Non-confidential Annex I to the CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

International Chemical Identification:

n-Hexane

EC Number: **203-777-6**

CAS Number: **110-54-3**

Index Number: **601-037-00-0**

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Numerical data demonstrating the correlation between the incidence and magnitude of adverse neurological effects and n-hexane exposure and co-exposure levels to other toxic substances

Wang et al. 1986

Table 1: Wang et al. 1986 – Relationship between frequency of polyneuropathy and the concentration of *n*-hexane in the cleaning solvent used by the Press Proofing Factories.*

Cases	Content of *n*-hexane			
	> 50%	49% – 10%	< 10% Total	Total
number with polyneuropathy	15	0	0	15
number normal	14	22	8	44
Total	29	22	8	59

*Mantel extension for the trend $X_{M\text{-}EXT} = 4.04$ ($p < 0.0001$)

Table 2: Wang et al. 1986 – Frequency of abnormal nerve conduction velocity (NCV) and the concentration of *n*-hexane in the major solvent used by the press proofing factories.*

Cases	Content of *n*-hexane			
	> 50%	49% – 10%	< 10% Total	Total
number with wjth abnormal NCV	16	1	0	17
number normal	8	21	8	37
Total	24	22	8	54

*Mantel extension for the trend $X_{M\text{-}EXT} = 4.47$ ($p < 0.0001$)

Table 3: Wang et al. 1986 – Frequency of polyneuropathy and the air concentration of *n*-hexane) at press proofing factories.*

Cases	Content of n-hexane			
	> 100 ppm	50 – 99 ppm	< 50 ppm	Total
number with polyneuropathy	6	0	2	8
number normal	0	6	34	40
Total	6	6	36	48

*Mantel extension for the trend $X_{M\text{-}EXT} = 4.49$ ($p < 0.0001$)

Table 4: Wang et al. 1986 – The right side motor nerve conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV) studies among normal controls and different categories of workers.*

	normal control	workers from factories without clinical cases in which 3 – 9% *n*-hexane was used	workers from factories without clinical cases in which 10 – 49% *n*-hexane was used	workers from factories without clinical cases in which ≥50% *n*-hexane was used	workers from factories with clinical cases in which ≥50% *n*-hexane was used
n-hexane air level	-	0-23 ppm	11-93 ppm	34-41 ppm	22-190 ppm
age	10-80[a]	26.7 ± 11.9	28.3 ± 9.9	30.7 ± 13.6	24.2 ± 7.8
median	61.2 ± 5.8	54.3 ± 2.8****	58.3 ± 3.6**	55.0 ± 2.1***	44.3 ± 8.3****
MNCV	(150)	(8)	(22)	(6)	(18)
Ulnar	59.9 ± 7.2	52.8 ± 6.5***	56.6 ± 4•9**	53.1 ± 4.2	40.4 ± 7.8****
MNCV	(150)	(8)	(22)	(6)	(18)
Median	56.1 ± 4.8	54.1 ± 5.4	56.6 ± 5.4	58.7 ± 7.6	47.6 ± 8.6****
SNCV	(74)	(8)	(22)	(6)	(15)[b]
Ulnar	52.4 ± 4.6	49.2 ± 5.5	51.3 ± 5.1	49.7 ± 2.3	43.8 ± 7.2****
SNCV	(63)	(7)	(22)	(6)	(15)[b,c]
Peroneal	53.4 ± 6.1	46.8 ± 1.1	49.4 ± 3.5****	50.3 ± 4.1	35.4 ± 7.2****
MNCV	(150)	(8)	(22)	(6)	(18)[d]
Tibial	49.1 ± 5.2	45.9 ± 4.1	48.2 ± 4.0	48.1 ± 3.8	35.8 ± 6.3****
MNCV	(150)	(8)	(22)	(6)	(18)
Sural	50.3 ± 4.7	47.1 ± 3.1	49.0 ± 3.9	48.8 ± 3.9	38.7 ± 7~5****
SNCV	(57)	(7)	(22)	(6)	(15)[b,e]

*Numbers in parentheses represent number of persons studied; the unit is in m/sec, mean ± 1 S.D.
[a]Fifty persons for each age range: 10-35, 36-50, 51-80 years old.
[b]Three workers not measured.
[c]Includes two workers who had no measurable response. In these cases, the lowest value of other workers (34.1 m/sec) was used in the calculation of the mean.
[d]Includes two workers who had no measurable response. In these cases, the lowest value of other workers (27.0 m/sec) was used in the calculation of the mean.
[e]Includes six workers who had no measurable response. In these cases, the lowest value of other workers (3 1.8 m/sec) was used in the calculation of the mean.
**p < .05 if compared with the normal controls.
***p < .01 if compared with the normal controls.
****p < .001 if compared with the normal controls.

Co-exposure levels to other potentially toxic substances**:**

All samples were analyzed by gas chromatography for *n*-hexane and benzene. Additionally, samples of bulk cleaning solvents from all 16 factories were also analyzed to determine their chemical compositions.

Table 5: Wang et al. 1986 – Frequency of polyneuropathy and the air concentration of benzene at the press proofing factories.*

	Concentration of benzene		
Cases	> 5ppm	< 5ppm	Total
No. with polyneuropathy	0	7	7
No. Normal	5	43	48
Total	5	50	55

*Chi-square = 0.81 (p > 0.1).

Governa et al. 1987

Table 6: Governa et al. 1987 – Principal characteristics of the 40 studied workers employed in 4 small shoe factories

Characteristic	Plant A	Plant B	Plant C	Plant D
Workers (number)	10	10	11	9
Age (years)				
Mean	23.1	38.5	30.7	32.2
Extreme values	16-36	17-58	16-54	17-50
Stature (cm)				
Mean	163.2	167.1	171.5	166.1
Extreme values	152-178	160-180	162-184	160-179
Weight (kg)				
Mean	58.2	63.6	67.7	62
Extreme values	48-73	52-76	56-86	49-77
Alcohol consumption (g/d)				
Mean	14.1	19.3	17.4	16.3
Extreme values	0-30	0-40	0-25	0-30
Smoking habits (cigarettes/(d)				
Mean	6	4.5	8.1	6.6
Extreme values	0-20	0-15	0-20	0-20
Duration of exposure (yr)				
Mean	7.5	17.2	11.4	12.9
Extreme values	1-19	2-28	1-27	2-25

Table 7: Governa et al. 1987 – Hexane metabolite concentrations[a] in urine samples from 40 shoemakers studied, at the end of a weekly work shift

Metabolite	Mean (mg/l)	SD (mg/l)	Median (mg/l)	Extreme values (mg/l)	Cases above limit of detection (N)
2-Hexanol	0.59	1.29		0.10-6.10	11
2,5-Hexanedione	6.8	4.62	6.6	0.50-19.00	40
γ-Valerolactone	3.31	3.36	1.77	0.33-15.50	40
2-Methyl-2-pentanol					1
3-Methyl-2-pentanol					0

[a] Concentration corrected to a specific gravity of 1.024.

Table 8: Governa et al. 1987 – Cyclohexane and trichloroethylene metabolite concentration in urine samples from 40 shoemakers studied, at the end of a weekly work shift

Metabolite	Mean (mg/l)	SD (mg/l)	Median (mg/l)	Extreme values (mg/l)	Cases above limit of detection (N)
Cyclohexanol	1.55	3.78		0.1-15.30	9
Cyclohexanone	0.23	0.68		0.1-3.80	7
Trichloroethanol	2.97	3.45	2.18	0.1-18.58	34

[a] Concentration corrected to a specific gravity of 1.024.

Table 9: Governa et al. 1987 – Scores kept for the electroneuromyographic abnormalities observed in 40 shoemakers studied

Scores	Electroneuromyographic abnormalities observed[a]
0	No electroneuromyographic abnormalities
3	One or more borderline conduction velocities and/or one or more borderline distal latencies
4	Pathological increase in more than one distal latency
5	Pathological decrease in one or more conduction velocities and pathological increase in one or more distal latencies
8	Pathological decrease in one or more conduction velocities and pathological increase in one or more distal latencies associated with motor action potential abnormalities and/or decrease in motor action potential number in a single muscle, or, one or more borderline conduction velocities and one or more borderline distal latencies associated with motor action potential abnormalities and/or decrease in motor action potential number in multiple muscles
10	Pathological decrease in conduction velocities pathological increase in distal latencies associated with motor action potential abnormalities and decrease in motor action potential number in multiple muscles.

[a] The values of conduction velocities and distal latencies are considered borderline if they are from 2 to 3 standard deviations and pathological when they are over 3 standard deviations.

Table 10: Governa et al. 1987 – Number of cases (N) and electroneuromyographic scoring (ENMG-S)

N	23	3	1	2	6	5
ENMG-S	0	3	4	5	8	10

Table 11: Governa et al. 1987 – Correlation of electroneuromyographic scoring on urinary concentrations of the *n*-hexane, cyclohexane, and trichloroethylene metabolites in 40 shoemakers studied (nonparametric analysis)

Metabolite	Kendall's τ	Significance
2-Hexanol	-0.0526	
2,5-Hexanedione	0.4179	$p < 0.01$
γ-Valerolactone	0.3667	$p < 0.01$
Cyclohexanol	-0.0461	
Cyclohexanone	-0.05	
Trichloroethanol	0.2282	

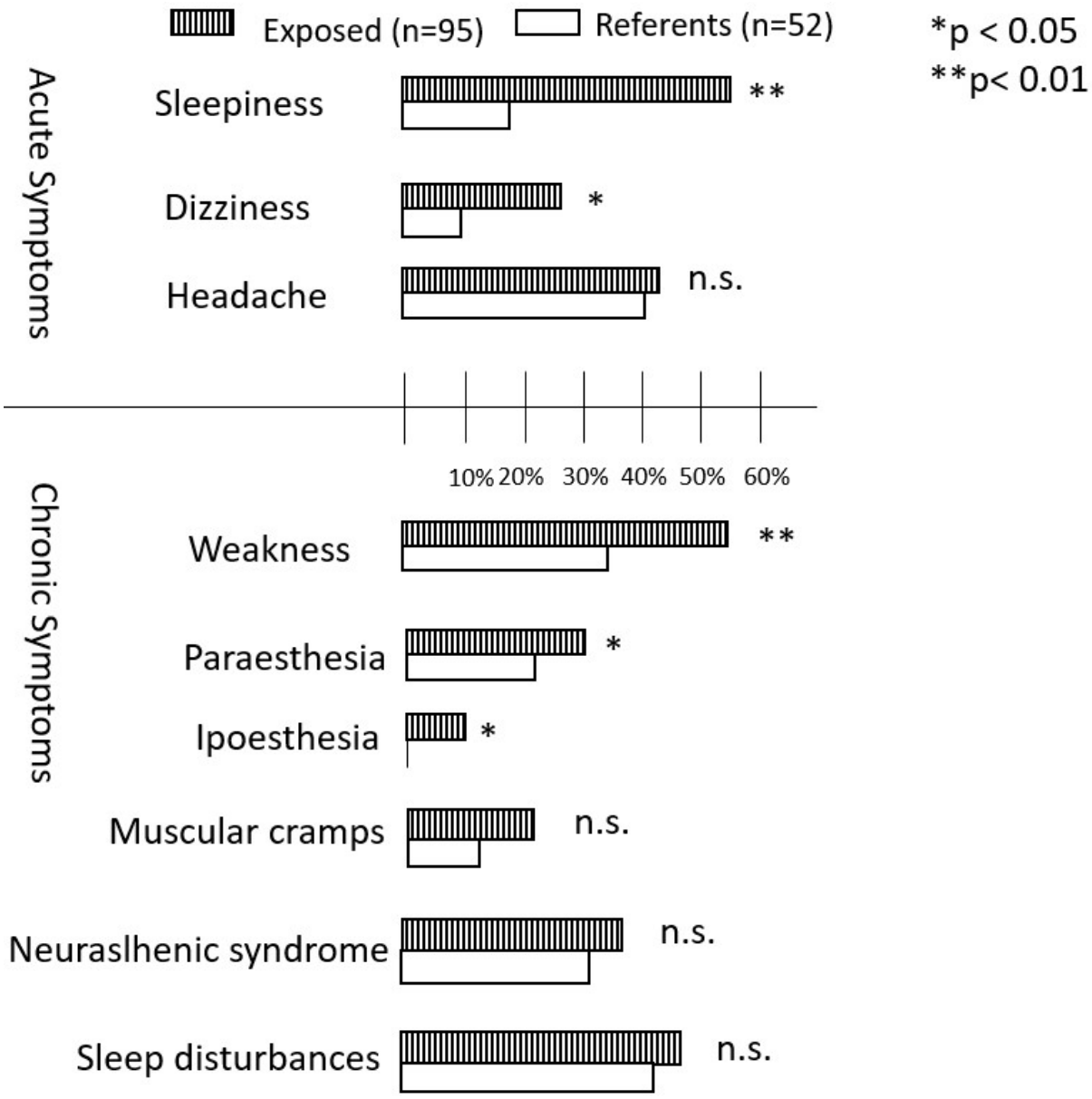
Mutti et al. 1982

Table 12: Mutti et al. 1982 – Organic solvent concentrations (mg/m^3) in the breathing zone of the examined workers (number of the weighted average samples = 108)

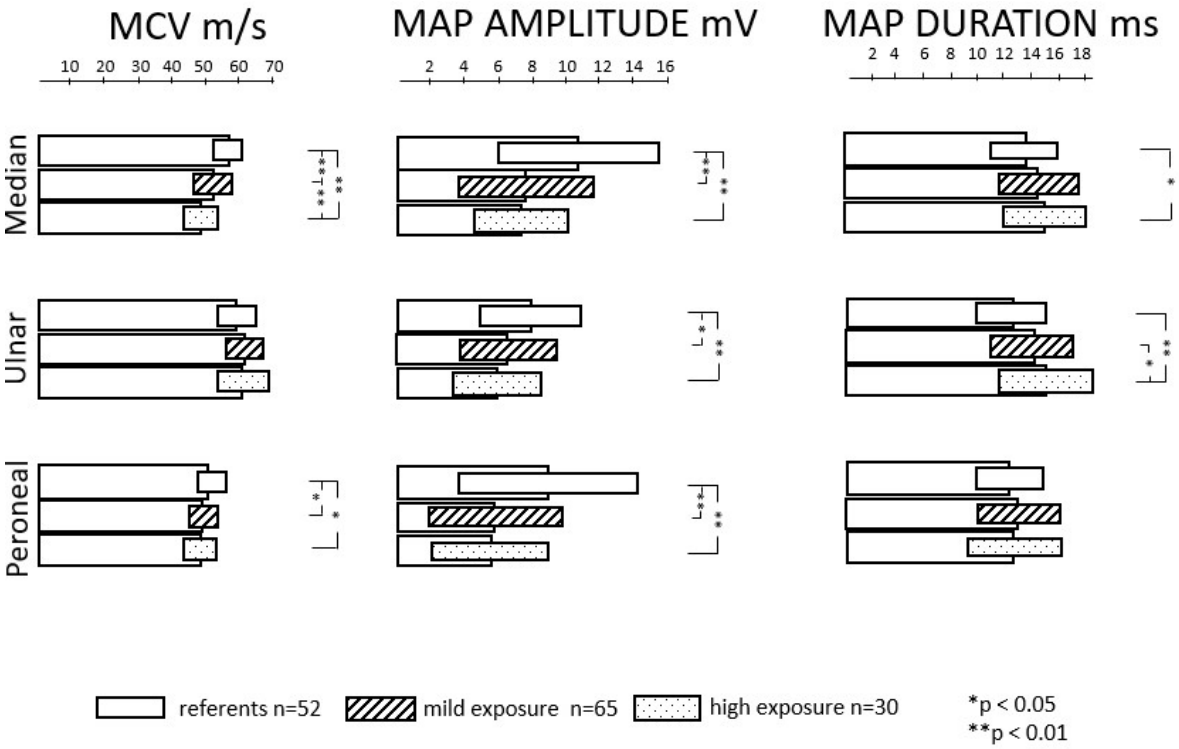
Group	No. of sub-jects	n-Hexane		Cyclohexane		M.E.K.		Ethyl acetate		Hygienic effect[a]	
		Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median
Referents	52										
Mild exposure	65	243	173	263	198	65	48	157	90	1.75	0.81
High exposure	30	474	362	447	386	223	171	290	352	2.34	1.91

[a] The hygienic effect is the ratio between the measured concentration of the compound and its TLV. When specific information about synergism does not exist, the sum of the ratios does not exceed 1.0, which is the TLV for the mixture (ACGIH 1979).

Table/Figure 13: Mutti et al. 1982 – Differences between the frequencies of neurological symptoms in 95 workers with long-term exposure to organic solvents (dark columns) and 52 referents (light columns). The figure is modified from the original article.



Table/Figure 14: Mutti et al. 1982 – Means (wide columns) and SD (bars) of motor conduction velocity parameters among 52 referents (light bars) and two sub-groups of workers with mild (dashed bars) and heavy (dark bars) exposure to organic solvents. The figure is modified from the original article.



Neghab et al. 2012

Table 15: Neghab et al. 2012 – 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

Chemicals	n	Average[a]	SD	Median	GM	TWA[b]	TLV-TWA[c]	TLV-TWA[d]	BEI
HEX	84	115 (17-298)	59.8	99.4	104	83.2 (52-119)	176	141	NA
Free 2,5-HD	27	0.23 (0.12-0.36)	0.06	0.196	0.21	NA	NA	NA	0.4

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 2020. d. The 9.2-h TLV-TWA calculated from Brief and Scala's equation. HD: hexadione, 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 16: Neghab et al. 2012 – Motor nerve conduction studies in the right upper and lower extremities for exposed workers and normal controls*

Nerve		Exposed workers (n=27)	Normal controls (n=20)
Median			
	DL (ms)	3.6 ± 0.07	3.7 ± 0.1
	MAP (mV)	6.1 ± 0.4	6.3 ± 0.6
	MCV (wrist-elbow) (m/s)	58.6 ± 3.2	57.4 ± 4.4
Ulnar			
	DL (ms)	3.1 ± 0.1	3 ± 0.14
	MAP (mV)	5.4 ± 0.7	5.2 ± 0.3
	MCV (wrist-elbow) (m/s)	56.5 ± 4.2	57.7 ± 3.1
Posterior tibial			
	DL (ms)	4.2 ± 0.2	4.3 ± 0.4
	MAP (mV)	5.7 ± 0.6	5.9 ± 0.9
	MCV (ankle-popliteal fossa) (m/s)	52.2 ± 4.5	52.08 ± 5.2
	F-Wave Latency (ms)	48.3 ± 0.6	48.8 ± 0.2
Peroneal			
	DL (ms)	4.1 ± 0.23	4.2 ± 0.31
	MAP (mV)	3.3 ± 0.11	3.6 ± 0.19
	MCV (ankle-fibula head) (m/s)	53.4 ± 3.70	52.6 ± 2.9

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

Table 17: Neghab et al. 2012 – Sensory nerve conduction studies in the right upper and lower extremities for exposed workers and normal controls

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

* Significantly different from the corresponding value for the normal control.. DL: distal latency, SAP: sensory nerve action potential, SCV: sensory nerve consuction velocity.

Table 18: Neghab et al. 2012 – Correlation between sensory nerve action potential (SAP) amplitudes and urinary concentration of free 2,5-HD in exposed workers

Nerve	Spearman correlation coefficient	p
Median	−0.67	<0.001
Sural	−0.52	<0.008

HD: hexanedione

Iida 1982

Table 19: Iida 1982 – Symptoms and signs of 93 cases of neuropathy in the study from 1968

	Number of cases	Percentage of total, 93 cases
Cranial nerve involvement		
Anosmia	5	5.4
Blurring of vision	13	14
Constriction of visual field	7	7.5
Optic nerve atrophy	2	2.2
Retrobulbar neuritis	1	1.1
Numbness over the face	5	5.4
Weakness of facial muscles	2	2.2
Sensory disturbance		
Numbness	93	100
Dysaesthesia	21	22.6
Pain or tenderness	5	5.4
Muscle weakness	40	43
Muscle atrophy	8	8.6
Reflexes		
Hypoactive	36	38.7
Hyperactive	10	10.8
Pathological reflexes	0	0
Micturition disturbance	1	1.1
Skin changes		
Coldness, redness, roughness	55	59.2
Emaciation	14	15.1
Anaemia	3	3.3

Table 20: Iida 1982 – Neuropathy classification based on the mode of involvement and clinical course of polyneuropathy in the study from 1968 (%in parentheses)

	III	II	I	R	Missing	Death
Spring, 1968	8 (8.6)	32 (34.4)	53 (57.0)			
Summer,1970	0	5 (5.5)	34 (37.8)	51 (56.7)	3	
Spring, 1972	0	0	7 (7.9)	82 (92.1)		1*

Group I, sensory neuropathy; group II, sensorymotor polyneuropathy; group III, sensorymotor polyneuropathy with amyotrophy; R, completely recovered case

*Died of gastric cancer

Table 21: Iida 1982 – Symptoms and signs of 21 cases of polyneuropathy during rescreening in Spring 1981

	Number of cases	Percentage of total, 21 cases
Cranial nerve involvement		
Tinnitus	1	4.8
Floating by postural change	5	23.8
Sensory disturbance		
Numbness	12	57.1
Dysaesthesia	6	28.6
Pain or tenderness	1	4.8
Muscle weakness	6	28.6
Muscle atrophy	0	0
Reflexes		
Hypoactive	10	47.6
Hyperactive	3	14.3
Pathologic	0	0
Micturition disturbance	0	0
Skin changes		
Coldness, redness, roughness	4	19

Table 22: Iida 1982 – Polyneuropathy classification based on the mode of involvement and clinical course of polyneuropathy during rescreening in Spring 1981

	Number of cases
Group I, sensory neuropathy	20* (95.2%)
Group II, sensorymotor polyneuropathy	1 (4.8%)
Group III, sensorymotor polyneuropathy with amyotrophy	0

*Including 5 cases with asymmetrical distribution.

Bachman et al. 1993

Table 23: Bachman et al. 1993 – Prevalence (%) of symptoms and signs.

	Exposure category									
	Unexposed (n=63)		Low (n=24)			High (n=39)			Total (n=126)	
Symptoms	n	%	n	%	p	n	%	p	n	%
Pain In arms or legs	10	15.9	7	29.2	0.225†	11	28.2	0.134*	28	22.2
Chronic pain	4	6.3	2	8.3	0.666*	7	17.9	0.099†	13	10.3
Weakness in arms or legs	4	-6.3	1	4.2	1.000†	4	10.3	0.478†	7	7.1
Chronic weakness	1	1.6	0	0	1.000†	3	7.7	0.155†	4	3.2
Difficulty walking	2	3.2	1	4.2	1.000†	4	10.3	0.199†	7	5.6
Chronic difficulty walking	0	0	1	4.2	0.276†	4	10.3	0.019†	5	4
Tingling hands and feet	0	0	3	12.5	0.019†	3	7.7	0.053†	6	4.8
Chronic tingling	0	0	2	8.3	0.074†	1	2.6	0.382†	3	2.4
Numb hands and feet	3	4.8	1	4.2	1.000†	3	7.7	0.672†	7	5.6
Chronic numbness	0	0	1	4.2	0.276†	1	2.6	0.382†	2	1.6
>1 limb-related symptom	15	23.8	10	41.7	0.100*	16	41	0.066*	41	32.5
Headache	15	23.8	4	16.7	0.471*	14	35.9	0.118*	33	26.2
Chronic headache	7	11.1	0	0	0.183†	7	17.9	0.330*	14	11.1
Dizzy	3	4.8	1	4.3	1.000†	2	5.1	1.000†	6	4.8
Chronic dizziness	1	1.6	0	0	1.000*	1	2.6	1.000†	2	1.6
> 1 head-related symptom	17	27	4	17.4	0.359*	15	38.5	0.225*	36	28.8
Stomach pain	9	14.3	3	12.5	1.000†	5	12.8	0.835*	17	13.5
Chronic stomach pain	3	4.8	0	0	0.558†	0	0	0.285†	3	2.4
Nausea	3	4.2	1	4.2	1.000†	2	5.1	1.000†	6	4.8
Chronic nausea	1	1.6	0	0	1.000†	0	0	1.000†	1	0.8
>1 abdominal symptom	11	17.5	3	12.5	0.749†	6	15.3	0.785*	20	15.9
Abdominal signs on examination of feet										
Pain sensitivity	13	20.6	7	29.2	0.398*	7	18.4	0.787*	27	21.6
Two-point discrimination	31	49.2	14	58.3	0.446*	17	44.7	0.663*	62	49.6
Walking on heels	1	1.6	0	0	1.000†	1	2.6	1.000†	2	1.6
Walking on toes	0	0	0	0	-	0	0	-	0	0
Light touch	2	3.2	2	8.3	0.304†	1	2.6	1.000†	5	4
Proprioception	0	0	0	0	-	0	0	-	0	0
>1 abnormal sign	37	58.7	16	66.7	0.498*	19	50	0.393*	72	57.8

†Fisher's exact test, prevalence compared to unexposed category. *Pearson's χ^2 test (d.f. = 1), prevalence compared to unexposed category.

Table 24: Bachman et al. 1993 – Vibrotactile sensitivity - tuning fork extinction time (seconds) and vibration thresholds (units)

		Exposure category				
	Unexposed (n=63)	Low (n=24)		High (n=39)		Total (n=126)
	Mean ± SD	Mean ± SD	p*	Mean ± SD	p*	Mean ± SD
Tuning fork	7.45 ± 2.39	7.74 ± 1.91	0.598	6.56 ± 1.89	0.05	7.23 ± 2.19
Forced choice	2.28 ± 0.91	2.13 ± 0.81	0.478	2.45 ± 1.03	0.385	2.30 ± 0.93
Method of limits						
Dominant foot	4.26 ± 1.44	3.57 ± 0.97	0.035	4.28 ± 1.75	0.978	4.14 ± 1.49
Non-dominant foot	4.06 ± 1.26	3.95 ± 2.03	0.751	4.32 ± 2.12	0.438	4.12 ± 1.72
Dominant hand	2.88 ± 0.92	2.29 ± 0.76	0.007	3.24 ± 1.75	0.169	2.88 ± 1.25
Non-dominant hand	2.99 ± 0.89	2.43 ± 0.80	0.008	3.24 ± 0.31	0.313	2.96 ± 1.15

*t test, mean compared to unexposed category.

Chang et al. 1993

Table 25: Chang et al. 1993 – Symptoms and signs in 20 patients with *n*-hexane neuropathy

	Number (%)	
	Upper limbs	Lower limbs
Numbness	8 (40)	14 (70)
Paraesthesiae	5 (25)	13 (65)
Pain	2 (10)	9 (45)
Cramp	1(5)	8 (40)
Weakness	7 (35)	15 (75)
↓Pain	2 (10)	6 (30)
↓Light Touch	1 (5)	4 (20)
↓Vibration	1 (5)	5 (25)
↓Joint position	0 (0)	1 (5)
Proximal wasting	1 (5)	2 (10)
Distal wasting	2 (10)	4 (20)
Proximal weakness	1 (5)	3 (15)
Distal weakness	3 (15)	5 (25)
Hyporeflexia	9 (45)	9 (45)

Table 26: Chang et al. 1993 – Nerve Conduction Study

		Asymptomatic		
	Control n = 20	Healthy worker n = 10	Subclinical n = 26	Symptomatic n = 20
Age (years)	26.9 (4.4)(20-35)	25.8 (6.4)(16-37)	26.7 (7)(17-43)	28.2 (5.8)(16-38)
Amplitudes of SAP (uV)				
Median	37 (11)(20-65)	27 (6)*(20-40)	24 (8)*(11-41)	15 (5)*(5-24)
Ulnar	15 (4)(8-22)	14 (3)(10-18)	12 (5)(5-24)	7 (4)*(0-15)
Sural	24 (10)(12-45)	22 (6)(15-35)	18 (7)*(2-40)	11 (8)*(0-34)
Amplitudes of MAP (mV)				
Median	7 (2)(3-11)	8 (3)(4-13)	6.7 (2. 4)(3.2-12.5)	4.6 (2.2)*(1.1-8)
Ulnar	5-7 (2.1)(2.8-10)	6.5 (1.9)(4-10)	4 (2.2)*(1-8)	3.6 (1.5)*(0.9-6)
Posterior tibial	6.6 (2)(3.5-11)	6.7 (2.3)(5-12)	5.3 (2.5)(2.2-15)	2.9 (1.7)*(1-7)
Common peroneal	4-4 (1.5)(2-7)	4.3 (1.4)(3-7)	3.6 (1.4)(1.5-7)	1.8 (1.4)*(0.25-6)
Distal Latency of SAP (ms)				
Median	2.3 (0.3)(1.9-2.8)	2.3 (0.1)(2.1-2.5)	2.6 (0.3)*(2.2-3.2)	2.9 (0.3)*(2.4-3.8)
Ulnar	2.1 (0.3)(1.7-2.8)	2.1 (0.1)(1.9-2.3)	2.3 (0.3)(1.9-3.1)	2.7 (0.4)*(2.0-3.5)
Sural	3.3 (0.3)(2.8-3.6)	3.1 (0.2)(2.8-3.3)	3.3 (0.3)(2.8-4.2)	3.7 (0.6)*(2.3-4.6)
Distal Latency of MAP (ms)				
Median	2.9 (0.4)(2.3-3.8)	3.0 (0.2)(2.7-3.3)	3.6 (0.5)*(2 8-4.8)	4.3 (1.2)*(2.6-7.2)
Ulnar	2.2 (0.3)(1.8-2.8)	2.3 (0.3-3)(2.1-2.8)	2.6 (0.5)*(2.0-3.9)	3.0 (0.7)*(2.2-4.5)
Posterior tibial	4.1 (0.6)(3.2-5.2)	3.9 (0.6)(3.1-4.8)	4.4 (0.6)(3.2-5.8)	5.6 (1.2)*(3.4-8.4)
Common peroneal	3.9 (0.5)(3.3-4.7)	3.5 (0.4)(3.0-4.2)	4.2 (0.7)(3.0-5.5)	5.4 (1.2)*(3.5-8.8)
Motor Conduction Velocity (m/s)				
Median	59 (5.9)(48-68)	57 (5)(48-65)	55 (6.7)*(43-73)	46 (6.5)*(37-57)
Ulnar	61 (5.8)(44-69)	59 (6)(52-71)	55 (7.8)*(44-79)	48 (7.5)*(38-69)
Posterior tibial	50 (6.4)(41-66)	46 (3.4)(41-51)	45 (4.7)*(36-55)	38 (6.5)*(26-51)
Common peroneal	51 (4.5)(43-63)	46 (3.8)(40-53)	45 (511)*(36-56)	37 (7.1)*(26-54)

Mean (SD)(range), *p < 0.05 compared with control.

Table 27: Chang et al. 1993 – Number (%) of workers with other abnormalities

	Symptomatic peripheral neuropathy n=20	Subclinical peripheral neuropathy n=26	Asymptomatic healthy worker n=10
Systemic upset*	11 (55)	5 (19.2)	0 (0)
Subclinical optic neuropathy**	2 (10)	3 (11.5)	0 (0)
Autonomic neuropathy***	0 (0)	0 (0)	0 (0)
CNS symptoms****	5 (25)	0 (0)	0 (0)
CNS signs*****	2 (10)	0 (0)	0 (0)
Abnormal liver function test	0 (0)	1 (3.8)	1 (10)

*Weight loss >5 lb, anorexia.

**Delayed P100 latency in VEP (visual evoked potential).

***Postural hypotension, impotence, urinary difficulty, constipation, diarrhoea, anhidrosis,hyperhidrosis.

****Headache, deteriorating memory, drunken feeling, vertigo.

*****Hyperreflexia.

Co-exposure levels to other potentially toxic substances**:**

The used solvents contained a variable percentage of toluene but no methyl *n*-butyl ketone (MBK) or methyl ethyl ketone (MEK); moistening solutions contained only trace amounts of phosphate at 42 ppm. The printing inks contained 0.6-8.2 pg/g lead, <0.05-0.95 pg/g mercury and no volatile organic compound; time weighted average air concentrations: 30 to 110 ppmV (0.11-0.39 mg/L; mean 63 ppmV, 0.22 mg/L) for *n*-hexane, 57 to 340 ppmV (mean 130 ppmV) for isopropyl alcohol (IPA) and 11 to 46 ppmV (mean 26 ppmV) for toluene; concentrations were higher in the personal air samples from the offset machine workers, 80 to 210 ppmV (mean 132 ppmV) for *n*-hexane, 20 to 680 ppmV (mean 235 ppmV) for IPA, and 20 to 84 ppmV (mean 50 ppmV) for toluene; no potentially confounding chemicals detected (on MBK, no MEK).

Huang et al. 1991

Table 28: Huang et al. 1991 – Prevalence of neurological symptoms and signs among workers in different levels of *n*-hexane exposure

	Index of exposure			
	I	II	III	p*
Number of workers	5	8	31	p < 0.05
% of female	100	85.7	64.5	
Age (years)	19.3 + 3.2	21.4 + 3.2	27.9 + 4.8	
Duration of work (months)	34.2 + 36.8	25.2 + 21.2	31.7 + 19.2	
Job title	Cement coating, nylon fiber winding	Gas injection, outer-layer production	Others	
n-Hexane concentration (ppm)	110 and 86	75		
Number of polyneuropathy cases	5	2	0	
Symptoms				
General malaise	5	6	15	p < 0.05
Muscle pain	5	3	9	p < 0.05
Limb weakness	5	2	0	p < 0.01
Limb numbness	5	1	0	p < 0.01
Headache or dizziness	3	4	10	p > 0.05
Body weight loss	3	6	2	p < 0.01
Anorexia	1	1	1	p > 0.05
Emotional instability	2	1	0	p < 0.01
Signs				
Muscle weakness in extremities	5	0	0	p < 0.01
Numbness in extremities	5	0	0	p < 0.01
Hyporeflexia or areflexia in UE	5	1	2	p < 0.01
Hyporeflexia or areflexia in UE	5	2	0	p < 0.01

*, χ^2 test for trend
UE, upper extremities
LE, lower extremities

Table 29: Huang et al. 1991 – Motor neuron conduction studies among workers exposed to *n*-hexane

		Median			Ulnar			Peroneal			Tibial		
		DL (ms)	Amp (mV)	NCV (m/s)	DL (ms)	Amp (mV)	NCV (m/s)	DL (ms)	Amp (mV)	NCV (m/s)	DL (ms)	Amp (mV)	NCV (m/s)
I	Mean	5.1[a]**	4.1[a]**	39.8[a]**	3.8[a]**	4.9[a]**	37.8[a]**	6.5[a]**	3.3[a]*	30.8[a]**	8.0[a]**	3.9[a]*	32.4[a]**
	SD (n=9)	0.8	2.7	4.6	0.5	2.1	3.4	0.8	1.4	4	1.8	1.4	3.2
II	Mean	3.6[a]	11.5	52.2[a]	2.7[b]	8.7	51.9[a]	4.7[b]	5.1	43.6[a]	6.1[b]	7.6	44.7[a]
	SD (n=8)	0.4	2.6	5	0.3	1.8	4.4	0.5	1.5	3.5	0.7	3.9	4.5
Controls	Mean	3	10.9	60.4	2.4	9.1	60.5	4.2	5.9	51	5.3	9.8	49
	SD (n=9)	0.4	2.4	4	0.4	1.8	4.2	0.5	2.5	3.2	1	2.9	3.4

*DL, distal latency; Amp, amplitude of evoked muscle potential; NCV, nerve conduction velocity; I or II vs controls, [a] = p < 0.01, [b] = p < 0.05; I vs II, ** = p < 0.01, * = p < 0.05.

Table 30: Huang et al. 1991 – Sensory nerve conduction studies among workers exposed to *n*-hexane

		Median nerve			Ulnar nerve			Sural nerve		
		DL (ms)	Amp (uV)	NCV (m/s)	DL (ms)	Amp (uV)	NCV (m/s)	DL (ms)	Amp (uV)	NCV (m/s)
I	Mean	3.1[a]	14.8[a]	52.7 [a]*	2.5[a]*	15.3[a]**	51.4[a]**	3.6[a]*	8.4[a]**	41.8[a]*
	SD (n=9)	0.7	9.8	4.6	0.3	11.1	2.8	0.5	2.8	5.3
II	Mean	3.2[a]	23.3[a]	58.6[a]	2.8[a]	33.3	57.7[a]	3.3[b]	15.5[b]	49.5
	SD (n=8)	0.2	11.1	5.8	0.1	5.8	46	0.4	3.5	8.2
Controls	Mean	2.5	42	65.8	2.1	41	66	3	29	49.4
	SD (n=52)	0.4	18	3.6	0.3	14.4	5	0.3	15.1	4.2

*DL, distal latency; Amp, amplitude of antidromic evoked sensory nerve action potentials; I or II vs controls, [a] = $p < 0.01$, [b] = $p < 0.05$; I vs II, ** = $p < 0.01$, * = $p < 0.05$.

Öge et al. 1994

Table 31: Öge et al. 1994 – Needle electromyography

Muscles (n = 27)	Fasciculation potentials	Fibrillations, positive sharp waves	Long duration polyphasic MUPs	Reduced interference
FDI	5	9M, 2S	5+, 20±	6+, 3±
EDC	6	12M, 4S	15+, 9±	9+, 4±
FCR	5	9M, 4S	7+, 18±	1+, 3±
TA	7	20M, 4S	17+, 9±	17+, 2±

For simplification, 1+ and 2+ fibrillations and positive sharp waves were taken together as “mild” (M), and 3+ and 4+ as “severe” (S). The amount of long duration polyphasic motor unit potentials and reduced interference patterns were indicated as (±) and (+), according to the severity of pathological findings. M, mild; S, severe; MUP, motor unit action potential; FDI, first dorsal interosseous; EDC, extensor digitorum communis; FCR, flexor carpi radialis; TA, tibialis anterior.

Table 32: Öge et al. 1994 – Sensory conduction studies (HPNP: hexane polyneuropathy group; normal: control group)

Nerves	HPNP	Normal
Ulnar		
Recordable cases	27/27	24/24
Onset latency (ms)	2.6 ± 0.47	1.92 ± 0.21
Peak latency (ms)	3.3 ± 0.56	2.53 ± 0.24
Amplitude (uV)	7.1 ± 4.8	22.02 ± 8.2
Median		
Recordable cases	27/27	24/24
Onset latency (ms)	2.99 ± 0.58	2.14 ± 0.24
Peak latency (ms)	3.69 ± 0.58	2.75 ± 0.23
Amplitude (uV)	11.08 ± 7.16	31.3 ± 10.7
Sural		
Recordable cases	18/23	24/24
Onset latency (ms)	4.06 ± 0.66	3.11 ± 0.35
Peak latency (ms)	5.1 ± 0.87	3.87 ± 0.35
Amplitude (uV)	12.32 ± 7.82	25.10 ± 8.37
Medial plantar		
Recordable cases	12/26	24/24
Onset latency (ms)	7.33 ± 0.96	4.3 ± 0.51
Peak latency (ms)	8.5 ± 1.27	5.06 ± 0.51
Amplitude (uV)	1.60 ± 0.69	4.11 ± 2.11

The differences of al latency and amplitude values between HPNP and normal groups were significant ($p < 0.001$).

Table 33: Öge et al. 1994 – Motor conduction velocities (HPNP: hexane polyneuropathy group; normal: control group)

Nerves	Segment	HPNP (n=27)	Normal (n=24)	p
Ulnar (abductor digiti minimi)	Distal latency (R)	5.1 ± 1.1 (3.7-7.1)	2.91 ± 0.44 (2.2-3.9)	<0.001
	Distal latency (L)	4.65 ± 0.98 (3.5-7.8)		<0.001
	Elbow-wrist (R)	40.2 ± 6.3 (25-52.3)	60.67 ± 6.67 (50-70)	<0.001
	Elbow-wrist (L)	41.5 ± 6.1 (29.5-55.9)		<0.001
	Axilla elbow (R)	52.24 ± 11.57 (33.7-7	61.69 ± 7.9 (51.8-78)	<0.01
	Axilla elbow (L)	49.8 ± 10.7 (29-73.4)		<0.001
	Neck-axilla (R)	59.6 ± 8.9 (47.9-78)	66.6 ± 7.74 (52-80)	0.01
	Neck-axilla (L)	57.9 ± 9.7 (43.6-80)	64.6 ± 8.8 (52-80)	0.02
Median (abductor pollicis brevis)	Distal latency	5.69 ± 1.32 (3.3-8.5)	3.4 ± 0.48 (2-4)	<0.001
	Elbow-wrist	39.2 ± 5 (31.8-48.8)	59.07 ± 5.8 (50-73)	<0.001
	Axilla-elbow	50.24 ± 7.2 (40-65.3)		
Tibial (abductor hallucis)	Distal latency	10.28 ± 4.1 (4.6-25.6	5.1 ± 0.53 (4.2-5.8)	<0.001
	Popliteal fossa-ankle	30.59 ± 4.85 (21.6-38	46.4 ± 3.5 (40-52)	<0.001
Peroneal (extensor digitorum brevis)	Distal latency	8.95 ± 1.72 (4.8-12.8	4.60 ± 0.74 (3.2-6)	<0.001
	Below fibular head-ankle	32 ± 5.6 (22.2-45.4)	50.3 ± 4.5 (44.1-66)	<0.001

Latencies were measured to the onset of the first negative deflection of the muscle response. Distal latencies (ms) and nerve conduction velocities (m/s) are given as mean ± SD. Ranges are shown in parentheses. Recording muscles are indicated in

the first column following the names of the nerves. Right (R) and left (L) side values for ulnar nerve conduction studies of HPNP cases are given separately. Motor conduction studies of the other nerves were performed on only one side. Statistical significance of the differences between consecutive segments of the nerves: Ulnar nerve, elbow-wrist/axilla-elbow-right: p< 0.001, left: p=0.001; axilla-elbow/neck-axilla-right: p = 0.01, left: p<0.01. Median nerve, elbow-wrist/axilla-elbow: p <0.001.

Sanagi et al. 1980

Table 34: Sanagi et al. 1980 – Subjects

Group		Exposed	Exposed in the past	Control
Number of subjects		14	5	14
Age (yr)	A	38.3	33.4	36
	R	24-50	21-42	24-50
Stature (cm)	A	160.7	165.6	162.1
	R	156-170	161-173	150-171
Weight (kg)	A	57.8	61	55.9
	R	47-73	50-77	48-65
Alcohol consumption (g/day)	A	22.5	0	33
	R	0-81	0	0-81
Smoking habits (cigarettes/day)	A	15.1	10.6	10
	R	0-45	0-20	0-30

A, average; R, range. The groups hereafter will be referred to in the tables as follows: Exposed E; Exposed in the past: EP; Control: C.

Table 35: Sanagi et al. 1980 – Neurological symptoms from the questionnaire

Answer		Persistent			Persistent and transient		
Group		E	EP	C	E	EP	C
Headache	(%)	14	20	0	86[a]	60	43
Feeling heavy in head	(%)	21	20	7	71	40	43
Vertigo or dizziness	(%)	0	0	0	50	60	38
Anosmia or dysnosmia	(%)	7	0	7	46	20	14
Disturbance of vision	(%)	57	40	43	-	-	-
Double vision	(%)	0	0	7	36	20	21
Tinnitus	(%)	7	0	0	36	40	29
Hearing deficit	(%)	71[a]	20	14	-	-	-
Dysphagia	(%)	0	0	0	29	0	29
Dysarthria	(%)	0	20	0	14	40	21
Pain in the neck, shoulder or arm	(%)	21	0	0	71	80	43
Lumbago or leg pain	(%)	14	20	0	54	60	50
Arthrodynia	(%)	0	0	0	36	20	29
Muscle pain	(%)	0	20	0	50	20	14
Oversensitivity to cold in legs	(%)	0	0	0	8	20	14
Dysesthesia in limbs	(%)	0	20	0	29[a]	40	0
Numbness in limbs	(%)	14	20	0	21	40	0
Stiff shoulders	(%)	14	0	14	64	100	64
Fatigability of arms	(%)	0	0	0	57	40	36
Fatigability of legs	(%)	14	20	7	79	80	46
Muscle weakness	(%)	0	20	0	29[a]	40	0
Writing deficit	(%)	14	40	36	-	-	-
Unsteady gait	(%)	0	0	0	21	20	7

[a] Figures are significantly different from those of the control group ($p<0.05$)

Table 36: Sanagi et al. 1980 – Neurological tests

Group	E	EP	C
Muscle strength			
Grip power (kg)	45.3 ± 2.9	45.3 ± 5.7	44.9 ± 5.2
Jumping on the foot (cm)	21.3 ± 3.6[b]	26.4 ± 4.1	26 ± 6.2
Vibration sensation			
Radial processes (s/16 s)	13.8 ± 2.4[b]	14.9 ± 2.4	15.4 ± 1.6
Medial malleoli (s/16 s)	12.2 ± 2.1	13.3 ± 0.7	13.4 ± 2
Position sense			
Barrany's test (cm)	0.8 ± 0.4	0.3 ± 0.1	0.7 ± 0.5
Mann's test (%)[a]	21	0	0
Co-ordination skills			
Knee slapping (times/15 s)	2.4 ± 4.8	26.2 ± 2.9	24.5 ± 2.8
Floor tapping (times/15 s)	39.9 ± 7.7	44.6 ± 4.6	42.6 ± 6.0

Average ± S.D.

[a] Prevalence of the subjects who could not maintain the balance over 20 s.

[b] Figures are significantly different from those of the control group (P<0.05).

Table 37: Sanagi et al. 1980 – Muscle stretch reflexes

Group			E	EP	C
Biceps reflex	(-) & (±)	(%)	54	20	21
Triceps reflex	(-) & (±)	(%)	36	20	36
Pronator reflex	(-) & (±)	(%)	68	60	50
Knee jerk	(-) & (±)	(%)	36	40	7
Ankle jerk	(-) & (±)	(%)	7	0	7

Table 38: Sanagi et al. 1980 – Nerve stimulation studies on the right median and ulner nerves

Group	E	EP	C
MMCV (m/s)	57.3 ± 3.4	56.3 ± 3.7	57.5 ± 3.2
MAP e/w (%)	97.2 ± 5.2	99.2 ± 4.7	100.3 ± 5
RL (ms)	2.26 ± 0.46	2.2 ± 0.32	2.19 ± 0.32
CVSF (m/s)	48.5 ± 4.5	50.8 ± 2.2	49.9 ± 4.4
dSCV (m/s)	66.4 ± 6.9	67 ± 3.7	65.2 ± 5.9
pSCV (m/s)	62.8 ± 3.6	63.9 ± 3.3	62.0 ± 3.4
MNCV (m/s)	72.5 ± 3.4	68.3 ± 6.4	71.3 ± 3.8

Average ± S.D.

CVSF measurement was performed on the right ulnar nerve, and the other measurements on the right median nerve. Skin temperature at the wrist were 32.7 ± 1.0, 31.7 ± 1.4, 32.6 ± 1.2 °C in groups E, EP and C, respectively. The temperature of the examination room was adjusted at 25°C (25.1 ± 0.7°C).

Table 39: Sanagi et al. 1980 – Nerve stimulation studies on the right posterior tibial nerve

Group	E	EP	C
MMCV (m/s)	46.6 ± 2.3[a]	48.3 ± 3.3	48.3 ± 2.1
MAP k/a (%)	90.1 ± 7.4	93.1 ± 14.8	88.9 ± 11.8
RL (ms)	2.55 ± 0.48[a]	2.74 ± 0.58[a]	2.21 ± 0.34
CVSF (m/s)	38.6 ± 2.2	38.9 ± 3.5	39.1 ± 1.5
dSCV (m/s)	42.6 ± 5	41.5 ± 3.1	41.7 ± 3.9
MNCV (m/s)	59.1 ± 3.4	62 ± 4.1	60.2 ± 3.3

Average ± S.D.

[a] Figures are significantly different from those of the control group (P<0.05). Skin temperature at the ankle were 30.9 ± 1.2, 30.8 ± 0.3, 30.9 ± 1.4 °C in groups E, EP and C, respectively. The temperature of the examination room was adjusted at 25°C (25.2 ± 0.8°C).

Huang and Chu 1989

Table 40: Huang and Chu 1989 – Clinical data on 5 workers with n-hexane intoxication

Case	Age/Sex	Duration of exposure	Neurological symptoms	Neurological signs	Sleeping in the workroom
1	18/M	24 M	Muscle cramp, weakness and distal numbness	Distal sensory impairment, Yes absence of DTR, limb weakness, hand muscle atrophy, hyperhidrosis, impotence	Yes
2	17/M	22 M	Muscle cramp, weakness and distal numbness	Distal sensory impairment, Yes absence of DTR, limb weakness, hand muscle atrophy, hyperhidrosis	Yes
3	18/M	16 M	Muscle cramp, weakness, blurred vision and tinnitus	Distal sensory impairment, Yes absence of DTR, limb weakness, hand muscle atrophy, hyperhidrosis	Yes
4	19/M	5 M	Fatigue, muscle soreness and distal numbness	Decreased DTR, distal limb weakness	Yes
5	26/M	30 M	Absent	Absent	No

Table 41: Huang and Chu 1989 – Motor nerve conduction velocity among 5 workers with n-hexane exposure

	Median		Ulnar		Peroneal		Tibial	
Case	NCV(m/s)	Amp(mv)	NCV(m/s)	Amp(mv)	NCV(m/s)	Amp(mv)	NCV(m/s)	Amp(mv)
1	29.2*	3.0*	25.3*	5	20.5*	0.4	23.3*	0.5
2	30.2*	1.0*	27.2*	2.5*	-	-	20.3*	0.1*
3	41.4*	3.0*	41.1*	2.0*	29.3*	1.2	38.8	1.5
4	38.4*	10	40.5*	11	38.7*	1.5	28.5*	4.5
5	58.5	6.5	50.9	8	38.0*	2	41.9	7
Mean ± SD	39.5 + 11.8**	4.7 + 3.7**	37.0 + 10.7**	5.7 + 3.8**	31.6 + 6.7**	1.3 + 0.5**	30.6 + 9.5**	2.7 + 3.0**
Normal	60.3 + 3.8	10.6 + 2.1	60.9 + 4.4	9.0 + 1.8	50.5 + 3.9	5.9 + 2.6	48.4 + 3.4	8.6 + 2.8

1. *Indicates value prolonged beyond the upper normal limit.
2. **Indicates statistical significance with $p<0.001$when compared with the control group.
3. -Indicates absence of response

Table 42: Huang and Chu 1989 – Median and tibial SEPs among 5 workers with n-hexane exposure

		Median				Tibial	
Case		N13	N20	N13-N20	N22	P40	N22-P40
1	L	17.9*	24.1*	6.2	28.0*	58.4*	30.4*
	R	18.0*	23.8*	5.8	26.5*	54.6*	28.1*
2	L	18.2*	24.9*	6.7	26.4*	53.4*	27.0*
	R	17.9*	23.9*	6	27.0*	54.4*	27.4*
3	L	17.0*	22.9	5.9	28.1*	46.1*	18
	R	17.0*	22.5	5.5	26	45.2*	19.2
4	L	16.8*	22.9	6.1	26.9*	44.5	17.6
	R	16.6*	22	5.4	26.9*	47.3*	20.4
5	L	16.4	22.3	5.9	26.1	42.3	16.2
	R	16.7*	21.5	5.8	23.1	41.1	18
Mean ± SD		17.3 + 0.7**	23.1 + 1.1**	5.9 + 0.4	26.4 + 1.4**	48.7 + 6.0**	22.3 + 5.4**
Control		13.9 + 0.9	19.6 + 1.3	5.7 + 0.8	21.9 + 1.5	38.3 + 2.2	16.9 + 1.2

1. Values are in ms.
2. *Indicates latency prolonged beyond the upper normal limit.
3. **Indicates a statistical significance with $p<0.001$when compared to the control group.

Co-exposure levels to other potentially toxic substances**:** benzene 9.65 ppmV; toluene, carbon disulfide, acrylamide, methyl n-butyl ketone (MBK) and triorthocresyl phosphate (TOCP) were not detected; analysis of the coloring agents showed absence of arsenic and lead.