmers, office clerks, or construction workers, because the miners in two sites were minority and they had a similar traditional custom of living habits to the above villagers. Initially, 30 miners and smelters and 62 villagers without mercury exposure volunteered as the study population. Of them, three villagers suffered from cerebral palsy, kyphosis or severe scoliosis, and one exposed worker and two villagers had loss of fingers or forearm contracture due to either injury or malformation. Two villagers refused the postural sway test with eyes closed. In addition, neither two exposed workers nor three villagers provided urine samples enough to determine both the urinary mercury and creatinine concentrations. Since we excluded these subjects, the study subjects were comprised of 27 mercury-exposed workers and 52 unexposed subjects. Probably, both groups belonged to the socioeconomic lower class in China judging from their living conditions and education durations.

The nature of the procedures used in this study was explained to all subjects, and the study was performed with the informed consent and approval of the Ethics Committee of the National Institute for Minamata Disease (NIMD). Urine samples were collected in the morning. Total mercury in urine was determined by cold vapor atomic absorption spectrophotometry at the NIMD (Murata et al. 2006; Sakamoto et al. 2004), according to the method of Akagi et al. (2000). The method involved sample digestion with HNO_3, $HClO_4$, and H_2SO_4 followed by reduction to elemental mercury vapor by $SnCl_2$. The detection limit was 0.01 ng/g. Also, urinary creatinine level (Cre) was analyzed by Hitachi 7170A Automatic Analyzer in Guizhou Provincial People's Hospital. The urinary mercury level (UHg) was corrected by Cre excretion. Results given in μg of total mercury may be converted to nmol by multiplying with 5.

One trained examiner examined postural hand tremor and postural sway, using the Neurobehavioral Test System (CATSYS 2000, Danish Product Development Ltd, Denmark). Hand tremor was measured successively for each hand for 16.4 s, by asking the subjects to hold a light stylus, containing a biaxial micro-accelerometer, as he would hold an ordinary pen, with the elbow joint bent at a right angle and free of body contact or any obstacles (Després et al. 2000; Iwata et al. 2005b, 2006; Murata et al. 2004; Nadeau et al. 2003). The stylus was held horizontally, parallel to the abdomen at approximately 10 cm in front of the navel and the index finger was positioned about 1 cm from the tip of the stylus. During the recording, subjects looked at the tip of the stylus, breathed normally and relaxed. The frequency analysis of tremor intensity (m/s^2) in the 0.9–15 Hz band (total) for each of the dominant and non-dominant hands was conducted with the fast Fourier transformation (FFT) method, and square root of each power spectrum density (PSD) within frequency bands of 1–6, 6–10, and 10–14 Hz was calculated. The total PSD represents a sum of three frequency-specific PSDs. The center frequency of hand tremor was not used in this study because it depends on the distribution of frequency-specific PSDs.

The postural sway was quantitatively measured on a platform placed on a horizontal board (Iwata et al. 2005a, b, 2006; Murata et al. 2004). The subject was instructed to stand quietly on a platform for 66 s with eyes open and also with eyes closed. Main parameters measured both times were: sway area (mm^2; area traveled by the center of force), transversal sway (mm; mean deviation in the medio-lateral direction, Dx) and sagittal sway (mm; mean deviation in anterior–posterior direction, Dy). The spectral analysis of the Dx and Dy was conducted with the FFT method to identify the frequency-specific sway; and, square root of each PSD within frequency bands of 0–1, 1–2, and 2–4 Hz served as measures of the amount of postural sway for each frequency range.

The differences in basal statistics between the exposed workers and unexposed subjects were analyzed by the Student *t* test or Fisher exact test. Also, the analysis of covariance was used to evaluate the difference in neuromotor parameters to control for age, height, and drinking and smoking status (Araki et al. 1997; Iwata et al. 2005a). Drinking status was scored as "nondrinker" = 0 and "drinker" = 1; also, smoking status was scored as "nonsmoker" = 0 and "smoker" = 1. Logarithmic transformation of the UHg (i.e., $\log_{10}$[UHg]) was used because of skewed distributions. The significance of the relationships between the UHg and parameters of hand tremor and postural sway was tested by multiple regression analysis to control for the above possible confounders. All analyses, with two-sided *P* values, were performed by using the Statistical Package for the Biosciences (Murata and Yano 2002).

Results

Neither the mercury-exposed workers nor unexposed subjects seemed to be apparently unhealthy. As shown in Table 1, no significant difference in age, height, or drinking or smoking status was seen between the two groups. The geometric means of the Cre-adjusted and unadjusted UHg were 228 (range 22.6–4,577) μg/g Cre and 301 (26.2–3,662) μg/l in the 27 exposed workers, respectively; and, 2.59 (1.01–17.4) μg/g Cre and 2.14 (1.18–3.74) μg/l in the 52 unexposed subjects, respectively. Although body weight was significantly different between the two groups (Table 1), the body weight was not used as a confounder or covariate because it did not affect any results of the below analyses at all (data not shown, $P > 0.05$).

The tremor intensities in dominant and non-dominant hands were significantly larger in the exposed workers than in the unexposed subjects, even when controlling for age, height, and drinking and smoking status (Table 2); especially, the frequency-specific tremor intensities at 1–6 Hz for dominant hand and 10–14 Hz for both hands were larger in the former (Bonferroni multiple comparison method, $P < 0.05$). Any postural sway parameters did not significantly differ between the exposed workers and unexposed subjects (Table 2). Among the 27 exposed workers, the Cre-corrected UHg, i.e., $\log_{10}$[UHg (μg/g Cre)], was significantly, but not so strongly, related to only the transversal sway with eyes open (Dx) and the frequency-specific Dx at 0–1 Hz (Table 3; Fig. 1); also, the relations were similar in using the uncorrected UHg, i.e., $\log_{10}$[UHg (μg/l)] (data not shown). Though the number of the above exposed workers was only 27, the benchmark dose (BMD) and the 95% lower confidence limit of BMD (BMDL) of UHg were calculated to be 769 and 406 μg/g Cre for the Dx with eyes open, respectively; and, 773 and 407 μg/g Cre for the frequency-specific Dx at 0–1 Hz, respectively, in using the *k*-power model of BMD calculations, with P_0 (i.e., abnormal probability of the endpoint in unexposed subjects) = 0.05 and BMR (i.e., excess risk of the endpoint in exposed subjects) = 0.05, formulated by Budtz-Jørgensen et al. (2001).

Discussion

In the present study, the tremor intensities in both dominant and non-dominant hands were significantly

Table 1 Characteristics of 27 mercury-exposed workers and 52 unexposed subjects

	Exposed workers		Unexposed subjects		*P* value[a]
	Mean	SD (or %)	Mean	SD (or %)	
Age (years)	41	10	39	13	0.459
Height (cm)	161.9	7.5	162.2	4.7	0.835
Body weight (kg)	55.7	8.2	51.2	5.2	0.013
Education (years)	5.6	3.5	6.0	4.2	0.710
Number of drinkers	12	(44%)	31	(60%)	0.238
Number of smokers	23	(85%)	39	(75%)	0.392

[a] Student *t* test or Fisher exact test

Table 2 Differences (mean ± SD) in tremor and postural sway parameters between 27 mercury-exposed workers and 52 unexposed subjects after controlling for age, height, and drinking and smoking status: results of analysis of covariance

	Exposed workers	Unexposed subjects	*P* value	*P* value for covariates			
				Age	Height	Drinking	Smoking
Tremor intensity (m/s^2)							
Dominant hand (Hz)							
Total	0.234 ± 0.111	0.172 ± 0.077	0.006	0.466	0.744	0.170	0.327
1–6	0.090 ± 0.038	0.071 ± 0.019	0.004	0.620	0.730	0.008	0.084
6–10	0.160 ± 0.063	0.143 ± 0.063	0.258	0.961	0.595	0.268	0.172
10–14	0.112 ± 0.076	0.071 ± 0.051	0.007	0.259	0.988	0.141	0.798
Non-dominant hand (Hz)							
Total	0.209 ± 0.111	0.143 ± 0.054	0.001	0.170	0.533	0.050	0.418
1–6	0.085 ± 0.027	0.073 ± 0.019	0.027	0.377	0.420	0.055	0.019
6–10	0.123 ± 0.053	0.109 ± 0.056	0.290	0.317	0.348	0.213	0.437
10–14	0.108 ± 0.077	0.060 ± 0.029	< 0.001	0.225	0.511	0.024	0.817
Postural sway							
Eyes open							
Sway area (mm^2)	224 ± 112	204 ± 78	0.382	0.101	0.742	0.717	0.155
Transversal sway (Dx, mm)	2.83 ± 0.69	2.89 ± 0.87	0.783	0.299	0.436	0.282	0.563
Dx at 0–1 Hz (mm)	3.52 ± 0.88	3.56 ± 1.03	0.890	0.314	0.498	0.252	0.598
Dx at 1–2 Hz (mm)	0.47 ± 0.20	0.46 ± 0.15	0.802	0.302	0.084	0.035	0.384
Dx at 2–4 Hz (mm)	0.17 ± 0.07	0.18 ± 0.06	0.448	0.072	0.453	0.078	0.644
Sagittal sway (Dy, mm)	3.11 ± 0.92	3.53 ± 1.20	0.136	0.622	0.137	0.191	0.318
Dy at 0–1 Hz (mm)	3.92 ± 1.14	4.32 ± 1.41	0.220	0.526	0.150	0.125	0.240
Dy at 1–2 Hz (mm)	0.49 ± 0.17	0.45 ± 0.12	0.246	0.243	0.733	0.554	0.413
Dy at 2–4 Hz (mm)	0.22 ± 0.06	0.23 ± 0.07	0.656	0.544	0.434	0.091	0.706
Eyes closed							
Sway area (mm^2)	346 ± 180	318 ± 182	0.529	0.167	0.697	0.289	0.511
Transversal sway (Dx, mm)	3.40 ± 1.08	3.12 ± 0.96	0.268	0.781	0.833	0.543	0.338
Dx at 0–1 Hz (mm)	4.22 ± 1.32	3.83 ± 1.17	0.204	0.799	0.912	0.536	0.328
Dx at 1–2 Hz (mm)	0.71 ± 0.25	0.75 ± 0.33	0.581	0.064	0.066	0.574	0.768
Dx at 2–4 Hz (mm)	0.26 ± 0.08	0.27 ± 0.11	0.734	0.007	0.363	0.322	0.304
Sagittal sway (Dy, mm)	3.43 ± 0.78	3.58 ± 1.32	0.607	0.103	0.966	0.371	0.514
Dy at 0–1 Hz (mm)	4.26 ± 1.04	4.38 ± 1.59	0.729	0.123	0.891	0.366	0.567
Dy at 1–2 Hz (mm)	0.76 ± 0.26	0.72 ± 0.31	0.613	0.058	0.907	0.630	0.377
Dy at 2–4 Hz (mm)	0.33 ± 0.11	0.35 ± 0.16	0.555	0.004	0.353	0.151	0.847

larger in the mercury-exposed workers with the mean UHg of 228 μg/g Cre than in the unexposed subjects with the mean UHg of 2.59 μg/g Cre. Such increased tremor has been confirmed by many previous reports (Albers et al. 1988; Biernat et al. 1999; Chapman et al. 1990; Fawer et al. 1983; Frumkin et al. 2001; McCullough et al. 2001; Netterstrøm et al. 1996; Roels et al. 1982); in an exceptional case, Boogaard et al. (1996) failed to find any significant difference in intentional tremor between mercury-exposed workers with the median UHg of 17 (range 3.5–71.9) μg/g Cre and the control subjects with the median UHg of 2 μg/g Cre. Additionally, tremor in patients with Minamata disease has been reported to be different from physiological tremor and other pathological tremors from the viewpoint of frequency and amplitude (Yamanaga 1983), while the toxico-kinetics and -dynamics differ between elemental mercury and methylmercury. Since the mean UHg in the above-cited reports ranged from 20 to 200 μg/g Cre, the Chinese workers exposed to elemental mercury vapor may have had the highest exposure levels. In any way, elemental mercury vapor appears to cause increased tremor in workers exposed occupationally.

In terms of the tremor frequency, the tremor intensities at 1–6 and 10–14 Hz were significantly larger in the mercury-exposed workers than in the unexposed subjects (Table 2). The increased tremor at a high frequency (i.e., 10–14 Hz) is almost accordant with the findings provided by Chapman et al. (1990) and Verberk et al. (1986). Likewise, younger patients with essential tremor exhibit tremor frequencies in the range of 8–12 Hz (Elble 2005). By contrast, no researchers have observed a change in the low tremor frequency among mercury-exposed workers. Accordingly, this report may be the first to show the effect of elemental mercury on the tremor intensity in the low frequency for dominant hand. The classic resting tremor of Parkinson disease is a rhythmic 4–6 Hz pill rolling finger movement superimposed upon rhythmic

Table 3 Relations of urinary mercury (UHg, μg/g Cre), age, height, and drinking and smoking status to tremor and postural sway parameters in 27 mercury-exposed workers: results of multiple regression analysis

	Standardized regression coefficients					R^2
	log[UHg]	Age	Height	Drinking	Smoking	
Tremor intensity						
Dominant hand						
Total (Hz)	−0.348	−0.221	−0.207	−0.148	0.249	0.287
1–6	−0.147	−0.175	−0.173	−0.227	0.263	0.202
6–10	−0.244	−0.133	−0.280	−0.209	0.415	0.363
10–14	−0.379	−0.245	−0.119	−0.121	0.142	0.261
Non-dominant hand						
Total (Hz)	−0.183	−0.314	−0.242	−0.218	0.259	0.260
1–6	−0.066	−0.461	−0.111	−0.183	0.399	0.366
6–10	0.004	−0.214	−0.338	−0.187	0.465	0.299
10–14	−0.232	−0.250	−0.207	−0.259	0.158	0.238
Postural sway						
Eyes open						
Sway area	0.173	0.031	−0.074	−0.034	−0.164	0.089
Transversal sway (Dx)	0.502*	−0.120	0.062	−0.095	0.075	0.237
Dx at 0–1 Hz	0.496*	−0.117	0.008	−0.117	0.086	0.238
Dx at 1–2 Hz	−0.074	0.032	0.129	−0.004	−0.096	0.023
Dx at 2–4 Hz	−0.031	−0.021	−0.020	−0.062	−0.143	0.021
Sagittal sway (Dy)	−0.070	0.163	0.264	0.285	−0.064	0.160
Dy at 0–1 Hz	−0.071	0.150	0.221	0.299	−0.104	0.155
Dy at 1–2 Hz	−0.242	0.150	0.051	0.121	−0.244	0.108
Dy at 2–4 Hz	−0.140	0.118	−0.200	−0.141	−0.038	0.083
Eyes closed						
Sway area	0.196	−0.109	−0.001	−0.008	0.016	0.045
Transversal sway (Dx)	0.356	−0.099	−0.037	0.000	0.148	0.116
Dx at 0–1 Hz	0.346	−0.075	−0.040	0.015	0.130	0.110
Dx at 1–2 Hz	−0.092	0.097	0.190	−0.064	−0.096	0.044
Dx at 2–4 Hz	−0.076	0.095	−0.074	0.051	0.010	0.025
Sagittal sway (Dy)	−0.013	−0.100	0.103	−0.015	−0.100	0.036
Dy at 0–1 Hz	−0.019	−0.141	0.111	−0.008	−0.101	0.053
Dy at 1–2 Hz	−0.047	0.101	−0.129	−0.136	−0.017	0.045
Dy at 2–4 Hz	0.064	0.131	−0.380	−0.262	−0.146	0.274

R^2 Contribution ratio
$*P < 0.05$

extension and flexion movement of the wrist and pronation/supination movement of the forearm (Lang and Zadikoff 2005), but the site or sites of the primary tremor generator remain unclear although the cerebellum, thalamus, pallidum, subthalamic nucleus, etc. have been implicated as the possible central oscillator. Cerebellar tremor is a proximal 3–5 Hz tremor in one or both extremities ipsilateral to a lesion of the deep cerebellar nuclei or the outflow tracts of these nuclei in the superior cerebellar peduncle (Seeberger and Hauser 2005). Also, inhaled mercury vapor results in accumulation of mercury, with highest concentrations in the cerebellum and brainstem nuclei of rats and mice (Cassano et al. 1969). On the basis of these clues, further study is required to elucidate the pathophysiology of tremor at 1–6 Hz due to mercury exposure.

Another finding of this study was that some postural sway parameters with eyes open were weakly associated with the UHg in the exposed workers, whereas the significant association may disappear if a multiple significance test with the Bonferroni inequality and the Fisher *z* transformation be done (Morrison 1976) and we failed to find any significant differences between the exposed workers and unexposed subjects. The absence of significant differences may have been due to the fact that their jobs among the mountains called for a great deal of postural stability, because transversal sway with eyes open (mean ± SD) in Japanese 60 control subjects free from lead exposure was 2.88 ± 0.76 mm (Iwata et al. 2005a) and it was similar to the value in the Chinese unexposed subjects (Table 2). On the other hand, chloralkali plant workers with the mean UHg of approximately 72 μg/l performed worse than unexposed subjects on tremor but not on postural sway (Frumkin et al. 2001). On the basis of clinical cases, three lesions involved in postural instability have been speculated as follows (Araki et al. 2000; Mauritz et al. 1979): (1) a sway of non-specific frequency with eyes open (low Romberg quotient, i.e., the ratio of sway with eyes closed to that with eyes open is low) is increased in the lesion of the vestibulocerebellum, (2) a sway of high frequency (2–4 Hz) in the anterior–posterior direction

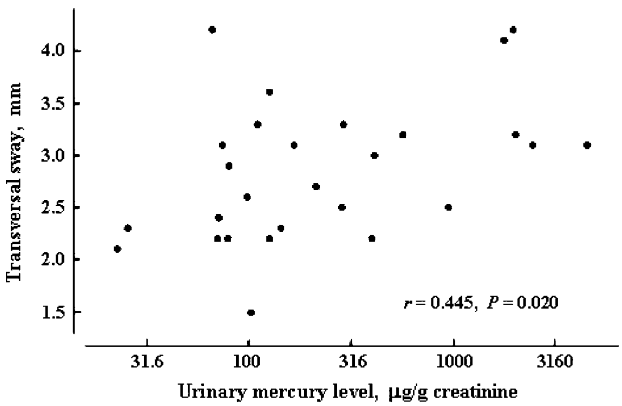

Fig. 1 Pearson product–moment correlation (*r*) between log-transformed urinary mercury level (μg/g Cre) and transversal sway (mm) of postural sway test with eyes open in 27 mercury-exposed workers

with eyes closed (high Romberg quotient) mainly rises in the lesion of the anterior cerebellar lobe, and (3) an omnidirectional sway of low frequency (1 Hz or less) with eyes closed (high Romberg quotient) becomes greater in the lesion of the spinocerebellar afferent pathway. Taken together, high-level exposure to elemental mercury vapor may result in postural instability and the subclinical lesion of the vestibulocerebellum due to mercury may also be possible if the above lesions hypothesis were correct.

In this study, the mercury-exposed workers did not put on respiratory protection in working at the workplaces and any information about working duration could not be obtained because of illegal employment. For this reason, the exposure levels were estimated only from their urine samples at the time of the examination. Also, since the exposed workers were engaged in mining and/or smelting work at the small-scale mercury mining sites, it was difficult to discriminate miners and smelters from them exactly. On the other hand, we considered age, height, and drinking and smoking status as confounders/covariates in the data analysis because these factors, not including body weight, are regarded as main confounders (Araki et al. 1997; Iwata et al. 2005a, b, 2006); whereas, body weight was excluded from Tables 2 and 3 inasmuch as it did not affect our outcomes as mentioned in the Results. Thus, it is suggested that our findings were not heavily influenced by measurement, selection or confounding bias.

In conclusion, we suggest that high-level exposure to elemental mercury vapor may affect a part of postural sway parameters. Also, the BMDL of UHg for them was speculated to be more than 400 μg/g Cre; whereas, the BMDL is estimated to be smaller if the sample number is smaller (Budtz-Jørgensen et al. 2001; Crump 2002; Dakeishi et al. 2006). By contrast, the minimal risk level of elemental mercury affecting hand tremor seemed to be around 20 μg/g Cre (Agency for Toxic Substances and Disease Registry 1999). In this sense, the postural sway test may not be a sensitive method for the neurotoxic assessment of elemental mercury or methylmercury (Grandjean et al. 1997; Murata et al. 2004), different from lead (Iwata et al. 2005a). The implication of these observations is that the effects of elemental mercury vapor differ considerably among neuromotor functions such as hand tremor, postural sway, reaction time, and hand coordination (Frumkin et al. 2001). Further study with a large number of subjects is necessary to identify the pathophysiological lesions due to elemental mercury vapor exposure, as well as the primary center or site involved in each neuromotor function.

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