Field Study

Electrophysiological Studies of Shoemakers Exposed to Sub-TLV Levels of n-hexane

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Abstract: Electrophysiological Studies of Shoemakers Exposed to Sub-TLV Levels of n-hexane: Masoud NEGHAB, et al. Department of Occupational Health, School of Health and Nutrition and Research Center for Health Sciences, Shiraz University of Medical Sciences, Iran—Background and Objectives: Exposure to n-hexane, a neurotoxic solvent, has been associated with sensorimotor polyneuropathy, both in occupationally exposed workers and in glue-sniffing addicts. The present study was carried out to ascertain whether exposure to sub-TLV levels of n-hexane was associated with electrophysiological abnormalities and to determine if these possible abnormalities have any correlations with parameters such as the biological exposure index (BEI) of this neurotoxic chemical, workers’ TWA exposure to n-hexane and/or duration of employment. Materials and Methods: Twenty-seven asymptomatic male workers from 6 shoemaking workshops were studied and compared with a group of 20 age- and sex-matched normal controls with no history of exposure to any neurotoxic agent. They underwent physical examinations as well as conventional needle electromyographic examinations and sensory and motor nerve conduction studies of upper and lower extremities. The TWA exposure to n-hexane and urinary concentration of free 2,5-hexanedione were also determined. Data were analyzed using version 16.0 of the SPSS/PC statistical package. Results: The TWA exposure to n-hexane was estimated to be 83.2 mg/m³. Electrophysiological studies showed that the amplitudes of sensory nerve action potential (SAP) for median and sural nerves were significantly lower in exposed subjects than in unexposed normal controls. Additionally, a significant correlation was found between these decreases and the urinary concentration of free 2,5-hexanedione. Conclusion: The significant decrements in SAP amplitudes for the median and sural nerves may be considered as appropriate indicators for early detection of n-hexane-induced peripheral neuropathy in asymptomatic workers with current exposure to sub-TLV levels of n-hexane. (J Occup Health 2012; 54: 376–382)

Key words: Asymptomatic shoemakers, Electrophysiological studies, n-hexane, Peripheral neuropathy, 2,5-hexanedione

n-Hexane (HEX) is a solvent that has many applications in the chemical and food industries, either in pure form or as a component of the commercial hexane mixture. HEX is a neurotoxic solvent and can cause sensorimotor polyneuropathy, mainly affecting distal sensory and motor nerves, both in industrial settings1-6 and in glue-sniffing addicts7-10. In occupationally exposed workers following a sufficient level of exposure to HEX, subjects gradually experience weakness and/or numbness and paresthesia in their distal extremities2, 4, 6. The severity of the neuropathy and the related clinical signs and symptoms are proportional to the intensity, duration and frequency of exposure9, 11, 12. Following continued exposure or recurrent episodic exposures to higher concentrations, motor signs and symptoms can also appear4, 13. In workers with mild neuropathy, sensory disturbances may be the only clinical findings, and sensory and motor nerve conduction velocities (SCV and MCV) may be either normal or mildly reduced as compared with normal subjects. Furthermore, conventional needle electromyographic examinations may show some abnormalities such as minimal signs of denervation2, 14. In asymptomatic workers exposed to HEX, a subclinical neuropathy can be detected by
certain abnormalities in nerve conduction studies (NCS) such as diminished amplitudes of sensory nerve action potentials (SAP) in the sural, median and ulnar nerves compared with age-matched normal controls\(^1\)\(^2\). In patients with clearly established neuropathy, all the above changes became much more pronounced, and marked decreases in MCV and SCV and obvious prolongation of distal and F-wave latencies (DL) also occur\(^2\)\(^3\)\(^4\)\(^5\), suggesting that the primary neurotoxic effect of 2,5-hexanediol (2,5-HD) is axonal with secondary demyelination\(^2\)\(^6\). The neurotoxic effects of HEX are related to 2,5-HD\(^7\)\(^8\)\(^9\), an active \(\gamma\)-diketone that is the only neurotoxic metabolite of HEX. Recent studies have shown that axon atrophy is the morphological hallmark of \(\gamma\)-diketone neuropathy\(^1\)\(^0\)\(^1\)\(^1\)\(^2\)\(^3\)\(^4\)\(^5\) and that regardless of exposure rate (100–400 mg/kg/day), it is an early consequence of 2,5-HD neurotoxicity and a necessary event in the pathophysiological process that leads to \(\gamma\)-diketone neurological toxicity\(^1\)!\(^6\).

Use of the urinary concentration of free 2,5-HD has been proposed for biological monitoring of workers exposed to HEX\(^8\)\(^9\)\(^10\)\(^11\)\(^12\)\(^13\)\(^14\), and the American Conference of Governmental Industrial Hygienists (ACGIH) proposed a value of 0.4 mg/l as the reference value for it\(^15\).

In industrial settings, peripheral neuropathy has been reported\(^1\)\(^6\)\(^1\)\(^7\)\(^1\)\(^8\)\(^1\)\(^9\)\(^2\)\(^0\)\(^2\)\(^1\)\(^2\)\(^2\)\(^3\)\(^4\)\(^5\), following exposure to a wide range of HEX concentrations, ranging from 106 to 8,800 mg/m\(^3\). However, limitations such as the lack of accurate exposure estimates, failure to report air concentrations of HEX and therefore failure to report time-weighted average (TWA) exposure of workers and absence of control populations do not allow a valid conclusion to be drawn from many of the earlier studies. Likewise, some studies did not specify whether the hexane was a commercial formulation or HEX. Moreover, in most studies, the air concentrations of HEX and urinary concentration of 2,5-HD either were not measured or measured after development of peripheral neuropathy in workers, usually several days after cessation of exposure to HEX.

Given the above, this study was undertaken with the following objectives:

1-To find out whether exposure to sub-TLV levels of HEX is associated with any electrophysiological abnormalities detectable in asymptomatic workers by electrophysiological tests.

2-To determine if any correlations exist between these possible abnormalities and parameters such as the urinary concentration of free 2,5-HD, workers’ TWA exposure to HEX, and length of exposure.

**Materials and Methods**

**Subjects and study design**

This cross-sectional study was carried out at local traditional shoemaking workshops in Kermanshah city in western Iran. Thirty-eight asymptomatic male workers occupationally exposed to glues containing HEX in 6 shoemaking workshops as well as 20 age- and sex-matched normal controls were studied.

Shoemakers continued to be engaged in the same tasks and did not change their tasks periodically. Additionally, they worked very closely together in small groups of 4 to 8 in the confined spaces of small traditional workshops (maximum area of 20 m\(^2\)). Therefore, they could be considered to be similar as far as their exposure to HEX was concerned.

All cases underwent the same investigation procedures including electrophysiological studies, medical history, detailed physical and neurological examinations and biochemical tests such as complete blood count (CBC), erythrocyte sedimentation rate (ESR), blood urea nitrogen (BUN), routine kidney, liver, and thyroid function tests (KFT, LFT and TFT) and urinalysis. Each employee responded to a brief questionnaire providing information with regard to demographic variables, smoking habits, history of exposure to neurotoxic chemicals in second jobs, if any, or leisure time activities, their detailed occupational history and specific questions concerning all jobs held before employment at the workshop under study, particularly those associated with the risk of neurotoxicity. Workers using potentially neurotoxic medications, those with a history of cranioencephalic traumatism and/or serious traumatism to the limbs, hereditary or acquired neuromuscular diseases, metabolic disorders, alcoholism or history of exposure to neurotoxic compounds other than HEX, those with confirmed or suspected liver, kidney or thyroid disease and those with abnormal CBC, ESR, BUN, KFT, LFT or TFT results were excluded from the study.

The concentration of HEX in air samples collected in the breathing zones of the workers was measured, and the workers’ TWA exposure was determined. For biological monitoring, urine samples were collected from the shoemakers at end of their shifts at the end of the workweek (Thursday). All participants and workers signed an informed consent form before commencement of the study. The protocol of the study was approved by the university ethics committee, and the study was conducted in accordance with the Helsinki Declaration\(^2\)\(^7\) of 1964 as revised in 2000.

**Electrophysiological studies**

Electrophysiological studies including sensory and motor nerve conduction studies of the right and left extremities (median and ulnar nerves in the upper limbs, posterior tibial and peroneal nerves in the lower limbs and the sural nerve) and a needle electromyography (EMG) on distal muscles were performed.
by the physiatrist author. Using a Medelec Synergy Electromyogram with surface recording and stimulating electrodes, the segmental nerve conduction velocities (NCVs) were assessed according to the method of Oh[20]. The distance between the stimulus site and recording site was constant for all examined subjects. The skin temperature was measured on the dorsal surface and maintained above 31°C. All examinations were performed by the same person to minimize interobserver variability. The results were compared with 20 age- and sex-matched normal controls, selected from our laboratory staff, without a past history or current exposure to any solvent or other neurotoxic agents. The maximum difference for matching age was 1 year.

**Exposure assessment**

1) **Air monitoring**

A total of 12 subjects were selected (2 workers from each workshop) for air sampling in order to determine the TWA exposure to HEX. For this purpose, 84 air samples were collected (7 air samples for each worker) and analyzed by the method recommended by the NIOSH[20]. Briefly, partial-period consecutive air samples (75% of work shift) were collected from the breathing zones of workers at a flow rate of 0.2 l/min utilizing calibrated battery-powered constant flow pumps and charcoal tubes (SKC 226-01) under normal operating conditions. After air sampling, with 1 ml of carbon disulfide, adsorbed HEX vapors were desorbed, and then 1 µl of the sample was injected into a Varian CP-3800 gas chromatograph equipped with a flame ionization detector (GC–FID). The procedures by which individual exposure to HEX was evaluated have been discussed in detail elsewhere[20], and the reader is referred to the other paper for a full description.

2) **Biological monitoring**

The urinary concentration of free 2,5-HD (without acid hydrolysis) was determined by the methodology published by Perbellini et al.[31] as modified by Dos Santos et al.[21], because its concentration is directly related to the neurotoxic potential of HEX. Urine samples were collected from the shoemakers at the end of their shifts at the end of the workweek (Thursday) and stored at −4°C until analysis. Urine samples with a specific gravity below 1.01 gr/cm³ or higher than 1.03 gr/cm³ were discarded. To determine the concentration of free 2,5-HD, 1 g of NaCl, 60 µl of cyclohexanone (as internal standard) and 2 ml of dichloromethane were added to 5 ml of a urine sample and shaken for 90 seconds, and the mixture was then centrifuged (~2,300 g) for 15 minutes. Finally, 1 µl of the extracted sample was injected into a Varian CP-3800 gas chromatograph equipped with a flame ionization detector (GC–FID). The protocol followed to determine urinary concentrations of free 2,5-HD has been described in detail in another paper of the authors, in which the results of biological monitoring of traditional shoemakers were published[20], and the reader is referred to the other paper for a full description.

**Statistical analysis procedures**

Data were analyzed using SPSS, version 16.0 on a personal computer. Neurological data of exposed workers and normal controls were compared by the Mann-Whitney non-parametric U-test. Relationships between the electrophysiological abnormalities and parameters such as the urinary concentration of free 2,5-HD, workers’ TWA exposure to HEX and duration of employment were assessed by Spearman’s non-parametric test. A p value less than 0.05 was considered statistically significant.

**Results**

Of the 38 workers exposed to HEX in 6 shoe-making workshops, 11 workers did not meet the requirements for electrophysiological studies and were excluded from the study. The number of workers in each workshop ranged from 4 to 8. Some of them wore gloves during work, but most of them did not. The average age (yr) and length of exposure (yr) for workers exposed to HEX were 25.9 ± 6 years (17–44 years) and 4.2 ± 2.9 years (0.5–12 years), respectively. The exposed subjects were working 6 days a week in 9.2 hours daily shifts. Only seven percent of shoemakers were smokers.

Qualitative analysis of the air samples by a private analytical company, on a fee for service basis, using an Agilent 7890A/5975C GC-MS instrument revealed that HEX, cyclohexane, pentane, toluene and ethyl acetate were present in the workshops’ atmospheres. The results of environmental exposure and biological monitoring of workers are displayed in Table 1. As shown, the TWA exposure to HEX and urinary concentration of free 2,5-HD in the workers were 83.2 mg/m³ and 0.23 mg/l, respectively, which are lower than the TLV-TWA and Biological Exposure Index (BEI) proposed by the ACGIH (TLV-TWA= 176 mg/m³, BEI=0.4 mg/l) for this solvent.

The results of electrophysiological studies of the right upper and lower extremities in exposed workers and normal controls are exhibited in Tables 2 and 3. As can be noted, no significant differences exist in the mean amplitude of motor nerve action potential (MAP), SCV, MCV and distal and F wave latencies (DL) between exposed workers and normal controls. Although the means of SCV for the median, ulnar
Table 1. Statistical analysis for n-hexane (HEX) present in the shoemakers’ breathing zone air samples (mg/m$^3$), urinary concentration of free 2,5-HD (mg/l) and reference values proposed by the American Conference of Governmental Industrial Hygienists (ACGIH) in 2010

<table>
<thead>
<tr>
<th>Chemicals</th>
<th>n</th>
<th>Average$^a$</th>
<th>SD</th>
<th>Median</th>
<th>GM</th>
<th>TWA$^b$</th>
<th>TLV-TWA$^c$</th>
<th>TLV-TWA$^d$</th>
<th>BEI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEX</td>
<td>84</td>
<td>115 (17−298)</td>
<td>59.8</td>
<td>99.4</td>
<td>104</td>
<td>83.2</td>
<td>176</td>
<td>141</td>
<td>NA</td>
</tr>
<tr>
<td>Free 2,5-HD</td>
<td>27</td>
<td>0.23 (0.12−0.36)</td>
<td>0.06</td>
<td>0.196</td>
<td>0.21</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.4</td>
</tr>
</tbody>
</table>

a. Average HEX concentration in workers’ breathing zone air samples. b. Average shoemakers’ 9.2-h TWA exposure measurement. c. The 8-h TLV-TWA exposure proposed by the ACGIH in 2010. d. The 9.2-h TLV-TWA calculated from Brief and Scala’s equation. HD: hexanedione, SD: standard deviation, GM: geometrical mean, TWA: time weighted average, TLV-TWA: threshold limit value-time weighted average, BEI: biological exposure index, NA: not applicable.

Table 2. Motor nerve conduction studies in the right upper and lower extremities for exposed workers and normal controls*

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Exposed workers (n=27)</th>
<th>Normal controls (n=20)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DL (ms)</td>
<td>3.6 ± 0.07</td>
<td>3.7 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>MAP (mV)</td>
<td>6.1 ± 0.4</td>
<td>6.3 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>MCV (wrist-elbow) (m/s)</td>
<td>58.6 ± 3.2</td>
<td>57.4 ± 4.4</td>
<td></td>
</tr>
<tr>
<td>Ulnar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DL (ms)</td>
<td>3.1 ± 0.1</td>
<td>3 ± 0.14</td>
<td></td>
</tr>
<tr>
<td>MAP (mV)</td>
<td>5.4 ± 0.7</td>
<td>5.2 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>MCV (wrist-elbow) (m/s)</td>
<td>56.5 ± 4.2</td>
<td>57.7 ± 3.1</td>
<td></td>
</tr>
<tr>
<td>Posterior tibial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DL (ms)</td>
<td>4.2 ± 0.2</td>
<td>4.3 ± 0.4</td>
<td></td>
</tr>
<tr>
<td>MAP (mV)</td>
<td>5.7 ± 0.6</td>
<td>5.9 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>MCV (ankle-popliteal fossa) (m/s)</td>
<td>52.2 ± 4.5</td>
<td>52.08 ± 5.2</td>
<td></td>
</tr>
<tr>
<td>F-Wave Latency (ms)</td>
<td>48.3 ± 0.6</td>
<td>48.8 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Peroneal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DL (ms)</td>
<td>4.1 ± 0.23</td>
<td>4.2 ± 0.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MAP (mV)</td>
<td>3.3 ± 0.11</td>
<td>3.6 ± 0.19</td>
<td></td>
</tr>
<tr>
<td>MCV (ankle-fibula head) (m/s)</td>
<td>53.4 ± 3.7</td>
<td>52.6 ± 2.9</td>
<td></td>
</tr>
</tbody>
</table>

* No significant difference exists between the two groups. DL: distal latency, MAP: motor nerve action potential, MCV: motor nerve conduction velocity.

Table 3. Sensory nerve conduction studies in the right upper and lower extremities for exposed workers and normal controls

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Exposed workers (n=27)</th>
<th>Normal controls (n=20)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DL (ms)</td>
<td>3.4 ± 0.6</td>
<td>3.3 ± 0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>SAP ($\mu$V)</td>
<td>37 ± 3.1*</td>
<td>39.4 ± 3.1</td>
<td>0.003</td>
</tr>
<tr>
<td>SCV (3rd finger-wrist) (m/s)</td>
<td>55.4 ± 2.4</td>
<td>57.6 ± 3.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Ulnar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DL (ms)</td>
<td>3 ± 0.2</td>
<td>3 ± 0.7</td>
<td>0.2</td>
</tr>
<tr>
<td>SAP ($\mu$V)</td>
<td>34.9 ± 3.3</td>
<td>35.9 ± 2.8</td>
<td>0.1</td>
</tr>
<tr>
<td>SCV (5th finger-wrist) (m/s)</td>
<td>52.8 ± 3.5</td>
<td>54.4 ± 3.0</td>
<td>0.056</td>
</tr>
<tr>
<td>Sural</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DL (ms)</td>
<td>3.2 ± 0.5</td>
<td>3.2 ± 0.1</td>
<td>0.4</td>
</tr>
<tr>
<td>SAP ($\mu$V)</td>
<td>25 ± 1.8*</td>
<td>27 ± 4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SCV (foreleg-lateral malleolus) (m/s)</td>
<td>49.1 ± 3.8</td>
<td>50.6 ± 1.4</td>
<td>0.5</td>
</tr>
</tbody>
</table>

* Significantly different from the corresponding value for the normal controls. DL: distal latency, SAP: sensory nerve action potential, SCV: sensory nerve conduction velocity.
and sural nerves of exposed workers were lower than those of normal controls, the differences were not significant. In contrast, the amplitudes of SAP for the median and sural nerves were significantly lower in exposed workers than in control subjects.

The decreased SAP amplitude for the median and sural nerves correlated significantly with the urinary concentration of free 2,5-HD (Table 4). This decrement did not correlate with workers’ TWA exposure and length of exposure.

**Discussion**

Although past exposure monitoring data were not available, given the facts that the subjects had only been employed in shoemaking workshops during the course of their employment and had not changed their jobs and that the situations in the small traditional workshops, in which they had been working, had not changed, it would be plausible to assume that the past and present exposure scenarios for the studied subjects during the course of their employment are, more or less, similar and that the estimated exposure levels of HEX and urinary 2,5-HD concentrations reflect both the past and present situations.

The subjects in this study worked in extended work shifts and thus both their daily working hours (9.2 hours) and weekly working days (6 days) were higher than the bases on which TLV-TWA was set by the ACGIH (8 hours per day and 5 days per week). The ACGIH recommends the application of Brief and Scala’s equation to correct the effects of differences in work and rest periods on workers’ exposure in extended work shifts. Applying this equation, the TLV-TWA exposure to HEX for a 9.2 hours shift was calculated to be 141 mg/m³. Therefore, the workers’ TWA exposure to HEX (83.2 mg/m³) in this study neither exceeded the 8-hours TLV-TWA proposed by the ACGIH (176 mg/m³) nor the 9.2-hours TLV-TWA (141 mg/m³) calculated from Brief and Scala’s equation (Table 1). As discussed earlier, results of environmental and biological monitoring of shoemakers exposed to HEX in our study have been published in detail elsewhere.

As explained in the results section, the amplitudes of SAP for the median and sural nerves were significantly lower in exposed workers than in control subjects. It is noteworthy that the exposed subjects had no family history of neuromuscular diseases. Additionally, they were free from other known risk factors related to neurological functions such as alcoholism, diabetes mellitus and/or abnormal biochemical tests. Similarly, in physical examinations, stretch reflexes were normal and no electromyographic signs of denervation were detected. Moreover, none of the workers complained of weakness, tingling and/or numbness in their extremities. Therefore, the fact that HEX was the only neurotoxic chemical present in the workshops indicates that these abnormalities in NCS are likely to be the direct consequence of occupational exposure to the neurotoxic solvent, HEX.

These findings are in agreement with the observations of Pastore et al., who found significant decreases in mean amplitudes of SAP for the sural, median and ulnar nerves in asymptomatic workers exposed to HEX with a mean urinary concentration of total 2,5-HD of 11.02 ± 4.5 mg/l and an unknown air concentration of HEX. Chang et al. also reported a reduction in the mean amplitude of SAP in the median nerve of asymptomatic healthy workers exposed to HEX as the only significant abnormality in NCS compared with age- and sex-matched normal controls.

While no statistically significant differences in SCV and MCV of the studied nerves of exposed workers were found compared with normal controls in our study, some authors have reported notable decreases in SCV and MCV and significant decreases in the amplitudes of SAP and CMAP in asymptomatic workers exposed to HEX. For instance, Mutti et al. reported statistically significant increases in MAP duration and decreased MCV in the median and ulnar nerves in a group of 95 shoe factory workers compared with unexposed workers matched for sex, age and duration of employment. The TWA for HEX of the 108 breathing zone air samples taken was 243 mg/m³ in the mildly exposed group and 474 mg/m³ in the highly exposed group, exceeding the TLV-TWA proposed by the ACGIH and the TWA exposure in our study by 2.4 and 5.7 times, respectively. Therefore, this excessive exposure and concurrent exposure of workers to methyl ethyl ketone (MEK), which is known to potentiate the neurotoxicity of 2,5-HD, may well explain the diminished MCVs in the study of Mutti et al.

In contrast, Wang et al. reported diminished MCVs among a group of workers exposed to <88 mg/m³ of HEX (approximately one-half of the TLV-TWA). The authors proposed that their finding may be related to prolonged exposure due to extended work shifts. However, the fact that in their study only single random one-hour period air samples were taken...
These investigations were partially supported by funding from the vice chancellor for research affairs, Shiraz University of Medical Sciences. We are grateful to the employers and employees of the shoemaking workshops for their helpful cooperation. The authors would like to hereby declare that the investigations undertaken and described in this article are part of the results of the thesis of the second author of this paper, Mr. Soleimani, MSc student of Occupational Health, supervised by Professor Neghab, the paper’s first author.

References


indicates that the actual workers’ exposures were not evaluated properly.

In the current study, the differences between the SCV values of the groups were not significant. However, the mean SCVs for the median, ulnar and sural nerves of the exposed workers were lower than those of the normal controls (Table 3). These findings are compatible with those of other authors12,14 and further confirm the fact that the primary neurotoxic effect of 2,5-HD is axonal, with secondary demyelination as a consequence of axonal damage7,11.

No correlation was found between the decreased amplitudes of SAP and TWA exposure to HEX. In contrast, a significant correlation between decreased amplitudes of SAP for the median and sural nerves and urinary concentration of free 2,5-HD was found (Table 4). This is similar to the observations of Governa et al.31, who found statistically significant correlations between the urinary concentration of total 2,5-HD (mean 6.8 mg/l) and certain scores utilized for evaluation of electoneurographic abnormalities. Conversely, these findings are not consistent with the observations of Pastore et al12, who did not find any correlations between abnormal results of neurological studies and the urinary concentration of total 2,5-HD (mean 11.02 ± 4.5 mg/l) in 20 asymptomatic workers exposed to HEX.

These discrepancies may well be explained by the effects of urine PH. It is known that increasing the acidity of urine during hydrolysis increases the amount of 2,5-HD by conversion of the other non-neurotoxic metabolites of HEX to 2,5-HD, specially 4,5-dihydroxy-2-hexanone89.

In line with a number of other studies1,2,6,13,26, we did not observe any correlations between the abnormal results of NCS and duration of exposure (employment). This finding, which seems unusual, may be explained, at least in part, by the differences in susceptibility of workers to HEX due to individual differences in metabolism of this chemical by cytochrome P-450.

In conclusion, the findings of this study collectively indicate that under the exposure scenarios described in this study (exposure to sub-TLV levels of HEX in extended work shifts), occupational exposure to HEX is associated with NCS abnormalities as reflected by significant decreases in the amplitudes of SAP for the median and sural nerves. Additionally, decreased SAP amplitudes for the median and sural nerves correlated significantly with the urinary concentration of free 2,5-HD but not with the workers’ TWA exposure and duration of employment. Therefore, one might tentatively conclude that these abnormalities are likely to be considered as appropriate criteria for early detection of HEX-induced peripheral neuropathy in asymptomatic workers exposed to sub-TLV levels of HEX who have not yet manifested symptoms of neuropathy. Similar conclusions have been reached by Pastore et al.12.


