

Neurophysiological changes in workers exposed to organic solvents in a shoe factory

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MUTTI A, CAVATORTA A, LUCERTINI S, ARFINI G, FALZOI M, FRANCHINI I. Neurophysiological changes in workers exposed to organic solvents in a shoe factory. *Scand j work environ health* 8 (1982): suppl 1, 136-141. Motor conduction velocity (MCV) was measured in the median, ulnar, and peroneal nerves of 52 referents and 95 workers from a shoe factory, in a search for dose-effect and dose-response relationships between exposure to organic solvents and subclinical impairment of the peripheral nervous system (PNS). According to the environmental concentrations, the exposure was expressed as the sum of the products between the median hygienic effect (ranging from 0.08 to 2.89) and worktime (from 1 to 29 a) in every job. The motor action potential (MAP) amplitudes, durations and shapes of the exposed workers were significantly affected even if to a different extent and significance level when compared to those of the MCVs of the referents. The MCVs of the median ($t = 3.17$, $p < 0.01$) and peroneal ($t = 2.11$, $p < 0.05$) nerves were reduced as compared to reference values. In the exposed group, the MCV of the median nerve was negatively correlated with exposure score ($r = 0.45$, $p < 0.01$) but not with age. No relationship was found between MCVs of the ulnar and peroneal nerves and exposure. The MCV of the median nerve was particularly slow in a subgroup of workers with an exposure score of > 20 ($t = 2.30$, $p < 0.05$ vs the other exposed workers; $t = 5.56$, $p < 0.01$ vs the referents). This exposure score represents only 50 % of the maximum allowable score for a worktime of 40 a. Even if none of the examined workers showed clinical signs of polyneuropathy, evidence of subclinical effects on the PNS were found among subjects with long-term exposure to hexacarbon mixtures. Therefore, our results suggest the need for a lowering of current threshold limit values at least for n-hexane.

Key terms: hydrocarbons, long-term exposure, neurotoxicology, polyneuropathy, threshold limit values.

Industrial hydrocarbon solvents are known to cause impairment of nervous system function. Experimental, clinical, and epidemiologic investigations have shown that C_5 - C_7 alkane mixtures selectively affect the peripheral nervous system (PNS). Two recent reviews are available on this subject. One covers the experimental and clinical aspects (21) and the other the epidemiologic approach (9).

Despite the large number of papers concerning several outbreaks of acute polyneuropathy, characterized by symmetrical,

predominantly distal motor deficit (1, 15), only few data are available on the long-term effects of exposure to hexacarbon mixtures (3, 16, 19). There is a lack of useful data on exposure-effect relationships because of insufficient exposure estimations.

Our aim was to verify whether subclinical effects are detectable in workers occupationally exposed to hydrocarbon mixtures in a shoe factory and to determine the exposure-effect relationship for PNS function, investigated by electroneurographic (ENG) methods. We have focused our attention mainly on the maximal motor nerve conduction velocity (MCV) because of its pathophysiological and prognostic meaning.

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Subjects and methods

Subjects

The exposed group consisted of 95 subjects (24 males and 71 females) from a shoe factory. Their worktime ranged from 1 to 29 a (mean 9.8, SD 8.4), exposure time from 1 to 25 a (mean 9.1, SD 8.0), and age from 16 to 62 a (mean 30.9, SD 11.7). They were apparently healthy workers, so no acute polyneuropathy was found.

One reference group was selected from the same factory; it was composed of 52 workers (12 males and 40 females) who were not exposed to organic solvents. Employment time varied from 4 months to 29 a (mean 10.2, SD 9.7) and age from 16 to 58 a (mean 29.6, SD 12.3). Worker self-selection was unlikely, even if possible. Turnover rates, in fact, were mainly caused by a seasonal increase in personnel. About 15 workers per year (from 12 to 20) were engaged in the last 10 a. Ten of them left the factory after a period of two to three months and five remained.

Exposure

This study was carried out in a shoe factory in which chemical hazards were concentrated in the fitting shop, where the components were assembled, glued, and pressed. The main source of exposure to organic solvents was evaporation from glued surfaces and open cans containing solvents. The environmental concentrations of the organic solvents were measured ac-

cording to a method described elsewhere (13). A total of 108 time-weighted average (TWA) estimations was performed, repeatedly covering all workplaces for 2 a. Table 1 summarizes the results. In many workplaces the environmental concentration of organic solvents was quite high, and over 50 % of the examined samples exceeded the current threshold limit value (TLV) of the American Conference of Governmental Industrial Hygienists (ACGIH) for the mixture. Higher hygienic effects were calculated on the basis of 1979 intended changes (4). It should be stressed that the estimations reported in table 1 were obtained during the last 2 a. Certainly, past exposure is underestimated, at least for the period before industrial hygiene improved in 1972.

Despite these limitations, an overall exposure score was calculated, according to the formula (1):

$$E = \sum c_i t_i$$

where E is the exposure score, c_i the median hygienic effect, and t_i the worktime (years) in every job.

Clinical investigation

Both the exposed and referent workers were examined by the same physician, who was a specialist in occupational medicine. The medical examination included a questionnaire concerning health and occupational history. Many laboratory tests en-

Table 1. Organic solvent concentration in the breathing zone (time-weighted average) of the exposed workers (N = 108).

Solvent	Threshold limit value ^a (mg/m ³)	Measured values (mg/m ³)		Hygienic effect ^b	
		Mean	Median	Mean	Median
Hexane	360	316	233	0.88	0.65
Cyclohexane	1,050	321	257	0.30	0.24
Methyl-ethyl ketone	590	115	87	0.19	0.15
Ethyl acetate	1,400	199	172	0.14	0.12
Total (mixture)	1.00	—	—	1.51	1.16

^a These threshold limit values have been taken from the American Conference of Governmental Industrial Hygienists (4).

^b The hygienic effect is the ratio between the measured concentration of the compound and its threshold limit value. When specific information about synergism does not exist, the sum of the ratios does not exceed 1.0, which is the threshold limit value for the mixture.

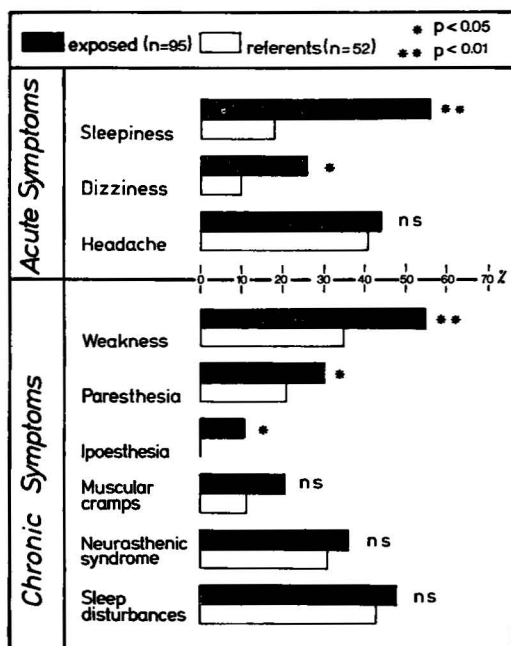


Fig 1. Differences between the frequencies of neurological symptoms in workers with long-term exposure to organic solvents and the corresponding frequencies of neurological symptoms in referents. (ns = not significant)

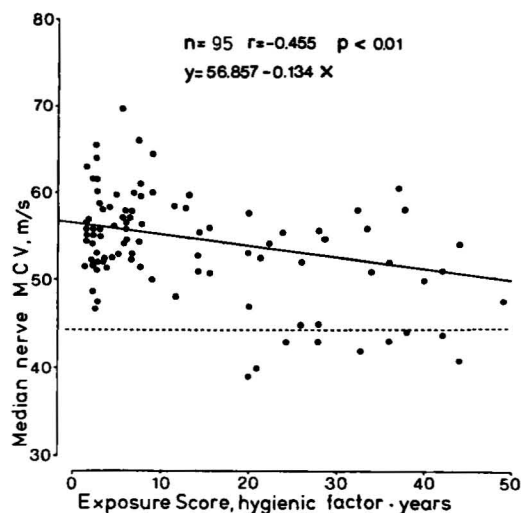


Fig 2. Regression line between overall exposure, calculated according to the formula (1): $E = \sum c_i t_i$, where E is the exposure score, c_i the hygienic effect, and t_i the worktime in each job, and the motor nerve conduction velocity (MCV) of the median nerve in the exposed group. The broken line represents the mean - 2 SD of the reference values.

abled us to exclude the presence of metabolic diseases such as chronic renal failure and diabetes.

Neurological symptoms were recorded by means of a questionnaire, which was administered by the same neurologist, who also examined all the subjects. The MCVs of the median, ulnar, and peroneal nerves were measured with skin electrodes (Disa 13 K 69) and a Disa 1500 electromyograph, according to routine methods (20). The ENG investigations were performed after the subject had been about 1 h in an air-conditioned room at 24°C. No systematic difference could be detected in the skin temperature of the exposed workers and referents.

Statistics were calculated on a CDC 6600 computer (Centro di calcolo dell'Università di Parma) with SPSS programs (14).

Results

Both acute and chronic neurological symptoms were more frequent in the exposed workers than in the reference group (fig 1). The exposed workers complained of sleepiness ($\chi^2 = 8.11$, $p < 0.01$) and dizziness ($\chi^2 = 5.34$, $p < 0.05$) while working. Chronic motor symptoms, ie, weakness in the limbs ($\chi^2 = 7.68$, $p < 0.01$), sensory disturbances, ie, hypesthesia ($\chi^2 = 4.33$, $p < 0.05$) and paresthesia ($\chi^2 = 5.11$, $p < 0.05$) also showed an increased prevalence.

A clear picture of polyneuropathy could not be established in the neurological examination, even though several minor signs were found. The mean values and standard deviations of the motor neurographic parameters are summarized in table 2. The motor action potential (MAP) amplitudes were significantly reduced in all nerves, despite the wide range of values in the reference group. The MCV was decreased in the median ($t = 3.17$, $p < 0.01$) and peroneal ($t = 2.11$, $p < 0.05$) nerves. The MAP duration was increased only for the ulnar nerve ($t = 2.52$, $p < 0.05$). No difference was found in the distal latencies. A significantly higher prevalence of abnormal shapes, ie, multi- or polyphasic, of the median ($\chi^2 = 8.36$, $p < 0.01$) and peroneal ($\chi^2 = 4.50$, $p < 0.05$) nerves was also observed in the exposed workers when com-

pared to the corresponding values of the referents.

Pearson's correlation coefficients were calculated between age and exposure score — taken as independent variables — and the motor neurographic parameters of the exposed workers. A highly significant relationship was found between the exposure score, but not age, and the MCV of the median nerve.

Fig 2 shows the linear regression for these two variables. The MCV was particularly reduced in a subgroup of workers with an exposure score of > 20 . Eight workers in this group had an MCV that was slower than the mean — 2 SD of the MCV of the referents (broken line in figure). This prevalence is statistically significant when compared to that of the referents ($\chi^2 = 9.52$, $p < 0.01$) or that of the less-exposed workers ($\chi^2 = 13.96$, $p < 0.01$).

A comparison of ENG parameters between the two exposed groups (cut-off = 20) and the referents is presented in fig 3. The median and peroneal MCVs were slower in the exposed workers than in the referents. An exposure-related decreasing trend was observed only for the MCV of the median nerve. Despite a wide standard deviation, the MAP amplitude and duration behaved similarly.

Discussion

Two main sources of bias may affect exposure-effect relationships in cross-sectional studies. Both the true exposure, because of eventual hygienic improvements, and the true effect, due to possible worker self-selection, might be underestimated. These errors are difficult to check if no historical data are available. Therefore we cannot definitely ascribe the subclinical effects found in the present study to the measured exposure level. However, a safety factor should be introduced in view of the environmental concentrations of organic solvents measured in the last 2 a, as representative of the overall exposure. These concentrations were near the current TLVs. Due to the relatively young ages and short worktimes, the exposure scores were mainly lower than 40, which represents the maximum allowable score for an exposure time of 40 a.

Even if the accumulated dose does not necessarily correspond to the accumulated effects, the overall exposure score in our study group was quite low (mean 13.8, SD 13.4). Functional changes in the PNS should have been low too. Moreover, the exposed group was mainly composed of healthy young people, and we did not have any reason to expect an increased preva-

Table 2. Electroneurographic parameters of workers exposed to hydrocarbon mixtures (N = 95) and of referents (N = 52)

Electroneurographic parameters	Exposed group		Reference group	
	Mean	SD	Mean	SD
Median nerve				
Motor conduction velocity (m/s)	54.08 **	5.89	57.15	5.09
Amplitude (mV)	7.69 **	3.99	10.83	4.84
Duration (ms)	14.60	4.75	13.61	2.47
Distal latency (ms)	3.47	0.71	3.44	0.46
Ulnar nerve				
Motor conduction velocity (m/s)	61.37	6.03	60.06	6.48
Amplitude (mV)	6.17 **	2.85	8.08	3.15
Duration (ms)	13.89 **	3.17	12.63	2.61
Distal latency (ms)	2.89	0.83	2.68	0.64
Peroneal nerve				
Motor conduction velocity (m/s)	50.60 *	4.37	52.21	4.56
Amplitude (mV)	6.04	3.81	9.05	5.50
Duration (ms)	12.83	3.08	12.26	2.65
Distal latency (ms)	4.29	1.13	4.45	0.94

* $p < 0.05$, ** $p < 0.01$ (Student's t-test).

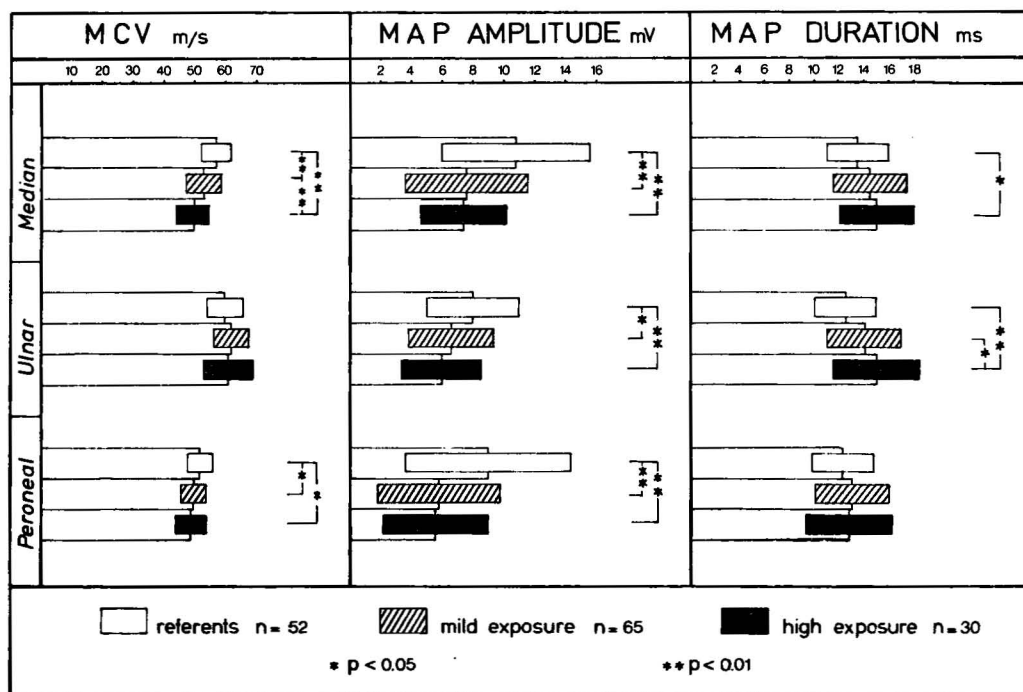


Fig 3. Means (wide columns) and standard deviations (bars) of motor nerve conduction velocities (MCVs) and of motor action potential (MAP) amplitudes and durations of the referents and two subgroups of workers with mild and high exposure. The two subgroups were distinguished according to the exposure score (cut-off = 20) calculated according to the formula (1): $E = \sum c_i t_i$, where E is the exposure score, c_i the hygienic effect, and t_i the worktime in each job.

lence of pathological findings. Nevertheless, a significant difference was found between the exposed and reference group for several subjective symptoms and ENG parameters. Some subjective symptoms were more frequent in workers exposed to hexacarbon mixtures, in agreement with the findings from workers with long-term exposure to other organic solvents, which suggested a toxic action on both the central (5, 8, 10, 12) and peripheral (5, 11) nervous system. ENG parameters were also affected, when compared to the reference values, even if to a different extent and significance level.

Our findings of a decrease in the MCVs of the median and peroneal nerves agree well with the results obtained for workers exposed to organic solvents that less selectively affect the PNS (5, 18). The decrease in MCV is consistent with both axonal neuropathy with subsequent paranodal swelling and primary demyelination. These anatomic changes have been described for rats after n-hexane and meth-

yl-n-butyl ketone intoxication (17, 22, 23, 24) and for chickens after percutaneous treatment with cyclohexane (6, 7).

The decrease in MAP amplitude in all the examined nerves was the most sensitive sign of PNS impairment, since it was also found in the group with the lowest exposure score (fig 3), a result supporting the hypothesis of predominantly axonal damage.

In our study, the ENG changes were exposure dependent, and they suggest the need for the lowering of current TLVs, at least for the main component n-hexane. As health-based safety criteria, the TLVs proposed by the ACGIH in 1979 as intended changes (4) seem to be more appropriate than the current ones.

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