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från YMK

Yrkesmedicinska kliniken
Sahlgrenska sjukhuset

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BESTÄLLNINGSLISTA

1991-10-07

Nr	År	Titel, författare	Pris
1	1978	Epidemiologisk utvärdering av "Cancerrisk vid aerosolexposition - oljedimma - inom mekanisk verkstadsindustri". Thiringer G, Johannisson B, Lillienberg L o a	25,-
2	1980	Hälsokontroll av oljedimexponerad personal. Järvholm B, Thiringer G	25,-
3	1982	Upprepad hälsokontroll av oljedimexponerad personal. Järvholm B, Hoffmann M, Sällsten G o a	25,-
4	1983	Luftvägssjukdomar och exponeringsförhållanden vid mjukpappers-tillverkning. Eriksson J, Järvholm B, Norin F	25,-
5	1983	Jämförande studier av kolrör (SKC) och dosimeter (3M) i fält vid mätning av styren, xylen och etylbensen resp etylacetat. Sällsten G, Hagberg S	25,-
6	1983	Blyexponering vid bilkylerenovering. Hoffmann M	25,-
7	1984	Förekomst av premaligna hudförändringar hos arbetare exponerade för mineralolja. Järvholm B, Fast K, Lavenius B, Tomsic P	25,-
8	1984	Effekter av lösningsmedelsexponering på kognitiva funktioner, neurofysiologiska funktioner och livsmönster. Ekberg K, Barregård L, Hagberg S o a	50,-
9	1982	Cancersjuklighet vid polering i rostfritt stål - en epidemiologisk studie vid tre verkstadsföretag. Järvholm B, Liliienberg L	25,-
10	1984	Synpunkter på en utvidgad hälsokontroll av anställda på fartyg med farlig last. Nilsson R	35,-
11	1985	Mortalitet och cancerincidens vid en skofabrik. Sällsten G, Barregård L	25,-
12	1985	Lungfunktionspåverkan av mjukpappersdamm. Järvholm B, Bake B, Brolin I o a	25,-
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14	1985	Mortalitet och cancerincidens hos arbetare exponerade för statiska magnetfält. Barregård L, Järvholm B, Ungethüm E	25,-
15	1985	Cancerrisk och dödsorsaker hos oljedimexponerade - uppföljning av en epidemiologisk studie. Järvholm B, Lavenius B, Sällsten G	30,-
16	1986	Kemiska hälsorisker i reprocentraler vid Göteborgs universitet. Lillienberg L, Nordlinder R	30,-
17	1986	Städare och arbetsmiljö. Nilson L, Thiringer G	30,-
18	1987	Påverkan på lungor och luftvägar vid mjukpapperstillverkning. Thorén K, Sällsten G, Bake B o a	30,-
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20	1987	Tankarbetarnas arbetsmiljö. Lillienberg L, Högstedt B, Järvholm B o a	30,-
21	1987	Dödlighet av astma, lungcancer, maligna lymfom och ventrikelcancer hos pappersarbetare och andra yrkeskategorier. Thorén K, Järvholm B, Hörte L G	30,-

22	1988	Rapport från seminarium om risker med organiska lösningsmedel. Edling C, Järvholm B	30,-
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25a	1988	Frånvaro bland städare på städcentralen vid Sahlgrenska sjukhuset i Göteborg, 1984. Herloff B, Nilson L	50,-
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26	1988	Undersökning av cytostatikahanterande sjuksköterskor inom Göteborgs sjukvård. Thiringer G, Järvholm B, Jönsson D o a	30,-
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28	1989	Hälsoundersökning, särskilt avseende genotoxisk påverkan, av sjömän på kemikalie- och produkt-tankfartyg. Nilsson R, Nordlinder R, Granung G o a	30,-
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32	1988	Statiska magnetfält kring två MRT-utrustningar vid två sjukhus. Mätrapport. Jonsson P, Barregård L, Thiringer G	30,-
33	1989	Dödlighet i astma och kronisk obstruktiv lungsjukdom samt i tumörer från andningsorganen och magsäck hos arbetare vid två finpappersbruk. Thorén K, Sällsten G, Järvholm B	30,-
34	1989	Förkomst av N-nitrosodietanolamin i nitritfria skärvätskor. Järvholm B, Zingmark P-A, Österdahl B-G	35,-
35	1989	Olika exponeringars betydelse för uppkomst av lungcancer i Göteborg. Järvholm B, Larsson S, Hagberg S o a	50,-
36	1990	Dödlighet och sjuklighet i luftvägssjukdomar hos mjukpappersarbetare. Del 1. Undersökning av astmaförekomst och luftvägssymtom. Torén K, Järvholm B, Sällsten G, Drake U, Hermansson R	50,-
37	1990	Psykiska arbetsskador i Göteborg. Bedömningar på försäkringskassan. Nilson L, Herloff B, Thiringer G	50,-
38	1990	Dödlighet och cancersjuklighet bland asbestexponerade industriarbetare i Göteborg. Sandén Å, Järvholm B, Larsson S, Thiringer G	50,-

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Foreword

The 9th Swedish-Yugoslav Health Meeting was held in Sweden 10th to 17th June 1990. These meetings started in 1970 and are alternately held in Sweden and Yugoslavia. The topics of the 9th meeting was organic solvents and vibration induced diseases.

During the week there were two seminars, one in Göteborg and one in Malmö. These proceedings summaries the presentations during the seminars. We, the participants of the seminars, acknowledge the financial support from the National Board of Social Health and Welfare and the excellent work with practical arrangements done by Mrs Barbro Jungstedt.

Bengt Järvholm

9th Swedish-Yugoslav Occupational Health days

Program, Seminar 1st day

12 June 1990, Hindås, Göteborg

Chairman: Bengt Järvholm

9.00	Srmena Krestev et al: Health hazards of workers exposed to carbon disulfide - results of an epidemiological study.
9.30	Gösta Axelsson: Exposure to organic solvents and pregnancy outcome.
10.00	Coffea
10.30	Jasminka Siriski et al: Benzene, toluene and xylene in ambient air and their metabolites in urine in different industries.
11.00	Rolf Nordlinder: Occupational and Environmental exposure to benzene in Sweden.
11.30	Gunnar Thiringer: Workman´s compensation and diseases caused by organic solvents in Sweden.
12.00	Lunch

Chairman: Dusan Djuric

13.00	Elisaveta Stikova et al: Influence of local vibration on serum protein and immunoglobin level.
13.30	Kjell Torén: Plasma viscosity and immunological parameters among dockers with vibration induced white fingers.
14.00	Zorica Brajovic et al: Metabolic changes of workers with chain saw.
14.30	Ralph Nilsson: Vibration induced disorders in the feet.
15.00	Coffea
15.15	General Discussion

Program 2nd day,

14 June, Malmö

Chariman: Dr Srmena Krstev

9.00	Dusan Djuric: "Antabuse test" for evaluation of genetic predisposition to carbon disulfide.
9.30	P Orbaek: Chronic toxic encephalopathy. Clinical picture, examination and prognosis.
10.00	Coffea
10.30	Rajka Turk: Bone marrow response in chronic experimental benzene poisoning.
11.00	B G Svensson: Mortality and cancer morbidity in Toluene exposed rotogravure printers.
11.30	Ljiljana Skender: Selection of biological indicators in occupational exposure to toluene and xylene.
12.00	J-E Karlsson: Exposure to solvents in a Swedish offset-rotation printingshop and neuroasthenic symptoms among the printers.
12.30	Lunch

Chairman: P Orbaek

13.30	Ljubomir Petrovic (or Kostadin Trickovic): Fingers´skin histopathology of patients with vibration syndroma and with sign of empty fingers "Prints in dough".
14.00	Ulf Hjortsberg: Tactile sensory dysfunction following vibration exposure.
14.30	Kostadin Trikovic: Vibration damping by the use of antivibration gloves and their application at work safety.
15.00	Coffea
15.20	General Discussion
16.00	Discussion - continuous cooperation - topics of next seminar

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HEALTH HAZARDS IN WORKERS EXPOSED TO CARBON DISULFIDE - RESULTS OF AN EPIDEMIOLOGICAL STUDY IN THE VISCOSE RAYON FACTORY

Krstev Srmena, Farkić B., Varagić Milica, Banićević Radmila, Galonić M., Trikić R., Braun C., Verwijst B.

Workers exposed to carbon disulfide are often complaining of variety of symptoms, among which paresthesiae, numbness, muscle pain, muscular weakness etc. are very common (1,2,3,4). Even nonspecific, they could be the early signs of polyneuropathy, perhaps the best known manifestation of chronic carbon disulfide intoxication.

Although it is quite frequent, the biochemical mechanism of CS2-induced polyneuropathy is unclear. Some proposed mechanisms suggest that CS2 derived dithiocarbamates bind to copper and zinc while the other suggest that CS2 reacts with pyridoxine causing neuropathy. Also, some experimental studies investigated the possibility that the clinically observed posterior paresis may be due to a direct effect of CS2 on the muscle, but no evidence for a primary myotoxicity of CS2 was established. The muscle lesions noted were similar to denervation atrophy and therefore resulted from the peripheral neuropathy (5).

Morphologically, polyneuropathy is a manifestation of the central peripheral distal axonal degeneration (1,4,6,7).

As a part of a large cross-sectional study concerned with the health hazards in the viscose rayon industry, neurological examination was performed in two groups of workers selected according to the different exposure levels to carbon disulfide. Positive neurological finding was a criterion for further neurophysiological examinations i.e. electromyoneurography (EMNG) and evoked potentials (EP).

MATERIAL AND METHODS

Subjects

Two groups of workers were selected according to the exposure level to carbon disulfide. First group (N = 97) consisted of spinners in the spinning room, exposed to the high carbon disulfide levels. Workers engaged in the viscose production, exposed to lower carbon disulfide

concentrations composed the second group (N = 37).

Mean age of the first group was 41.68 $\pm$ 7.35 years, mean length of employment 19.75 $\pm$ 6.57 years, and mean exposure duration 16.94 $\pm$6.07 years. Second group was somewhat older and with a longer employment and exposure duration (mean age 44.21 $\pm$.9.74 years, mean length of employment 20.27 $\pm$ 8.22 years, and mean duration of exposure 17.59 $\pm$ 7.17 years) but without statistically significant differences.

The criterion for selection was more than 5 years of exposure duration to carbon disulfide for both groups. For the second group a criterion was added, that all workers who ever worked in the plant departments with high carbon disulfide concentrations were excluded. All subjects were randomly selected from the plant personnel records.

Comparability of the groups

Both groups are male, and similar regarding the place of residence. The majority of workers in both groups are living in the rural regions, (83.% in the first group versus 78.4% in the second group), and the difference between two groups is not statistically significant (chi-square = 0.19, d.f. = 1).

As a confounder alcohol consumption was analyzed and as we can see on the table 1 there is no statistically significant difference in frequency of alcohol consumption (chi-square=2.49, d.f.=4). When analyzing the amount of plum brandy drunk per week (table 2), a slight difference is noticed. Workers from the first group more often declare that they do not drink at all (in 36.1% compared with 27.0% in the second group). Also, they are more often heavy drinkers, stating that they drink more than 10 glasses of plum brandy (one glass contains 50 ml of plum brandy) in 31.9% compared with 13.5% in second group. The difference is statistically significant at the level of 0.02.

There is no statistically significant difference in the consumption of beer (in bottles) per week (chi-square=2.84, d.f.=3), and wine is very rarely drunk among both groups.

The frequency of being drunk was analyzed as well, and as we can see on the table 3, there is no statistically significant difference between both groups. The same percentage of workers in both groups were last

time drunk previous week (5.2% versus 5.4%), as well as a month ago (12.4% versus 13.5%).

All data on alcohol consumption were obtained by a questionnaire, asked by an occupational health physician.

Exposure

Exposure estimation for carbon disulfide was made by using passive diffusive charcoal personal samplers - Draeger Orsa-5 badges, calibrated at the AKZO in Arnhem, Holland. The amount of adsorbed carbon disulfide in the charcoal of the badges were analyzed by converting to Cu-dietil-dithiocarbamate and measured colorimetrically at 420 nm (8).

In the first group, among the spinners mean carbon disulfide concentration is 57.72 mg/m^3, median 45.70 mg/m^3, minimum 5.00 mg/m^3, and maximum 157.35 mg/m^3. Workers engaged in the viscose production are exposed to the mean carbon disulfide concentration of 12.61 mg/m^3, median 8.22 mg/m^3, minimum 0.17 mg/m^3, and maximum 50.82 mg/m^3. As the results do not follow the normal distribution, for comparing concentrations in these two groups Mann-Whitney U test was used. The results show that the differences in the concentrations are highly statistically significant.

At the same time as personal sampling, static area sampling in the working environment was performed to determine concentrations of carbon disulfide and hydrogen sulfide.

Carbon disulfide in the air was determined by colorimetric method, in which case, in the presence of carbon disulfide, copper dithiocarbamate in reaction with diethylamineacid and copper sulfate was formed (9). Hydrogen sulfide in the presence of carbon disulfide was determined by spectrophotometry, in which case copper sulfate served as an absorbent (10). Mean value of carbon disulfide determined in the spinning room was 31.14 mg/m^3, with great variations from 0.02 to 268.84 mg/m^3 (median 14.64 mg/m^3). Similarly, hydrogen sulfide mean value is 17.85 mg/m^3 (median 3.09 mg/m^3) with great variations ranging from 0.02 to 343.76 mg/m^3.

Area sampling in the production of viscose showed that mean value of carbon disulfide is 12.25 mg/m^3 (median 10.39 mg/m^3) ranging from 0.02 to 68.28 mg/m^3. For hydrogen sulfide mean value is 0.42 mg/m^3 (median 0.40 mg/m^3) ranging from 0.39 to 0.86 mg/m^3.

Neurological examination

All workers were neurologically examined in the local Medical Health Center, in the little town where viscose rayon factory is located. Cases were diagnosed as Parestesiae cruris when only subjective symptoms were present as :parestesiae, weakness and pain in lower extremities, as well as hypersensitivity on palpation in the muscles of the lower limbs. Polyneuropathy was diagnosed when besides above mentioned sings and symptoms, positive neurological signs were present as: diminished superficial and vibratory sensation and/or diminished or absent muscle tendon reflexes. These diagnoses were indications for sending workers to further neurophysiological tests i.e. electromyoneurography.

Electromyoneurography

Electromyoneurography (EMNG) was performed at the EMNG unit of the Clinical Hospital for Neurology in Belgrade. It was done in a standard manner using concentric needle EMG by "Dissa-1500" apparatus. Examinations were conducted in the constant laboratory air temperature of 25°C, and taking into account the skin temperature.

In electromyography the electrical activity of the m. extensor brevis bill. was studied during maximal and weak voluntary contraction and during muscle relaxation. In the electroneurography, both peroneal nerves were electrically stimulated and the electrical response of muscle is recorded (motor conduction velocity - MCV) or of a nerve trunk i.e. n. suralis (sensory conduction velocity - SCV). The latencies from the stimulus to the response as F wave, were directly measured.

According to these analyses, neurologist especially trained in performing electromyoneurography estimated the existence of motor, sensory or sensorymotor polyneuropathy.

The motor polyneuropathy was established when following signs exist:

- neurogenic muscle damage,
- slowed motor conduction velocity,
- prolonged terminal latencies,
- decreased amplitude of evoked potentials, and
- prolonged latency of F response.

The sensory polyneuropathy was established when following signs exist:

- slowed sensory conduction velocity, and
- decreased amplitude of evoked potentials.

The sensorymotor polyneuropathy was established when both above mentioned signs were present.

RESULTS

After complete neurological examination, 40.2% of workers in the first group were diagnosed as free of neurological diseases and disorders, compared with 89.2% in the second group (table 4). Parestesiae cruris were diagnosed in 18.6% (18 cases) among the high exposed versus only one case in the low exposed, and polyneuropathy in 32.0% (31 cases) versus one case, respectively. Results were disturbing, since more than one half of the workers from the spinning department had neurological changes related to the carbon disulfide (49 spinners, 50.6%). In the same department 3 cases of polyneuropathy connected with alcoholisms and one with diabetes were diagnosed.

The next step in the analysis was to compare the prevalence of neurological signs and symptoms in both groups.

Hypersensitivity on palpation in the leg muscles existed in almost half of the subjects in the first group (49.5%), and in none among the second group (table 5).

Symmetric diminished muscle tendon reflexes were almost equally prevalent among both groups (12.4% versus 10.8%). Absent muscle tendon reflexes were found only among the workers with high carbon disulfide exposure (11.3%). Similar case is for diminished superficial (surface) and vibratory sensations, which were noticed only among the workers in spinning room (46.4% and 39.2% respectively).

Parestesiae. in legs, as a subjective complaints, were almost twice more prevalent in the first (82.5%) than in the second group (43.2%). Pain in the lower extremities were present in 85% among the workers exposed to high compared with 40.5% in the group exposed to low carbon disulfide levels. Similarly is for the complaint of weakness in the legs, which were present in 78.4% in the first group versus 37.8 in second group.

As it was mentioned above, according to the neurological examination, workers were sent to further EMNG testing. Results are presented on the table 6. It can be noticed that in 22 cases among the high exposed group (43.2%) polyneuropathy was diagnosed (more often motor than sensorymotor, but none case of pure sensory polyneuropathy). That means that in the whole study group in spinning room, among the spinners (total 97) before complete EMNG testing in 22.7% polyneuropathy is established.

In the second group, two workers were sent to EMNG testing, and in both cases findings were normal.

When analyzing the relationship between clinically diagnosed polyneuropathy and electromyoneurographically determined polyneuropathy in the first group (table 7) great percentage of normal EMNG findings could be noticed (58.1%). Diagnosis was confirmed in 32.2% (equal prevalence of motor and sensorymotor polyneuropathy). A different situation is when cases with the diagnosis of Parestesiae cruris were analyzed. Normal EMNG findings were present in 44.4% cases, but polyneuropathy was found in more than a half cases (55.53%).

Analysis according to the exposure duration in the first group (table 8) shows that the prevalence of clinically diagnosed polyneuropathy is highest in the group with 20-24 years of exposure, with sharp decrease in the group with 25-29 years of exposure. Electromyoneurographically confirmed polyneuropathy is the most frequent in the group with 15 - 19 years of exposure, also decreasing with the longer exposure duration. It could be due to the selection bias as workers with polyneuropathy were still removed from their working places.

DISCUSSION

Epidemiological studies in workers exposed to carbon disulfide very often reported the high prevalence of different symptoms related to polyneuropathy as parestesiae, muscle pain, muscular weakness etc. (1,2,3,4,11). The majority of conducted studies included the electromyography to confirm the diagnoses of polyneuropathy. The Finnish study on workers in viscose rayon factory (3) found that 48% of exposed men had polyneuropathy i.e. pathologically reduced conduction velocities in two or more nerves, as well as 28% borderline cases. These results are very similar to our findings where at least 43.2% of workers were found to have polyneuropathy diagnosed by EMNG.

Our investigation shows a statistically significant difference in prevalence of clinically diagnosed polyneuropathy as well as in presence of the relevant neurological signs and specific complaints in two examined groups exposed to different carbon disulfide levels. Different factors as age, place of residence and especially alcohol abuse were similarly distributed in both groups, so they did not influenced the results as confounders.

A great percentage of EMNG confirmed polyneuropathy in workers with only hypersensitivity of muscles of lower extremities on palpation and relevant symptoms (55.5%) was found in the high exposed. This finding obliges us to obtain resources for sending the rest of the workers to EMNG testing.

Furthermore, as the investigation is still ongoing, properly selected comparison group must be examined at the same way. To avoid the selection bias, which could be very strong in cross-sectional studies (12), it is planned to include retired workers (both retired at the age for retirement and retired as invalids). This is especially important in evaluation of the prognosis and progression of polyneuropathy, which is not only a scientific but also a very practical problem. According to the experimental studies in animals a tendency for repair and restitution of lost functions existed (1,13,14). However, former studies which investigated the existence of a recovery process after termination of carbon disulfide exposure in workers all concluded negatively (2,3,15). Exception is the study conducted in Japan, in workers exposed to CS2, where clear existence of recovery after cessation of exposure was found, but probably due to the low level

exposure and low mean age of the workers (16). In the Finnish study abnormal neurophysiological findings were still noted even in men who stopped working with carbon disulfide 10 years ago (2). So, the attempt must be made to resolve this problem, especially knowing that in the past workers were exposed to somewhat higher carbon disulfide levels.

Table 1: Prevalence of alcohol consumption is both examined groups

frequency	G R O U P S high exposed N	%	low exposed N	%
every day	28	28.9	12	32.4
at least once a week	27	27.8	14	37.8
at least once a month	5	5.2	2	5.4
rare	24	24.7	6	16.2
never	13	13.4	3	8.1
total	97	100.0	37	100.0

Table 2: Prevalence of amount of plum brandy drunk per week in both examined groups

plum brandy glasses	G R O U P S high exposed N	%	low exposed N	%
none	35	36.1	10	27.0
up to 4	22	22.7	11	29.7
5 to 9	9	9.3	11	29.7
10 to 19	20	20.6	4	10.8
more than 20	11	11.3	1	2.7

Table 3: Frequency of being drunk in both examined groups

being drunk	GROUPS high exposed N	%	low exposed N	%
never	28	28.9	8	21.6
a week ago	5	5.2	2	5.4
a month ago	12	12.4	5	13.5
a year ago	19	19.6	5	13.5
more than a year ago	33	34.0	17	45.9

Table 4: Established diagnoses after neurological examination

Diagnosis	GROUPS high exposed N	%	low exposed N	%
free of disease	39	40.2	33	89.2
Parestesiae cruris	18	18.6	1	2.7
Polyneuropathia	31	32.0	1	2.7
Polyneuropathia alcoholica	3	3.1	-	-
Polyneuropathia diabetica	1	1.0	-	-
Other	5	5.2	2	5.4

Table 5: Prevalence of the neurological signs and symptoms in both examined groups

signs and symptoms	GROUPS high exposed		low exposed	
	N	%	N	%
hypersensitivity on palpation in the leg muscles	48	49.5	-	-
diminished muscle tendon reflexes	12	12.4	4	10.8
absent muscle tendon reflexes	11	11.3	-	-
diminished superficial sennsations	45	46.4	-	-
diminished vibratory sensations	38	39.2	-	-
parestesiae in legs	80	82.5	16	43.2
pain in the legs	83	85.6	15	40.5
weakness in the legs	76	78.4	14	37.8

Table 6: Results of EMNG testing in both groups

diagnosis	GROUPS high exposed N	%	low exposed N	%
normal	28	54.9	2	100.0
motor polyneuropathy	14	27.5	-	-
sensorymotor polyneuropathy	8	15.7	-	-
other findings	1	2.0	-	-

Table 7: Relationship between clinically diagnosed and EMNG determined polyneuropathy in the high exposed group

EMNG finding	clinical diagnosis Parestesiae cruris N	%	Polyneuropathy N	%
motor polyneuropathy	8	44.4	5	16.1
sensorymotor polyneuropathy	2	11.1	5	16.1
other findings	-	-	1	3.2

Table 8: Polyneuropathy and expcsure duration in the high exposed group

Exposure duration		Diagnosis: clin. dg. polyneurop.	clin. dg. pares. cruris	EMNG dg. polyneurop.
5 - 9 years	N	5	1	4
	%	16.1	5.6	18.2
10 - 14 years	N	1	5	4
	%	3.2	27.8	18.2
15 - 19 years	N	7	8	8
	%	22.6	44.4	36.4
20 -24 years	N	16	4	5
	%	51.6	22.2	22.7
25 -29 years	N	2	-	1
	%	6.5	-	4.5

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Exposure to organic solvents and pregnancy outcome

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Introduction

Although the relationship between occupational lead exposure abd increased miscarriage and still birth rates has been known since the late 19th century, it was not until the 1970s that other occupational exposures were studied regarding possible reproductive failure. A number of epidemiological studies on spontaneous abortions among females exposed to anaesthetic gases were carried out (1). Other studies in that decade of reproductive effects from occupational exposure concerned laboratory work (2), metal industry (3) and chemical exposures such as hexaclorophene (4), vinyl chloride (5) and styrene (6). In 1990, approximately 100 papers have been published about occupational reproductive epidemiology, and in many of these effects from exposure to organic solvents were studied. In this paper a short review on studies about this kind of exposure and fetal damage is presented.

An environmental exposure may affect the embryo or fetus before as well as after conception. A mutational event in the male or female germ cells can result in maldevelopment or death of the embryo. After conception the agent may reach the embryo or fetus via the placental circulation leading to one or several effects such as spontaneous abortion, perinatal death, reduced birth weight, preterm birth, malformations, growth retardation and mental dysfunctions.

In addition to the level of exposure, the timing of exposure must be taken into consideration in the epidemiologic studies. The first trimester is the most relevant period in studies of spontaneous abortions and malformations, while exposure during the second and third trimesters must be considered when dealing with birth weight or length of gestation as end points.

There are several reasons why exposure to organic solvents have been studied with regard to reproductive failure. They dissolve lipids and high-molecularweight compounds, and it is thus likely that many organic solvents reach the placenta and the fetus. This has also been demonstrated in animal studies (7). In addition, animal tests have shown that organic solvents can induce malformations, growth retardation and

embryonal death (8). Another reason why research in this area was intensified was that clusters of spontaneous abortions and malformations were reported among laboratory employees in the 1970s. Today there are many epidemiologic studies on solvent exposure and outcome of pregnancy in the literature in other occupations such as painting (9), dry cleaning (10), graphic work (11), work in plastics industry (12), rubber industry (13) and microelectronics industry (14).

Pregnancy outcome among laboratory workers

In the fall, 1977 a female safety delegate in a quality control unit at Astra pharmaceutical industry directed attention to a suspected increase in the number of miscarriages and malformations among women employed in the laboratory. The suspicions were confirmed (15), and several studies about laboratory work and pregnancy outcome were carried out after this report (16-20). An increased frequency of abortions and malformations was found in all of these, and exposure to organic solvents was often suggested as a possible cause of the increase. In two studies (18, 20) the number of intestinal malformations was elevated.

These results gave rise to a case-control study on the relationship between gastrointestinal atresia and occupation during pregnancy (21). Seven of the 201 mothers of the cases were working in laboratories. The expected number was 1.9.

In two other Swedish studies, (22, 23), questions about exposure to organic solvents were included in a questionnaire to women engaged in laboratory work. One of the studies was a case-control study within a cohort. Nine out of the 26 cases (major malformations or perinatal deaths) and 16 out of the 50 controls reported exposure to organic solvents during the pregnancy.

The other study was a cohort study among university laboratory employees. When the 1160 pregnancies were divided into those with and without exposure to organic solvents during laboratory work, a slightly increased but not significant, difference in the rate of spontaneous abortion was found. No differences in birth weight, perinatal death rates or the prevalence of malformations were found between infants whose mothers reported exposure to solvents and those who did not.

In a Danish study carried out at the same time, no increase in the spontaneous abortion rate among laboratory workers exposed to solvents was found (24). In another study from Denmark, no increased risk of malformations of the gastrointestinal tract, extremities or oral clefts was found for children of laboratory workers (9). Nor there was any increase in defects of the central nervous system in occupations where solvents were used. In Finland, a slightly increased risk of spontaneous abortions was observed among Finnish laboratory assistants (OR=1.3) (25).

The results from these questionnaire studies among laboratory workers are thus inconsistent. One possible reason is that laboratory work may involve exposure to other chemicals than organic solvents. Differences in the intensity of exposures and types of solvents may also explain some of the inconsistency. Some of the studies were initiated after an observation of a cluster. The inclusion of the cluster in the study may have biased the result. It is also known that information in questionnaires about spontaneous abortions were verified from hospital records only in a few of the studies. As reporting bias has been indicated in one study, among laboratory workers (23), verification of pregnancy outcome as well as exposure seems to be of great importance.

Pregnancy outcome and solvent exposure in other occupations

Maternal exposure

An increased odds ratio of spontaneous aborations have been reported among women exposed to solvents in the pharmaceutical industry in Finland (26). The information about occupational exposures was collected from questionnaires completed by the occupational physician or nurse at the factory. The number of solvents used as well as exposure to methylene chloride was associated with increased odds ratios.

Exposure to tetrachloroethylene and pregnancy outcome among women working in dry-cleaning shops has been studied in Sweden (27) and Finland (10). In the Swedish study, the odds ratio for tetrachloroethylene exposure in the total material was 1.1. However, only a few pregnancies were highly exposed. In the Finnish study high exposure was associated with an increased risk of spontaneous abortion (OR=3.6). When data from the two studies were pooled, operating dry-cleaning machines at least several hours every week was associated with adverse pregnancy outcome. It is thus possible that peak exposures are more harmful to the fetus than a low long time exposure.

In a recent Finnish case-control study among women previously biologically monitored for solvents, the exposure classification was made upon the basis of work description, the use of solvents as reported in questionnaires and biological exposure measurements (11). The odds ratio of spontaneous abortion for solvent exposure in general was significantly increased. The increase was most consistent among workers exposed to aliphatic hydrocarbons and for exposed graphics workers. Also toluene exposed shoeworkers showed a significantly increased odds ratio.

In a large case-control study of malformations in Montreal, McDonald et al. reported that exposure to aromatic solvent showed a clear excess in a matched pair analysis, most evident in the urinary tract group (28). Most of the excess was associated with toluene exposure.

Exposure to unspecified organic solvents had previously been reported to increase the risk of defects of the central nervous system (29) and oral cleft (30). These two case-control studies were based upon material from the Finnish Register of Congenital Malformations. The women were asked in a personal interview to describe their work during the first trimester of the pregnancy. A third study, in part from the same register, showed an increased risk of ventricular septal defect after exposure to organic solvents during the first trimester (31).

In 1989, Ahlborg et al. (32) published results from the first prospective study on occupational exposure and pregnancy outcome. Among 3901 women who worked during pregnancy 115 reported exposure to organic solvents. The rate of spontaneous abortions and perinatal deaths was somewhat lower in this group in comparison to a reference group, and the women exposed to solvents gave birth to heavier infants than the unexposed women.

Paternal exposure

A few studies are published in which paternal exposure to organic solvents has been associated with unfavourable outcome of pregnancy. Savitz et al. (33) reported in a case control study that exposure to benzene was associated increased risk of small for gestational age. No effect was found on the risk of still birth. Previously, Olsen reported that infants whose father was a painter had a five-fold increased risk of congenital malformations in the central nervous system (9). Also an increased risk of spontaneous abortions has been reported after male exposure to organic solvents in general as well as high or frequent exposure to toluene or miscellaneous organic solvents (34).

Discussion

There are several things that must be considered in the interpretation of all these studies.

In addition to the previously discussed limitation that many of the studies during the 1970-ies and beginning of 1980-ies were small and that the pregnancies were not verfied, uncertainly in exposure classification is a problem in many studies. Biological monitoring during pregnancy or other measurements of exposure are rare. The classification of exposure is often based upon information from interviews or questionnaires, and in many cases the interview is made long time after pregnancy. The possibility of recall bias, but also a general underestimation of exposure must thus be considered. Both Ahlborg (27) and Lindbohm et al. (11) have shown underestimation of solvent exposure, leading to bias towards the null-hypothesis.

The dissimilarities in results between the studies can (in addition to chance alone) be due to different exposure levels. This seems to be a likely explaination to the different results in the studies of tetrachloroethylene exposure. It is also not unlikely that exposure levels in laboratories were higher 10-15 years ago than today. This could explain why so many studies made at that time showed significant associations.

In conclusion, exposure to some specific solvents seems to increase the risk of some types of adverse pregnancy outcome. Although occupational exposure to solvents quantitatively has little importance for risk of spontaneous abortion or malformation, an individually high exposure may be harmful.

There are thus reasons to continue the research, both in epidemiological and experimental studies to shed light on reproductive toxicity of solvent exposure.

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BENZENE, TOLUENE AND XYLENE IN AMBIENT AIR AND THEIR METABOLITES IN URINE OF EXPOSED WORKERS IN DIFFERENT INDUSTRIES

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The aim of this papir was to find out concentrations of aromatic hydrocarbons in ambient air of different industries, and concentrations of their metabolites in the urine of exposed workers. In paintshop of furniture industry, leather fancy goods gluing line, laboratories in oil industry and oil rafinery concentrations of benzene, toluene and xylene in the air were determined by means of gas chromatography. At the same time gaschromatographic and spectrophotometric methods were applied to determine phenol and hippuric acid, respectively, in urine of 137 exposed workers (devided in three groups according to concentrations of benzene, toluene and xylene in ambient air of their working places, and the relation of these concentrations). Results obtained were compared with the results of 49 healthy persons, not exposed professionally to aromatic hydrocarbons. The highest benzene concentrations in the air were determined in oil industry laboratories, where concentrations of phenol in urine were the highest as well. Toluene concentrations were the highest in the furniture factory (manually spraying division) followed with the highest concentrations of hippuric acid in urine. Xylenes were found on a few places, and in much lower concentrations. Average concentrations of phenol and hippuric acid in urine were statistically significantly higher in all three groups of exposed workers then in controls. Concentrations of air-borne aromatic hydrocarbons, predominantly in the form of aerosols, were found to be the highest in the furniture factory paintshop, were spraying was done manually. By parallel sampling of air on charcoal tubes with and without a material for speciale protective masks, it was found that these maske stoped over 60% of aromatic hydrocarbon aerosols.

Introduction - Great number of workers is exposed to benzene, toluene and xylene on their working places. These compounds, having very similar chemical structure but different metabolic pathways and

toxic effects, differ a lot in Maximum Allowed Concentrations (MAC) in the air of working places (1). This fact imposes the necessity of determining individual concentrations of these compounds out of mixture in industrial atmosphere. Gas chromatography is an analytical method that offers parallel analysis by sampling air on activated charcoal, silica gel or some other adsorbents (2,3).

In order to find out a possible risk for health it is necessary to determine concentrations of metabolites in biological samples of exposed workers. Experiments on animals exposed to benzene containing (^{14}C) showed out that biotransformation goes towards formation of phenol, which has a toxic effect on hematopoietic system, and is eliminated by urine. There are many papers on volonteers or workers exposed to toluene that consider hippuric acid to be one of the main metabolite (5,6,7).

We have not found any reference regarding determination of benzene, toluene and xylene in air by means of gas chromatography in Yugoslavia. In order to find out exposure level we determined concentrations of benzene, toluene and xylene in the air in different industries. We also determined urine phenol and hippuric acid concentrations in workers working at investigated working places in order to find the correlation between concentrations of aromatics in the air and there metabolites in urine.

Material and methods

Air analysis - Air concentrations of benzene, toluene and xylene were determined by gas chromatography on working places in furniture factory paintshop, leather fancy goods gluing line and oil industry laboratories and on 10 open air places in oil rafinery. Air samples (1-5 l) were collected on activated charcoal tubes (Casella, London) and desorbed in laboratory with 1 ml CS_2 (Alkaloid, Skopje). Half an hour later 2 /ul of solution was analysed by gas chromatography on Hewlett-Packard 5830 A, and column: 1,8 x 1/8", SS,10% Carbowax 20 M on Chrom W-AW DMCS,80-100 mesh:

Injector temperature: 150°C,
Column temperature : 60°C,
Detector: flame ionisation, 150°C,
Carrier gas: Nitrogen, at 15 ml/min.

Urine analysis - Phenol and hippuric acid concentrations were determined in urine collected next morning after the working day of 137 exposed workers divided in three groups according to the level and relation of benzene and toluen concentrations:

I - paintshop in furniture factory and leather fancy goods gluing line (30 workers),
II - Oil rafinery (69),
III - laboratories in oil industry (38).

The results obtained were compared with those of control group, consisting of 49 health, adults, not exposed professionally to aromatic hydrocarbons. Examined groups of workers did not vary statistically significantly by age (x^2=0.114; $p > 0.05$) and sex ($t = 0.711$; $p > 0.05$).

Phenol in urine was determined by hydrolise of 5 ml urine with 1 ml $HClO_4$ (Merck, Darmstadt) for 30 min. at water bath 95°C, extracted with 3x2 ml of diethylether (Kemika,Zagreb), dried with anhydrous Na_2SO_4 (Merck, Darmstadt). 1 µl of extract (final volume 2 ml) was analysed by gas chromatography on the same apparatus, column as air analysis and following conditions:

Injector temperature: 200°C
Column temperature : 170°C for 3.2 min, programed to 190°C at 10°C/min.
Detector:flame ionisation, 225°C,
Carrier gas: nitrogen, 30 ml/min.

Hippuric acid was determined by Ogata method (8) with pyridine and benzensulphonylchloride and spectrophotometric measurement on Perkin Elmer-Lambda 15 instrument.

To evaluate results we used statistical methods of central tendency (average - $\bar{x}$, standard deviation - SD, and

coefficient of variation - CV), level of statistical significance (x^2 and t-test) and centile.

Results

Average benzene air concentrations determined in all examined industries were below MAC in Yugoslavia (50 mg/m^3), but maximum values in some laboratories in oil industry exceeded it several times. In these laboratories workers were dealing with reagent grade chemicals such as benzene and toluene.

Average toluen air concentrations in paintshop of furniture factory and on gluing line in leather fancy goods factory were about two times higher then MAC in Yugoslavia (200 mg/m^3). In ten air samples collected in oil rafinery in open air we determined benzene in concentrations below 0.150 mg/m^3, and toluene and xylene were not determined. Xylene concentrations in air on working places were significantly higher (618 mg/m^3) only in furniture factory where the smaller furniture pieces were sprayed manually. In all other samples xylene was present only as impurity. Concentrations of benzene and toluene in the air are shown in Table 1.

Phenol concentrations in urine for all exposed workers, and for each above group separately were statistically significantly higher in comparison with the control group. Extremely high phenol concentrations (over 3000 /umol/l) were determined in urine of laboratory workers in oil industry (Table 2).

Hippuric acid concentrations were higher in the exposed group comparing to the controls, and the highest ones were on average in the group working on painting and gluing,where toluol concentrations in the air were found to be the highest (Table 3).

Concentrations of airborne aromatic hydrocarbons, predominantly in the form of aerosols, were found to be the highest in the furniture factory paintshop, where spraying was done manually. By parallel air sampling in tubes with and without protective masks, it was found that mask stoped over 60% of hydrocarbon aerosols.

Discussion

Benzene is considered to be highly toxic chemical agent and its MAC values are recommended to be reduced in many countries. There are not many papers about professional exposure to benzene, concentrations of phenol in urine of exposed workers and correlation of these two parameters. There are more papers about toluene exposure of workers and the relation of air concentrations and hippuric acid concentration in urine, but the results are not easy to compare because of different analytical methods applied (9).

Concentrations of benzene, toluene in the air samples from different industries determined by means of gas chromatography showed the necessity of such determinations. We have found that laboratory workers in oil industry, dealing with reagent grade chemicals, are highly exposed to benzene. Urine phenol concentrations in some workers of this group suggest that they might have been exposed even to higher concentrations of benzene. According to our results average concentration of phenol in urine of 36 controls was 50.0 μmol/l, and that being in agreement with 48.9 μmol/l determined by Angerer (10) for normal population by means of gas chromatography. Average concentration of phenol for a group of laboratory workers in oil industry was ten times higher than in control group and the higher exposure to benzene the higher concentrations of phenol in urine was. Gas chromatographic determination of phenol in urine is shown to be sensitive and selective method and should be included in periodical health check-ups of workers suspected of beeing exposed to benzene.

Workers on painting and gluing lines were exposed mostly to toluene, especially where, smaller pieces are sprayed manually, and concentrations were over 2000 mg/m^3. Hydrocarbons were present there mostly as aerosols and we found that the proposed protective masks would be both useful and comfortable.

Hippuric acid in urine in exposed workers was statistically significantly higher comparing to controls but not as high as some authors reported for such exposure to toluene (9). In our

opinion low solubility of hippuric acid is to be blamed for it. Spectrophotometric method for hippuric acid determination is not very specific test for toluene exposure, but can be very useful as an index of total exposure to aromatic hydrocarbons.

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Table 1. CONCENTRATIONS OF BENZENE AND TOLUENE IN AIR OU EXAMINED WORKING PLACES

Sampling places	n	Concentrations (mg/m^3)					
		Benzene			Toluene		
		$\bar{x}$	SD	Range	$\bar{x}$	SD	Range
Furniture factory paintshop	12	47.4	42.03	9.3 - 138.6	404.0	643.03	47.6 - 2373.8
Fancy leather goods-gluing line	9	32.1	20.31	5.6 - 71.3	360.1	265.56	51.5 - 794.0
Oil industry labaratories	8	37.1	89.50	Ø - 258.0	62.1	157.47	Ø - 451.0
Oil rafinery (open air samples)	10	0.05	0.044	Ø - 0.15		Ø	

n - number of places

$\bar{x}$ - mean value

SD - standard deviation

Table 2. PHENOL CONCENTRATIONS IN URINE

	Group of workers	Number	Concentrations (µmol/l)			
			$\bar{x}$	Range	SD	CV	C
Exposed workers	T o t a l	131	247.39	0 - 3808	499.2346	201.80	-
	I Gluing and painting	29	96.69	29 - 220	50.6205	52.35	40.13
	II Oil rafinery	65	130.89	0 - 878	166.8741	127.44	51.98
	III Oil industry - laboratories	37	536.60	34 - 3808	838.9217	156.34	17.33
	Controls	36	50.00	15 - 175	35.5906	71.18	84.48

$\bar{x}$ - mean concentration
SD - standard deviation
CV - coefficient of variation
C - centile at normal value of 85 µmol/l

Table 3. HIPPURIC ACID CONCENTRATIONS IN URINE

		Group of workers	Number	Concentrations (mmol/l) $\bar{x}$	Range	SD	CV	C
Exposed workers		Total	137	8.28	2.06 - 22.92	5.2826	65.38	-
	I	Painting and gluing	30	10.94	4.29 - 22.92	5.3847	49.22	24.03
	II	Oil rafinery	69	7.07	2.06 - 15.60	4.3812	62.00	53.72
	III	Laboratories in oil industry	38	8.26	2.88 - 16.90	6.9284	83.87	50.40
		Controls	49	5.32	1.95 - 11.96	2.1575	40.55	70.71

$\bar{x}$ - mean value

SD - standard deviation

CV - coefficient of variation

C - centile at normal value of 5,6 mmol/l

OCCUPATIONAL AND ENVIRONMENTAL EXPOSURE TO BENZENE IN SWEDEN

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Today there is no industrial use of benzene in Sweden. It is many years since benzene was used as solvent in paints and glues. Benzene has also been used to denaturate technical ethanol for industrial use.

Benzene is produced in small quantities in Sweden, mainly as a by-product in the coke-oven process at steel mills. Steamed cracked naphta with a benzene content of more than 30 % (v/v) is produced at an ethylene plant on the west coast of Sweden. All of the production is exported for further refining.

Although, there is no commercial production of benzene and no large benzene consuming industry in Sweden, benzene is present at many work places where petrochemical products with varying benzene content are used. Because of the high proportion of benzene in Swedish petrol, max 5 % (v/v), many workers are exposed to benzene originating from evaporated fuel and exhaust gases (1).

We have been studing the exposure to benzene at some crucial places along the Swedish distribution chain of petrol (2). The major sources of hydrocarbonemission to the environment are shown in table 1 (3).

The occupational exposure to benzene has been studied at the following work places

- crude oil tanker
- petroleum refinery
- petrol distribution at terminals
- petrol pump services
- garage workers
- tank cleaning
- drivers
- road workers
- work places near busy traffic

The exposure (8 h TWA) at some of the work places are summarized in table 2.

The exposure during the whole workday to benzene is at most work places low, mostly below the Swedish occupational standard (3,0 mg/m^3).

There are, however, still several work places with high exposure to benzene during short periods. High exposure to benzene during short periods have been detected at the following work places.

- Refinery workers at crude oil unit
- Refinery workers at laboratory
- Tanker crew during loading operation
- Top loading of rail and road tankers at terminals
- Petrol pump services
- Garage workers, especially fuel injection adjustment and petrol tank drainage

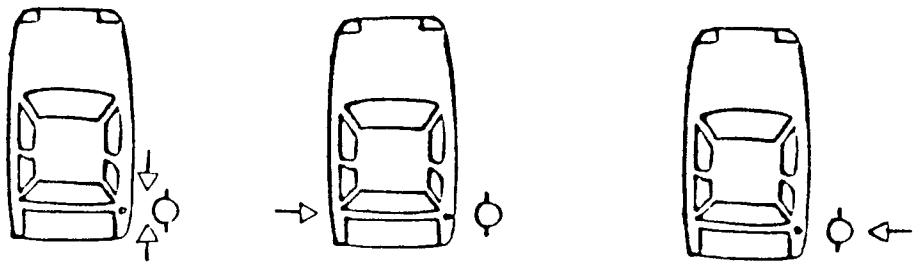
The exposure for these workers may well for a short period (15 min) exceed the STEL (16 mg/m^3). Exposure to several hundred mg/m^3 of benzene have been measured for tanker crew working with manual sounding. The highest concentration was obtained during the very last phase of the loading when the tanks were topped up.

One of the major emission sources of petrol vapour to the environment is service stations as earlier shown in table 1 . We have investigated the exposure to benzene when filling up cars at service stations (4). The influence of the following factors has been studied.

- Type of station (open or enclosed)
- Type of car
- Wind directions
- Wind speed
- Temperature
- Filling time
- Time of year (winter/summer)
- Octan index of the petrol

More than 200 samples were taken during regular filling of the car by the customers at self-service stations. The levels of benzene in the breathing zone of the refueller varied very much. The highest exposure was 26.3 mg/m^3 for a 2 minutes period and the lowest was below 0.01 mg/m^3 during the entire filling time.

The most important factor influencing the exposure was the wind direction in relation to the refueller locations. The influence of the wind direction in relation to the refueller on the exposure to benzene was studied at three different situations shown in figure 1. The result from the measurements are shown in table 3.



Case A Case B Case C

Figure 1. Wind directions in relation to the refueller.

The highest exposure was reached when the refueller had the wind in his/her back (Case C). At that situation the plume of vapour from the tank filling pipe is able to reach the breathing zone undisturbed.

The same situation was found when filling up vans, see table 4. Here to the plume of petrol vapours transported to the breathing zone is more or less undisturbed.

During the last years there has been a debate in Sweden about introducing vapour recovery systems at service stations (5). We have investigated the effect of a vapour recovery system on the exposure to benzene. The results are shown in table 5.

The results show that the exposure of benzene can be lowered with more than 85 % with such systems. Vapour recovery is now being rapidly introduced at Swedish service stations, mostly as a result of demands concerning environmental hazards.

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Tables

Table 1. Hydrocarbon emission during petrol distribution. Throughput 5,1 milj m^3/year.

Source	vol % of throughput	m^3/year
Refinery transport filling	0,018	918
Emission during terminal storage	0,045	2 295
Road tanker loading	0,054	2 754
Service station tank filling	0,16	8 100
Car filling	0,18	9 180
Leaks and spills	0,02	1 071
Total	0,48	24 378

Table 2. 8 h TWA exposure levels at some work places to benzene.

Work places	Benzene (mg/m^3)
Crude oil tankers	0,1 - 2
Petroleumrefinery	0,1 - 2
Petrol distribution	0,1 - 30
Petrol pump services	0,1 - 5
Garage workers	0,1 - 7
Tank cleaning	0,1 - 0,2
Drivers	0,01 - 0,1

Table 3: Exposure to benzene at different wind directions, (95 % CI).

Wind - direction	Number of samples	Benzene mg/m^3	
Case A	112	0,51	(0,39-0,67)
Case B	17	0,49	(0,20-1,2)
Case C	46	2,4***	(1,5-3,7)

*** = $p < 0,001$ (Case C versus case A or case B)

Table 4. Exposure to benzene when filling different types of cars, (95 % CI).

Type of car	Number of samples	Benzene mg/m^3	
Sedan	124	0,60	(0,45-0,81)
Van	51	1,34**	(0,85-2,1)

** = p<0.01

Table 5. Exposure to benzene at petrol stations with and without vapour recovery system, (95 % CI).

Type of stations	Number of samples	Benzene mg/m^3	
With recovery	30	0,13	(0,08-0,21)
Without recovery	175	0,76***	(0,59-0,98)

*** = p< 0,001

COMPENSATION
for occupational diseases (Sweden, 1977)

Gunnar Thiringer, M.D., associated professor

Occupational disease in Sweden

"All diseases or damages, that can be attributed to the work environment are called occupational diseases"

Before 1977 we had a list of occupational diseases and also a list of dangerous factors of the work environment.

The **judgement** includes two steps:

Step 1: There has to be some knowledge that a certain factor of the working environment causes the disease in question.

If so proceed to:

Step 2: The disease shall be looked upon as caused by that factor, if considerably stronger reasons do not speak against a connection.

The **decision** whether the disease is an "occupational disease" or not is made **by a panel** of lay assessors, such as representatives for politicians, unions and employers.

Loss of income
Law. National social insurance

Loss of body function
Agreement.

Insurance provided by
negotiations between
the **employers'** and
the **employees'**
organisations

Loss of income

"The injured person is guaranteed
unchanged economic conditions"

Ex.	Yearly income before the damage	100 000 SKR
	Present income	70 000 SKR
	The difference is payed by National insurance	30 000 SKR

Loss of body function

Calculated after the degree of **DISABILITY.**

Ex. A 50 year old man with a moderate damage
e.g. resulting in 20 % medical disability,
will get approx. 45-50.000 SEK single payment, free from tax.

In different cases there may be additional payments.

CEREBRAL FUNCTIONS AND ORGANIC SOLVENTS

Gunnar Thiringer

Exposure to organic solvents is known to cause acute intoxication if exposure is sufficiently high. During the last decade chronic effects have also been associated with long-term exposure. There are epidemiological studies indicating that occupational groups with heavy exposure to organic solvents, e.g. painters, varnishers and carpet layers, were suffering from neuropsychiatric disorders nearly twice as often as non-exposed workers. Psychological testing of workers exposed to solvents during long time frequently shows impaired CNS-function. Especially are there difficulties in memory and concentration as well as impaired perceptual and psychomotor speed and accuracy.

There is no throughout clear definition of this disease. The diagnosis, "chronic toxic encephalopathy" is based on **clinical** and neuropsychological evaluation and if needed neurophysiological examinations. The symptoms of a "typical" patient are increased fatigue, memory impairment, concentration difficulties and personality changes such as passivity. Sometimes the patient also complains of headache, dizziness, paresthesia, muscular pain or diminished strengh. Characteristic is the lack of specific neurological symptoms and a slow progress over time. Vague symptoms such as tingling and prickling sensations and even restless legs may indicate neuropathy and should be carefully noted when examining individuals exposed to solvents. These symptoms are rare.

Psychometry is the only method that can give "objective" measures regarding disturbance of cerebral function. It is very important to choose proper tests. Swedish psychologists have collaborated to design a test-battery applicable for both clinical practice and group studies on effects of occupational exposure to organic solvents. The test were assembled from different clinical test-batteries, e.g. that of Wechsler adult intelligence scale. A general intellectual reduction is rarely seen. Reduction of memory and perceptual capacities are "typical" as of psychomotor performance but not of

spatial ability.

Neurophysiological examinations such as nerve conduction velocity may be useful if a peripheral neuropathy is suspected. EEG has been used but there is no typical abnormality seen. If the EEG is abnormal other causes than exposure to solvents should be looked for. CT (computor tomography) and CBF (cerebral blood flow) are also useful in looking for differential diagnoses, such as Mb Alzheimer, Mb Pick and multi-infarct dementia.

It is very important to take into consideration various **differential diagnoses**, as chronic toxic encephalopathy in fact is rare. Most of our referred patients have acute, reversible symtoms or other diseases. Examples are alcoholism, endogenus depression, generalized arteriosclerosis, infectious encephalopathy (Borrelia, HIV, mononucleosis), brain-tumours, multiple sclerosis, stress, lead, mercury, hypothyreosis and lack of B_{12}-vitamin or folic acid.

An essential task for us is to identify, measure and evaluate the **exposure**. Occupational hygienists have interviews with many patients and visit several work places in order to get a solid picture of the situation. Measurements - solvents in air - are also performed. We believe that the exposure time must be at least 10 years full time at a level of threshold limit value for development of chronic toxic encephalopathy.

Neuropsychiatric disorders due to long-term exposure to solvents may thus be accepted as an occupational disease in Sweden. Patients beeing evaluated for suspected solvent related diseases now constitute one of the largest groups of patients seen at the Swedish clinics of occupational medicine. However, only 10 - 15 % of all suspected cases fulfill our criteria.

THE INFLUENCE OF LOCAL VIBRATIONS ON THE SERUM PROTEIN LEVEL AND IMMUNOGLOBULIN

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INTRODUCTION

There are numerous reports in the literature informing about the changes in the synthesis of proteins under influence of vibrations, changes in the capillary vessels permeability in cases of vibration disease, changes in the electrophoretic mobility of serum proteins, as well as for the causality between the blood viscosity and the level of α_1,α_2 and globulins that Carpentier, 1981 relates to the changes in microcirculation.(5) On the other hand, more frequently appear literary reports on clinical-immunologic changes with vibration disease (3), reduced general immunologic reaction of patients suffering vibration disease (12), influence of vibrations over immunological response induced with timus-dependant and timus-independant antigenes (6), changes of certain ferments in the correction of the immune response during vibrations (9), about direct effect of vibrations over humoral and cell factors of the immunity (2), as well as the usage of vitamins A and E for correction of the immune response during vibrations (lo).

The reports about the level of immunoglobulins IgG, IgA and IgM, induced us to carry out investigations on serum proteins and the level of immunoglobulins IgG, IgA, IgM, on workers professionally exposed to vibrations (4,8).

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MATERIAL

The investigation was carried out on a group of workers, working on manual forming of molds, in 3 different factories in Macedonia, in the field of metalworking and fireproof materials industry. The source of the local vibrations are the manual percussion rammers used by the workers while ramming the mold mixture into the molds of different shapes and dimensions.

This job is done in upright position of the body, for 8 hours a day. While doing this, the workers do not use any personal protective devices.

In order to avoid discrediting data of the investigation, all the workers with pathological conditions were eliminated during the investigation.

A group of 79 examinee was formed, at average 36.2 years of age and average professional exposure time of 1o.2 years.

The table no.1 shows the distribution of examined group of workers, the average age and professional exposure time.

Table 1. Distribution of examined group of workers according to the age and professional exposure time.

Group	Examinees Number	%	Age	Prof.exposure Rank	$\bar{X}$
I	25	31,6	31	1-5	3,36
II	22	27,8	33	6-1o	7,8o
III	2o	25,3	38,6	11-15	13,2o
IV	12	15,2	49,2	16-2o	25,7o
	79	1oo,o	36,2	1-33	1o,2o

The control group of 31 workers is defined according to the appropriate criteria.

METHODS

During the investigation, first were determined the relevant ecology parameters in the working environment as follows:

1. Microclimate (air temperature, relative humidity, airstream speed and real temperature).
2. Total noise level and spectral analysis of noise by means of precise Sound Level meter Bril Kjaer.
3. Defining the acceleration of vibrations at o,5;1;2;4;6;16;32; 63 and 125 Hz frequency by means of vibrometer Robotron ooo42.

The results show the mean value of total measurements.
The results are in accordance with the current standards, and for the vibrations, the recommendations of ISO 5349 are used.
The following investigations were made on workers from the examined and control group:
- electrophoresis of serum proteins on cellogel tapes.
The values are expressed in %.
- determining the immunoglobulin IgG, IgA and IgM by the single radial diffusion method. The values are expressed in g/l.

RESULTS

The results of the carried out microclimate measurements showed in table 2, show that the microclimate factors are in accordance with the recommended standard values.

Table 2. Results of the microclimate measurements

Values	Temperature °C	Relativne humidity %	Airstream speed m/s^2
Measured	16	50,o	o,o6
Allowed	14-18	75,o	o,o5

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The results of the noise measurements, showed in table 3., show that the noise is within tolerance.

Table 3. Results of noise measurements

Values	Total noise Db	Noise level (Hz)					
		31,5	63	125	25o	5oo	1ooo
Measured	89	8o	82	84	82	81	78
Allowed	9o	113,3	1o2,5	95,9	91	87,6	85

The results of the measurements of the vibration acceleration in different frequency ranges, are showed in Fig.1.

The results show that according to the ISO 5349, the vibrations with frequency of 1o-16 Hz, have rather bigger acceleration than the recommended one.

In such a case of professional risk in the working environment, we got down to laboratory data processing.

The table no.4 shows the results concerning the mean values of albumins, α_1, α_2, β and γ protein fractions in the serum of the examined and control group.

Table 4. Mean values of protein fractions in electrophoregram of workers of both examined and control group

Group	Albumins $\bar{X} \pm$ SD	$\bar{X} \pm$ SD	$\bar{X} \pm$ SD	$\bar{X} \pm$ SD	$\bar{X} \pm$ SD
Examined	59,3 3,2	3,1 o,7	8,o 1,3	1o,8 1,9	18,6 2,5
Control	61,o 1,6	3,8 o,7	8,1 1,2	1o,6 1,2	12,7 5,o
T-test	2,57	3,47	1,2	1,57	6,3
p	<o,o5	<o,o5	>o,o5	>o,o5	<o,o5

The results show that the mean values of albumins and α_1 fraction are statistically rather lower, and of γ higher in relation to the control group.

We tried to find out whether there are statistically important differences in the mean values of the examined parameters depending on the professional exposure time, in the examined group of workers.

Table 5. Mean value of protein fractions in the electrophoregram of examined group of workers, depending on the professional exposure time (PET)

PET	Alb.	α_1	α_2	β	γ
≤ 5	57,4	3,1	8,3	11,3	19,6
6-1o	58,8	2,8	8,2	1o,6	19,2
11-15	59,2	3,4	7,8	11,2	18,3
≥ 16	6o,1	3,1	8,1	1o,4	18,2
LSD o,o5	3,4	o,9	1,4	2,3	3,1

The results show that the mean values of albumin fraction are statistically rather higher in cases when the professional exposure time is longer than 16 years in relation to those with professional exposure time up to 5 years.

The rest of the examined parameters do not show important statistical variations in relation to the professional exposure time.

In continuation, we got down to determining the level of immunoglobulin IgG, IgA and IgM in the examined and control group of workers.

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Table 6. Mean values of IgG, IgA and IgM in the examined and control group of workers

Group	IgG		IgA		IgM	
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
Examined	15,8	3,6	2,8	o,8	1,6	o,4
Control	14,1	2,7	2,3	o,7	1,9	o,5
T	2,5		3,1		3,3	
P	<o,o5		<o,o5		<o,o5	

The results show that the mean values of immunoglobulin IgG and IgA of the examined group, are statistically rather higher in relation to the control group. The immunoglobulins IgM are statistically rather reduced.

The results of the statistic analysis show that there are not statistically important variations in the mean values of immunoglobulin IgG, IgA and IgM in the examined group of workers depending on the professional exposure time.

Table 7. Mean values of immunoglobulin IgG, IgA and IgM in the examined group of workers, depending on the professional exposure time (PET)

PET	IgG	IgA	IgM
⩽ 5	16,3	2,8	1,5
6 - 1o	16,8	2,5	1,8
11- 16	15,o	2,8	1,6
⩾ 16	14,6	2,9	1,7
LSD o,o5	4,4	1,o	o,6

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DISCUSSION

The results of our investigations show reducing of albumins and increasing of γ fraction, at normal level of total proteins, on vibration exposed workers.

According to Malčanov (1971), workers exposed to vibrations show reducing of the albumins and increasing of γ globulins. He explains that this disprotinemia is caused by disturbance of the central regulation of the metabolitic processis or by changing the permeability of blood vessels.(7)

Abramović (1972) reports that the vascular permeability is of phase character and depending on the stage of the desease it changes from increased to decreased permeability of the blood vessels, which is a basis for occurrence of distrophic changes (1).

Tzvetkov (1972) finds out changes in the synthesis of serum proteins, and he explains it as direct influence of the vibrations over the hepatal cells or probably with indirect influence of the vibrations over the complex neurohormonal regulation mechanisms(11)

It is important to point out that Satrov (1975) in 55% of vibration desease suffering patients, found out decreased immunological reaction tending to normalizing after the proper complex treatment. (12)

Asadulaev (1986) found out disproportion of the basic immunocompetitive cells (T and B lymphocytes) and change of their functional activity. He found out that the quantity of the circulating T-cells was reduced while the quantity of B-LY was increased with high level of serum globulins of all 3 types, The intensity of these changes depend on the professional exposure time.(3)

In order to find out whether the vibrations influent directly the immunocompetitive cells, or this influence is by means of

humoral factors, Lodina (1983) investigated the influence of vibrationa over the immunological response induced by timus-dependant and timus-independant antigenes. The results show that the humoral factor reduces the immune responce to timus-dependant antigen, and timus-independent antigen induces immune response through direct effect of B-LY. (6)

Prokopenko (1984) by his experiment found out that the vibrations led to occurrence of immunosuppression characteristics of the lymphocytes in the spleen and the timus, whilst the tripsine and the lisozime release the immunosuppression activity of the spleenocytes and timocytes. (9)

The same author in 199o, reports that during vibration exposure, from the muscular tissue in the circulation penetrates factor which activates the suppresson subpopulations of the immunoregulation cells of the spleen. (1o)

On the basis of numerous investigations, Alehina (199o) fins out changes in the ferment systems of the humoral immunity activity of the complement and the lisozime, but also changes in some other immunological parameters, concluding that the vibrations cause direct harmful effect over the immune cells and the humoral factors. (2)

The results of our investigation show increase of the immunoglobulins IgG and IgA and decrease of IgM, and are only a beginning of further investigations in the field of immunological changes in vibration exposure. We have to take into consideration that Bovenzi (1985) reports that the mechanical vibrations do not induce changes in the humoral immunity.(4)

It is also important the report of Okada (1971) who on the basis of the changes in the immunoglobulin IgM level, points to

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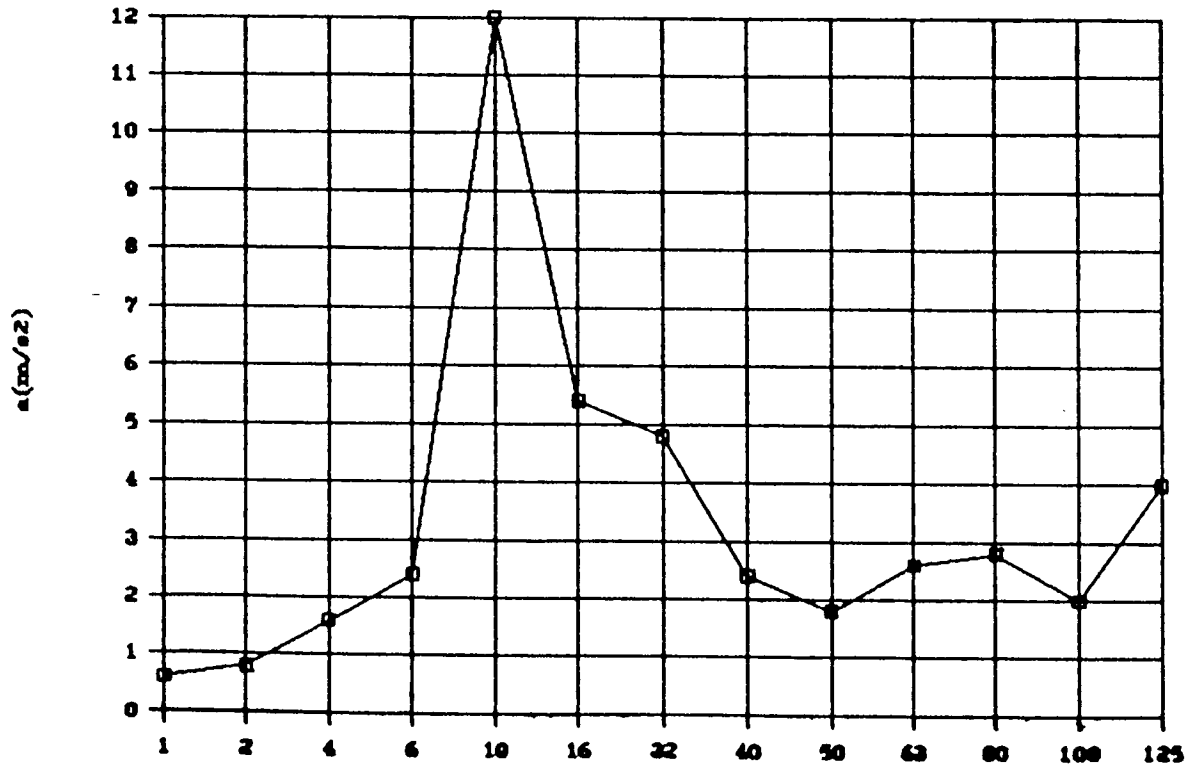
Raynaud's phenomenon, caused by vibrations in interval of 7-9 months after the occurrence of the changes, which may be of rather prognostic importance. (8)

It is clear that the problem of immunological changes in vibration exposure is complex one, and further additional investigations are to be made.

Fig.1. Description of the vibration acceleration measurement results.



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PLASMAVISCOSITY AND IMMUNOLOGICAL PARAMETERS AMONG DOCKERS WITH VIBRATION INDUCED WHITE FINGERS (VWF)

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INTRODUCTION

Among workers with long term exposure to hand-arm vibration the occurence of Raynaud's phenomena is known as vibration - induced white fingers (VWF). The pathogenetic mechanism of this disease is still uncertain and a lot of theories have been proposed. The influence of blood viscosity have gained some support when japanese researchers reported that patients with VWF had increased viscosity of both whole blood and plasma (1, 2). The immunoglobulin IgM and fibrinogen are important determinators of the plasma viscosity. There are one study indicating that VWF are associated with a slight increase of different immunoglogulins (3, 4), but others have not reproducted that results (4.5).

During the years a moderate increased concentration of IgM was observed among the VWF patients referred to our Department of Occupational Medicine. Considering the studies mentioned above a study was designed to further elucidate the pathogenesis of VWF with help of recent techniques with respect to analysis of viscosity but also immunological parameters would be looked upon. The study was performed on two groups, one with VWF and one consisting of healthy referents, unexposed to hand-arm vibrations.

MATERIAL

Selection of the VWF-group

The study was carried out in one of the ship-yards in Göteborg. In a health survey 77 dockers reported that they suffered from cold induced white fingers. 67 accepted a clinical investigation where the

subjects were classified according to the Stockholm Workshop scale for the classification of cold-induced Raynaud's phenomena in the hand-arm vibration syndrome (6). In that examination was 46 classified as cold-induced Raynaud's phenomena ($\geq$ stage 1). Further investigation with measurement of digital systolic blood pressure after segmental finger cooling was accepted by 40 men (7). Positive test (more than 70 % decrease of the systolic blood pressure the local finger cooling) was obtained among 34 men and negative test was obtained among 6 men.

As the VWF group were selected all men with positive test and with an exposure to hand-arm vibrations exceeding five years. Thirty men fullfilled these criterions and their occupations were welders (n=10), platers (n=10), plumbers (n=5), repairmen (n=3), carpenter (n=1) and engraver (n=1).

Selection of the referents

As referents were selected 30 men from the same shipyard, their occupations were foremen and office-workers. The referents were healthy, i.e. no signs of interferring disease of Raynaud's phenomena, and they were unexposed to hand-arm vibrations. The caracteristics of the two groups are shown in table 1.

METHODS

Sampling

From all subjects samples for analysis of blood, plasma and serum were obtained. The samples for plasma were obtained in containers

treated with ethylenediamine-tetra-acetate (EDTA). Both the sera samples and plasma samples were immediatly froozen and the blood were analysed in the same day.

Laboratory investigations

The plasma viscosity was measured at 27° C in a viscometer described by Gudmundsson et al (8). The levels of the immunoglobulins IgG, IgM and IgA, antinuclear antibodies (ANA) rheumatoid factor (RF), fibronection, fibrinogen, circulating immune complexes (CIC) were analysed in serum with routine methods. Hemoglobine concentration and erythrocyte sedimentation rate (ESR) were determined in blood.

Statistics

Differences between the means and the confidence intervals were evaluated with two-sided Students t-test. Furtheron the material was also analysed with multiple linear regression.

RESULTS

Viscosity in plasma was significantly decreased among the men with VWF, 1,64 m x Pascal x s compared with 1,75 m x Pascal x s on the referents ($p < 0,05$). The same tendency, but insignificant persisted when the material was stratified with regard to smoking habits or age (tab 2).

There were no significant differences between the VWF group and the healthy unexposed men with regard to the levels of the studied

immunological parameters (table 3). The concentrations of fibrinogen was insignificant increased among the referents.

Smoking showed a significant positive correlation with plasma viscosity when analysed with multiple linear regression (table 4).

DISCUSSION

Earlier studies on workers with VWF have shown an increased viscosity both in plasma and in whole blood (1, 9). Therefore the findings in the present study of decreased plasma viscosity among subjects with VWF was unexpected. The validity in the observation is supported by the fact that the same tendency persisted when the subjects were stratified according to different smoking habits or different age cathegories. However we have also analysed plasmaviscosity among 89 healthy blood-donors and among them the mean plasma viscosity was 1.67 m x Pascal x s (SE=0.015). This indicates that the referents in the actual study have a slightly increased plasma viscosity, which to some extent explains the observed difference.

Concerning the immunoglobulins the present study showed no abnormalities. These results are in accordance with two of the earlier cited studies (4.5).

In the study was found that smoking was positive correlated with increased plasma viscosity. Increased plasma viscosity among smokers has earlier been reported (10, 11), however there in one study was plasma viscosity not increased among smokers (12).

In conclusion the present study has showed a slight but significant decreased of plasma viscosity among workers with VWF. The biological significance this observation is uncertain. In the study there were no differences concering the immunoglobulins between the VWF-group and the referents.

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Table 1. Characteristic of the VWF-group and referents

	Exposed n=30	Referents n=30
Mean age	49.1	45.1
Smokers(n)	12	8
Ex-smokers(n)	10	7
Non-smokers(n)	8	14
Mean years working with vibrating tools (SD)	17.1(19.4)	-

Table 2. Plasmaviscosity (mxPascalxS) among dockers with VWF and unexposed referents (SE)

	VWF-group	Referents
All men	1.64 (0.027)* n=28	1.75 (0.034) n=29
Age> 50 year	1.63 (0.039) n=11	1.74 (0.061) n=9
Smokers	1.71 (0.060) n=11	1.83 (0.018) n=8
X-smokers	1.55 (0.043) n=9	1.84 (0.10) n=6
Non-smokers	1.63 (0.054) n=8	1.69 (0.048) n=14

*p < 0.05. Of technical reasons two samples in the VWF-group and one sample among the referents were excluded

(SE) = standard error

Table 3. Immunological parameters fibrinogen, hemoglobine and ESR among men with VWF (n=30) and healthy referents (n=30) unexposed for vibratins

	VWF-group	Referents
IgG (g/l)	10.76 (0.61)	10.75 (0.60)
IgM (g/l)	1.51 (0.93)	1.45 (0.98)
IgA (g/l)	2.65 (0.32)	2.24 (0.16)
CIC (abs 492 nm)	0.28 (0.025)	0.30 (0.25)
RF (mm)	3.3 (0.042)	2.87 (0.41)
ANA	1	1
Fibronectin (mm)	13.90 (0.19)	13.50 (0.16)
Fibrinogen(g/l)	3.14 (0.2)	3.25 (0.2)
Hemoglobine (g/l)	154.00 (1.91)	155.33(2.80)
ESR (mm)	7.08 (1.34)	9.06 (1.21)

CIC = circulating immune complexes

RF = rheumatoid factor

AMA = anti-nuclear antibodies

ESR = erythrocyte sedimentation rate

VWF = vibration induced white fingers

abs = absorbance

Table 4. Multivariate linear regression analysis of correlation between plasmaviscosity and age, exposure, smoking habits, IgG, IgM, fibrogen and circulating immune complexes.

Plasmaviscosity = a + b x age + c x exposure + d x smoke + e x IgG + f x IgM + g x fibrinogen.

Exposure = years working with vibrating tools
Smoke = 1 = non-smoker, 2 = ex-smoker, 3 = smoker
IgG = concentration g/l
IgM = concentration g/l
Fibrinogen = concentration g/l
CIC = circulating immune complexes

Parameter		Coefficient	Standard error
Intercept	(a)	163.29***	18.20
Age	(b)	0.10	0.27
Exposure	(c)	-0.44	0.26
Smoke	(d)	0.43*	3.18
IgG	(e)	-0.25	0.87
IgM	(f)	-7.22	5.11
Figrinogen	(g)	1.93	3.09
CIC	(h)	-0.29	19.76

*** $p < 0.001$

* $p < 0.05$

METABOLIC CHANGES IN WORKERS USING CHAIN SAW

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Summary

The examined group consisted of 44 workers who used chain saw for more then 10 years and were hospitalized at Belgrad Institute of Occupational and Radiological Health. Aside from the usual examination of the joint bone structures, additional analyses were perfomed on the peripheral circulation, neurological system as wellas laboratory standards: glycaemia, GTT test, total lipids, triglycerides, cholesterol, HDL, phopspholipids, immunoglobuline (IgG, IgA, IgM), C3 and C4 complements factors,haptoglobin, fibrinogen, rheuma factors, C reactive protein, prealbumin, albumin, total and cinjugated bilirubine, urinary cathecholamines and platelet aggregation.
Enzymes activity was also determined: GOT, GPT, AP, LDH, AL, CPK. The obtained results do not indicate significant metabolic changes in this group of workers.

Key words: vibration syndrome,metabolic parameters,skin temperature,age.

Introduction

Clinical picture of the syndrome caused by vibration shows disorders in the pripheral blood vessels,neuromuscular apparatus and joint bone structures.
Metabolic changes caused by total and local vibrations have not yet been studied in details. The available referantial data indicate that vibrations cause increase of aldolase activity, creatine phosphokinase, lactic dehydrogenase, cholesterol concentration, high density lipoproteins (HDL) cyclic 3-5 guanosine monophosphate increase in adrenaline, noradrenaline excretion, and increased blood viscosity and hematocrit (1,2,3).
The aim of this paper is to investigate some of the metabolic parameters and thereafter determine metabolic disorders coused by predominantly local vibrations.

Material and methods

The examined group consisted of 44 workers with the mean age of 50,25+6,9 years who worked with a chain saw for 18,70+ 5,29 years. They used different chain saw for different time periods. During work with the chain saw 29,55% of workers used the "antivibration" gloves, 59,09% used regular leather gloves, while 11,36% had no protection. Analysis of smoking habit: 23 workers (52,27%) were smokers, 8 (18,18%) were ex-smokers, and 12 (27,27) were non-smokers.
The study included a questionare (working history, subjective symptoms), initial chek-up, x-ray examination of hand and joints, electromyographic testing, neurologic examination and examination of the peripheral arm circulation.
The peripheral circulation was determined by the skin thermometry performed by ELLAB apparatus TF 5, and digital plethysmography of both midlle finges. Three measurements were performed: proir to (To) after the vasoconstricting provocation by cooling (5 minutes in he 10°C) (T1), and 15 minutes after restitution at the room temperature of 22-25°C (T2). The plethysmographic curves were quantitatively analysed by their morphologies.
The following biochemical parameters were determined: blood glucose, GTT-75 test, total lipides, triglycerides, cholesterol, HDL, phospholipids, immunoglobuline (IgG, IgA, IgM), prealbumine, albumine, transferrin, orosomucoid, haptoglobin, fibrinogen, C3, C4 complements factors, C reactive protein, rheuma factor, total and conjugated bilirubin. Following enzymes activity were determined GPT-EC 2.6.1.2. (Glutamic pyruvic transaminase), GOT-EC 2.6.1.1. (glutamic oxalacetic transaminase), AP-EC 3.1.3.1. (Alkaline phosphatase), LDH-EC 1.1.1.27. (lactic dehydrogenase), CHE-EC 3.1.1.7. (cholinesterase), AL-EC 4.1.2.13. (aldolase), and CPK-EC 2.7.3.2. (creatine phosphokinase).
Urinary adrenaline and noradrenaline were determined in the 24 urine sample by BIO-RAD method.
Glucose, lipides, triglycerides, cholesterol, HDL were determined by colorimetric method, enzymes activity were determined by UV spectrophotometric method, all protein component were measured immunochemical and nephelometrical method (Turbox).
Platelet aggregation were measured on ADP (1,5 ,umol) and on collagen 60 (,ug/ml).
The obteined metabolic resultes were analysed according to the age and the left hand skin temperature as indicator of the damaged peripheral circulation.
The statistical analysis were performed on the IBM PC using program SPSS+ (ONE WAY ANOVA and modified LSD).

Results

Based on the work history, the workers were exposed to vibrations 1068±226 hours per years average. Total exposure duration was 19153±7622 hours on average. Radiographically custic spots of cellular density in the small hand bones were discovered in 24 (54,55%) workers. Insufficiency of motor innervation of hand muscles was determined by electromyography in 6 (13,64%) workers.
Thermometry skin resultes are shown in Table 1.
Prior to the provocation pronounced hypothermia was noted with mean values aboput 25°C. Vasospasme was more exposed on the left hand after the provocation by cooling, while the restution was unsatisfactory in the set time period.
Clasiffication of stage in chaine saw workers by Stokholm Workshop scale are shown on Table 2.
Plethysmography findings showed that 45% of the workers had changes typical for lasting organic changes. In the 34% of workers the changes were functional (Table 3.).
Results of blood concentracion and GTT test are shown in the Table 4. Mean velues of spontaneus glycemia, even the GTT test, do not differ from physiological ones. No statisticaly significants differences were found when analysed according to the age and skin temperature.
Analysing certain lipides fractions in relation to the age, we found that triglycerides concentrations decreased with the older age. Other fractions show no mean value oscillation. (Table 5,6).
There are no differences in lipid concentrations relative to the skin temperature values.
Fibrinogen and IgA mean values moderately were increased with the older age (Table 7,8).
In relation to the skin temperature IgA mean values oscilate C3 complements factor linearly decreased, while rheuma factors (table 7,8) increases with the lower skin temperture. Haptoglobin mean values increase and prealbumin decrease with the older age was established by analysing other proteins (Table 9).
Considering the same parameters in the terms of skin temperature, certain oscillations in mean transferrin and orosomucoid values as welll as linear decrease in prealbumin concentration with the lower skin temperature were noted (Table 9).
Mean valeus of bilirubin (table 10), there are certain oscillations of total bilirubin in relation to skin temp.
Results of enzymes activity is shown in Table 11,12
Certain oscillations were noted in glutamic pyruvic transaminase and glutamic oxalacetic transaminase activity, while creatine phospho kinase activity increased considerably with the lower skin temperture.Adrenaline and noradrenaline excretion slightly decreased with the older age (Table 13).

In workers with very low skin temperatures in urine sampled during 24 hours, adrenaline excretion was considerably reduced while noradrenaline was only slightly reduced.
The analysed biochemical parameters indicate slight disorders in synthetic functions (drop in prealbumin and transferrin concentrations decreased in cholinesterase activity), absence of cholestasis signs (normal bilirubine, cholesterol, and alkaline phosphatase) and presence of discrete signs of necrosis (increased activity of GPT transaminase and CPK). Platelete aggregation in the group of workers investigated on ADP and collagene (Table 14) was bellow the lower refferential values for the applied method, on the ADP being somewhat lower than Collagene.

Discussion

The obtained results indicate the presence of vascular, bone and neuromuscular damages, all of which, excluding the other ethiologic factors, create a picture of the vibration syndrom. The changes are exceptionally notable in the vascular system and alone with age represent basis for comparing metabolic parameters.
Average exposure was 18 years, while the average yearly exposure was more than 1000 hours. Patient records of subjective symptoms indicate that the vascular disordes had been present 1-8 years prior to the diagnosis of vibration syndrom.
At the time of the investigation no disorders in carbohydrate metabolism were noted. Except for the drop in triglycerides, there were no disorders in the lipid metabolism. These results are in opposite to the claims of other authors (1), who related vibration to the increased concentrations of cholesterol and high densyty lipoproteins.

Increase in immunoglobuline IgA concentrations, fibrinogen and rheuma factor with older age and varios damage degree of blood vessels, as a non-specific indicator, cannot be related to the local vibration effects, prior to elimination of all other ethipatogenic mechanisms. Uneven and irrelevant increase of immunoglobuline M concentrations were also noted by the other authors. Significant decrease of the third and nonsignificant decrease of the fourth complement factors cannot be specifically related to the blood vessels damage. However, it indicated the complement system activation.
Changes in the other protein concentration (increased haptoglobine, and orosomucoid, and decreased prealbumin and transferrin) can be explaned by the decreased synthetic function of the liver, while haptoglobin is in accordance with the referential data, indicating that this glycoprotein increases in hand arm vibration syndrome. (2).

Increase in creatin phosphokinase activity is in correlation with the severity of the peripheral circulation damage. Other authors (2), also found increased activity of other sarcoplasmatic enzymes (aldolase, and lactic dehydrogenase). Physiological role of creatin phosphokinasis to ensure energy for muscle conntraction obtained from phosphocreatine.

The decreased adrenaline and noradrenaline excretion in relation to lower skin temperature are not in accordance with the refferential data (4). The decrease in the excreted hormones (catheholamins) in the studied workers could be explained by chronic effects of physical hazards (vibrations) which with time exhaust hormonal response to the physical stress.

Discrete changes in liver function cannot be related to the local vibration effects. There is no evidence in the literature that local vibrations cause liver functional damages.

The decrease of platelet aggregation in the study group is not in accordance with the previosly published data.

Conclusion

The obtained results indicate the presence of the vibration syndrom with vascular, bone and neuromuscular manifestations in examined workers.

Carbohydrate and fat metabolic changes were not found in the studied workers. The discrete changes in protein metabolism could related to the vibrations negative effects as well as to the disorder in sarcolemma energy transfer. Decreased adrenaline and noradrenaline excretion could be edxplained by chronic stress mehanism. Our results are preliminary and futher investigations, which should include a control group, could supply more precise explenations to the existing dilemmas.

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Table 1. Mean of skin temperature and cold provocation test

hand	n	To X	To SD	T1 X	T1 SD	T2 X	T2 SD
left	44	25,2	4,3	13,3	2,5	24,5	6,2
right	44	25,4	4,2	14,3	2,9	24,6	6,4

To-skin before test
T1-skin after cold provocation (5 min. on 10°C)
T2-skin after 15 min. of cold provocation

Table 2. Distibution of symptomatic stage in the invastigated group by Stocholm Workshop scale (revision Taylor Pelmear) 1987

stage	left hand		right hand	
	n	%	n	%
0	8	18,1	9	2o,5
1	15	34,2	17	38,6
2	17	38,6	14	31,8
3	4	9,0	4	9,1
4	—	—	—	—

Table 3. Results of finger plethysmography

hand	normal		organic change		functio change	
	n	%	n	%	n	%
left	10	22,7	19	43,2	15	34,1
right	8	18,2	21	47,7	15	34,1

Table 4. Values of glucose in blood and GTT in the investigated group by age and skin temperature

	age	n	glucose		GTT0		GTT2	
			X	SD	X	SD	X	SD
1	31-40	5	4,8	0,7	4,2	0,8	5,7	1,3
2	41-50	14	4,6	0,3	4,2	0,6	6,0	1,7
3	51 <	25	4,8	0,2	4,1	0,5	6,0	1,2
			NS		NS		NS	
skin t°		n						
1	30,1<	7	4,7	0,6	4,2	0,7	5,7	1,6
2	25,1-30	13	4,7	0,6	4,2	0,5	5,8	1,0
3	20,1-25	18	7,4	0,8	4,1	0,5	5,8	1,4
4	20,0 <	6	5,0	0,5	4,7	0,6	7,0	1,2
			NS		NS		NS	

Table 5. Values of lipids in blood in the investigate group by age and skin temperature.

	age	n	tot.lipids gr/l $\bar{X}$	SD	triglicer. mmol/l $\bar{X}$	SD	phophosphol mmol/l $\bar{X}$	SD
1	31-40	5	9,9	1,1	2,9	1,6	2,3	0,5
2	41-50	14	9,2	2,4	2,4	1,0	2,2	0,5
3	51 >	22	9,1	1,3	1,8	0,7	2,4	0,8
			NS		1:3*		NS	
	skin t°	n						
1	30,1<	6	8,6	1,0	2,0	0,7	2,2	0,2
2	25,1-30	12	9,0	1,1	2,2	1,3	2,3	0,5
3	20,1-25	14	9,6	1,1	2,2	1,0	2,4	0,6
4	20,0 >	6	9,4	1,0	2,0	0,5	2,4	1,4
			NS		NS		NS	

* p<0.05 LSD

Table 6. Values of cholesterol (mmol/l), HDL (mmol/l) and APOA1 (g/l) APOA2 (g/l) APOB (g/l) in the investigated group by age and skin temperature

AGE		Chol	HDL	APOA1	APOA2	APOB
	N	X	X	X	X	X
1 31-40	5	5,3	1,2	1,3	0,2	1,0
		±1,2	±0,5	±0,1	±0.1	±0.3
2 41-50	14	5,9	1,3	1,3	0,3	1,1
		±1,0	±0,3	±0,3	±0,1	±0,4
3 >51	22	5,8	1,3	1,3	0,3	1,1
		±1,0	±0,3	±0,3	±0,2	±0,4
		NS	NS	NS	NS	NS
Skin te	n					
1 30,1	6	6,2	1,2	1,2	0,3	1,0
		±0,2	±0,3	±0,2	±0,1	±0,4
2 25,1-30	12	5,5	1,3	1,3	0,3	1,0
		±1,1	±0,4	±0,2	±0,3	±0,3
3 20,1-25	14	5,9	1,3	1,3	0,3	1,1
		±1,1	±0,3	±0,3	±0,1	±0,5
4 <20,0	6	5,4	1,1	1,4	0,2	0,8
		±1,1	±0,3	±0,4	±0,04	±0,1
		NS	NS	NS	NS	NS

Table 7. Values ef immunoglobuline (A,M,G)(g/l) and C_3, C_4 (g/l) complements factors in the investigated group by age and skin temperature

AGE	n	Jg A X	Jg M X	Jg G X	C_3 X	C_4 X
1 31-40	5	1,3 ±0,4	1,2 ±0,8	13,0 ±2,1	1,2 ±0,3	0,2 ±0,1
2 41-50	14	2,1 ±0,9	1,7 ±1,2	12,3 ±2,3	1,0 ±0,4	0,3 ±0,1
3 >50	24	3,0 ±1,2	1,6 ±1,4	12,1 ±3,6	0,9 ±0,3	0,3 ±0,1
		3:1** 3:2**	NS	NS	NS	NS
Skin t°	n					
1 30,1	7	2,5 ±1,5	1,2 ±0,9	13,3 ±2,6	1,3 ±0,5	0,3 ±0,1
2 25,1-30	13	1,9 ±0,7	1,6 ±1,2	11,4 ±3,6	1,0 ±0,4	0,2 ±0,1
3 20,1-25	18	2,9 ±1,3	1,9 ±1,5	12,8 ±2,7	0,9 ±0,3	0,3 ±0,1
4 20,0<	5	2,5 ±1,0	1,3 ±0,7	11,5 ±3,1	0,8 ±0,2	0,2 ±0,1
		3:2*	NS	NS	1:2* 1:3** 1:4**	NS

Table 8. Values of fibrinogen, C-react.protein (CRP) and rheuma factor (RF) in the investigated group by age and skin temperature.

			fibrin. g/l		CRP mg/l		RF V/l	
age		n	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
1	31-40	5	2,5	0,4	2,8	3,1	65,2	12,1
2	41-50	14	3,2	0,9	2,5	3,3	76,5	31,0
3	51 <	24	3,5	0,8	2,0	2,2	93,8	87,4
			NS		NS		NS	
skin t°		n						
1	30,1<	7	3,4	1,1	2,0	0,4	60,0	23,4
2	25,1-30	13	3,0	0,8	1,9	0,2	70,8	15,5
3	20,1-25	18	3,3	0,7	2,1	0,4	82,0	25,1
4	20,0 >	5	3,5	1,0	2,0	0,4	166,0	184,8
			NS		NS		4:1**	
							4:2**	%
							4:3*	

* Significants LSD p<0,05

** Significants MOD LSD p<0,05

Table 9. Values of transferin (g/l), orosamucoid (g/l), haptoglobin (g/l), prealbumin (g/l) albumin (g/l) in the investigated group by age end skin temperature

Age		Transf.	Orosom.	Haptogl.	Prealb.	Albumin
	n	X	X	X	X	X
1 31-40	5	3,1	1,0	0,9	0,37	18,7
		±0,9	±0,6	±0,2	±0,07	±6,6
2 41-50	14	2,6	0,9	1,7	0,28	18,9
		±0,5	±0,4	±0,6	±0,07	±7,1
3 > 51	24	2,6	0,9	1,8	0,27	22,7
		±0,6	±0,3	±0,9	±0,05	±14,1
		NS	NS	3:1*	1:3** 1:2**	NS
skin t°	n					
1 30,1<	7	2,6	0,7	1,7	0,3	23,2
		±0,3	±0,2	±0,8	±0,09	±21,5
2 25,1-30	13	3,6	1,1	1,5	0,3	20,8
		±0,7	±0,4	±0,7	±0,05	±5,9
3 20,1-25	18	2,5	0,9	1,9	0,3	19,6
		±0,7	±0,3	±0,9	±0,06	±9,1
4 20,0 >	5	2,5	1,1	1,4	0,2	23,4
		±0,3	±0,3	±0,5	±0,05	±14,6
		2:3*	2:1*	NS	1:4*	NS

Table 10. Values of bilirubin and direct bilirubin in the investigated group by age and skin to

	age	n	Bilirubin /umol/l	Direct bilirubin /umol/l
1	31-40	5	15,5 ± 4,5	3,00 ± 0,6
2	41-50	14	12,8 ± 3,8	3,4 ± 2,5
3	51 <	25	12,2 ± 3,8	2,6 ± 1,17
			NS	NS
	skin to	n		
1	30,1 <	6	12,1 ± 3,1	2,7 ± 1,3
2	25,1-30	18	12,3 ± 3,8	2,7 ± 1,3
3	20,1-25	13	11,9 ± 3,8	2,7 ± 1,9
4	20,0 >	7	16,1 ± 3,8	3,9 ± 2,1
			4 : 3*	NS
			4 : 2*	

Table 11. Values of enzymes activities Aldolase AL, Lactic dehydrogenasa LDH, Creatine phosphokinase CPK, Cholinesterase CHE, in the investigated group by age and skin temperature.

	age	n	AL X	LDH X	CPK X	CHE X
1	31-40	3	1,9 ±0,6	140,0 ±13,7	31,9 ±10,9	2893 ±67,0
2	41-50	13	1,6 ±0,6	110,8 ±16,7	25,8 ±7,8	2534 ±430,1
3	50<	23	1,8 ±0,8	120,2 ±27,3	26,3 ±14,8	2852 ±534,2
			NS	NS	NS	NS
	skin to	n				
1	30,1<	6	2,0 ±1,1	115,8 ±20,8	21,2 ±1,8	2922 ±337,7
2	25,1-30	12	1,6 ±0,6	125,2 ±25,9	29,0 ±14,1	2704 ±380,9
3	20,1-25	15	1,7 ±0,6	116,9 ±26,6	23,1 ±8,7	2681 ±608,7
4	20,0>	6	1,9 ±0,6	113,6 ±17,2	37,2 ±18,2	2521 ±673,5
			NS	NS	4:1* 4:3*	NS

Table 12. Velues of enzymes activities Glutamic oxalacetic transaminase GOT, Glutamic piruvic transaminase GPT, Alkaline phosphatase AP in the investigated group by age and skin temperature.

	age		GOT		GPT		AP	
		n	X	SD	X	SD	X	SD
1	31-40	3	25,8	13,0	27,6	13,5	25,5	9,9
2	41-50	13	37,1	10,9	34,8	12,7	31,0	9,2
3	51<	23	28,4	10,3	29,1	16,7	30,4	11,9
			2:3**		NS		NS	
	skin t°	n						
1	30,1<	6	38,0	10,6	27,0	9,1	29,7	4,6
2	25,1-30	12	26,2	10,5	24,1	9,2	29,0	10,8
3	20,1-25	15	33,5	12,1	35,7	18,9	33,5	12,8
4	20,0>	6	24,8	5,1	34,7	15,9	24,8	8,5
			1:2*		3:2*		NS	
			1:4*					

Table 13. Values of urinary adrenaline and noradrenaline in the investigated group by age and skin temperature

			Adrenaline nmol/d		Noradrenaline nmol/d	
	age	n	$\bar{X}$	SD	$\bar{X}$	SD
1	31–40	5	60,9	± 19,7	117,9	± 13,5
2	41–50	13	50,6	± 20,0	131,7	± 68,7
3	51 <	24	47,8	± 27,8	114,0	± 59,3
			NS		NS	
	skin t°	n				
1	30,1 <	7	38,5	± 13,2	92,1	± 41,2
2	25,1–30	13	66,6	± 24,8	135,6	± 57,7
3	20,1–25	16	51,4	± 24,1	130,5	± 68,4
4	20,0 >	6	27,7	± 7,9	91,4	± 30,6
			2:1*		NS	
			2:4**			
			3:4**			

Table 14. Platelet aggregation in the investigated group

Methods	Plat. aggregat. (70-100%)		Platelet.agregation (<70%)		--
	n	%	n	%	X
ADP 1,5 /umol	18	41,9	2	58,1	60,6%
Collagen 50 /ug/ml	28	65,2	15	34,8	66,8%

"ANTABUSE TEST" FOR EVALUATION OF GENETIC PREDISPOSITION IN EXPOSURE TO CARBON DISULFIDE

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Healthy human subjects exhibit large variations in response to toxic substances, drugs and other xenobiotics. The magnitude of these toxicokinetic (pharmacokinetic) variations in subjects of the same age and sex, under similar environmental conditions, range from fourfold to fortyfold. More than 20 different host factors (genetic constitution, age, sex, health status, diet, way of life, etc.) are responsible for these variations, which interact dynamically (1).

Observing a dose-response curve for a toxicant on a human or animal population, it is usual to find a susceptible group of the subjects on one side, and a resistant group on the other side. The distribution curve may take form of a symmetrical or asymmetrical Gaussian curve.

We found a similar situation in a viscose factory, where workers are exposed to carbon disulfide. In 1963 a team of experts from the Institute of Occupational and Radiological Health in Belgrade started an intensive, broadly-based study on biochemical, toxicological and medical aspects of CS_2 toxicology on exposed workers. During these studies the problem of individual susceptibility to this toxicant emerged in the very beginning.

In the beginning of the study in viscose factory it was necessary to apply a reliable exposure test on workers exposed to CS_2. Determination of CS_2 in blood and urine did not produce reliable data on the level of exposure due to the existence of the free and bound fractions. In 1963 Vašak et al. (2) published a paper on a new exposure test for CS_2 using the iodine-azide reaction. The iodine-azide test (IAT) is based on a finding of Yoshida (3) that the iodine-azide reaction is catalyzed by CS_2 metabolites present in the urine of exposed animals:

$$2NaN_3 + I_2 \rightarrow 3N_2 + 2NaI$$

Vašak et al. (2) measured decoloration time in seconds (t) that elapsed from the moment of adding the reagent to the urine, Vašak determined the urine creatinine concentration (c) to calculate the exposure coefficient E:

$$E = c \times \log t$$

In 1964 we applied the IAT to establish the level of exposure of workers in our viscose factory and obtained a very good correlation with the average CS_2 concentration in the air (4). During this study we observed that one group of workers (recovery group) showed a "normal level" of the exposure coefficient before the work and an increased level at and of exposure each day. A second group of workers ("non-recovery group") showed an increased level of E at the beginning of work and highly increased level at end exposure.

Stokinger and Mountain (5) suggested the use of the "non-recovery" pattern of IAT for detection of hypersusceptible workers.

Continuing our study we established (6,7) that the "non-recovery" pattern represents an early sign of biochemical disorder and that this group of workers will develop symptoms of chronic posoning due to further exposure. We suggested that "non-recovery" pattern is consequence of a biochemical defect in the enzyme systems metabolizing sulfur compounds caused by CS_2.The "non-recovery" pattern represents an early sign of poisoning.

To evaluate this hypothesis, it was necessary to find a suitable sulfur containing-compound which can be used to determine the rate of metabolism of sulfur compounds in the human organism. For this purpose we selected the tetra-ethyl-thiuram-disulfide (TETD, Antabuse, Disulfiram) which is used in Yugoslavia for treatment of alcoholics.

In the organism Antabuse is metabolized to produce two molecules of diethyl-dithio-carbamate (DDC) and finally two molecules of diethylamine and two molecules of CS_2 - Figure 1.

Skalicka (8) determined the excretion of DDC in urine of alcoholics treated with Antabuse. We combined the determination of DDC and IAT in urine of 22 chronic alcoholics treated with Antabuse (9).

After oral administration of 0.5 g. of Antabuse we sampled the 6 hours urine fraction. The DDC excretion showed great variation from 5.2 to 771 µg/g creatinine (mean value: 158.4 DDC µg/g creatinine.

The differences in DDC excretion of chronic alcoholics, treated with Antabuse, could partly be ascribed to the differences in absorption, and mainly to individual differences in the rate of metabolism of this compound, which is probably genetically influenced. We supposed that Antabuse could be used for evaluation of the individual rate of metabolism of sulfur compounds and estimation of individual susceptibility to CS_2.

Development of "Antabuse test"

Therefore we decided to administer Antabuse orally to various groups of viscose workers (1o). For this purpose we selected three groups of workers in the viscose factory:

1. Eighteen workers from the viscose yarn production: These workers have been exposed to CS_2 for 11 to 15 years at an average level of 32 mg/m^3, a concentration below the level of maximum allowable concentration (50 mg/m^3), an indication that this group had not been dangerously exposed. No signs of chronic poisoning were observed. This group was considered as a "control group" of "normal DDC excretion" group, similar to the treated alcoholics, who are not exposed to CS_2 at all.

2. Twenty-one workers from staple-cell operation exposed to a high CS_2 concentrations for 7 to 14 years. The CS_2 concentration at times reached average values of 300 to 400 mg/m^3. Selected workers of this group, under constant medical surveillance, did not show any signs of poisoning and therefore, they were considered to represent the "resistant group" of workers.

3. Thirty-three workers who worked in staple-cell operation at one time under same conditions as group 2. During the exposure they developed on one or two occasions signs of chronic poisoning (polyneuritis) and were removed from exposure. They have worked since removal for five to ten years as gardeners, guards and so forth without CS_2 exposure. They are partially disabled and marked as "invalids" or "susceptible group".

DDC was determined in the 6-hour urine sample. The results of DDC determination in the urine of the three groups of workers defined above (10) are presented in Table 1. and 2.

The statistical evaluation of results and the correlation between groups are presented in Table 2. It is interesting that the mean level of DDC excretion in the resistant group (90.04 mg/g creatinine) is lower than in the control group (160.50 mg/g creatinine), but this difference is not statistically significant, owing to the wide spread in values among the controls. Neither group showed any signs of CS_2 poisoning: the resistant in spite of increased exposure, the control because of low exposure. Excretion of DDC is the lowest in invalids (49.70 mg/g creatinine) which is statistically highly significant in relation to the both control and resistant groups.

These results suggest that high exposure to CS_2 causes a disturbance in the metabolism of sulfur compounds. That means that CS_2 damages its own enzymatic system which also metabolizes other sulfur compounds. "Invalids" and "resistant" workers worked in the same operation exposed to high CS_2 concentrations (300-400 mg/m^3). It seems that "invalids" represent a group of susceptible workers in whom CS_2 injured the enzyme system metabolizing sulfur compounds to the less toxic metabolites. This injury is irreversible. In the "resistant" group, CS_2 caused a decrease in the metabolism of sulfur compounds, but not below a certain threshold at which metabolic conversion to the less toxic metabolites is prevented. Therefore, we suggested the use of the "Antabuse test" as a preemployment test of workers' acceptability for work with CS_2 exposure in viscose factory. We suppose that individuals with high metabolic capacity for Antabuse, (high DDC excretion) represent the resistant group, and that individuals with low DDC excretion represent the susceptible group. Cooper (11) included this test in his review on indicators of susceptibility to industrial chemicals.

In the meantime we isolated and identified in the urine of viscose workers all three CS_2 metabolites responsible for the iodine-azide reaction: mercaptothiazolinone (12), thiocarbamide (13) and thiocarbamide-mercapto-thiazoline carbamic acid (14). We also developed a method for the quantitative determination of thiocarbamide (thiourea) in urine of exposed workers (15).

Studies of other teams

In Bulgaria Pavlova and Usheva (16) monitored the DDC excretion in 35 healthy persons after oral administration of Antabuse. They sampled 4x6 hour urine samples (24 hours) after oral intake of Antabuse. The first and second urine samples showed almost identical DDC concentration with significant decrease in the following two urine samples. The IAT was increased in parallel with the increase in DDC excretion.

In an another Yugoslav viscose factory Besarabić (1) administered Antabuse to 61 workers exposed to CS_2 for about 4-5 years. She compared the level of DDC excretion with data on total and specific absenteeism. From the results obtained she concluded that a high rate of absence due to CS_2 specific morbidity, appeared in workers showing DDC excretion under 150 µg/g creatinine. Workers with DDC excretion above this value are less susceptible to the effects of CS_2. Besarabic proposed to accept for work with CS_2 only workers showing DDC excretion over 150 µg/g creatinine during the administration of the pre-employment Antabuse test. In 1979 the "Antabuse test" was cited in the WHO publication on CS_2 (18).

In Poland Podobinski (19) administered orally Antabuse to 96 workers in a viscose factory. He confirmed our observations that DDC excretion decreases with the level of exposure, but not with the duration of exposure. Podobinski supposed that an adaptation to CS_2 exists due to the induction of enzymatic system metabolizing sulfur compounds. Podobinski also compared DDC excretion with the simultaneous estimation of the liver damage using Bengal rouge I^{131} test. Obtained results suggested that long term exposure to the low concentrations of CS_2 may cause toxic effects mainly in the liver, damaging its metabolic function. Podobinski recommended the "Antabuse test" for the detection of changes in metabolism of CS_2 which probably precede the development of symptoms of chronic poisoning.

Discussion

We assume that an increased exposure to CS_2 injures the enzyme systems that metabolize sulfur compounds (CS_2, Disulfiram). Therefore, excretion of metabolites is retarded (nonrecovery) or decreased. This suppression of sulfur compound metabolism probably represents an early sign of CS_2 toxic effect, even an early sign of poisoning. Perhaps this phenomenon can explain later intoxication. For, if the primary toxic substance (here CS_2) and/or intermediates are more toxic than final metabolites, then suppression of their metabolism ("detoxification process") results in intoxication. In exposed workers the observed great variation in the capacity of this metabolic system results in susceptibility or resistance to the toxic agent. It seems that in the case of the resistant group the metabolism of sulfur compounds under CS_2 influence is not decreased below a certain threshold. Therefore, this group shows no signs of poisoning throughout the years of high exposure. On the other hand, under the same exposure in a majority of susceptible workers such a metabolic threshold limit was reached after shorter or longer exposure, and caused poisoning and disability (invalids). It is of importance to point out that in invalids this very low metabolic conversion persists even five to ten years after the and of exposure to CS_2. One possibility is that the metabolic disturbance, caused by CS_2, is irreversible in nature. We also observed that some of these workers, when intoxicated for the first time, showed soon early signs of intoxication when they returned to the same exposure after recovery. Therefore, they were removed later to nonexposed working places. This observation supports such hypothesis.

To explain this phenomenon we have to consider the metabolism of CS_2 and its effects on the enzyme system metabolizing sulfur compounds. After absorption into the human organism 10-30% of absorbed CS_2 is exhaled and partly eliminated by the skin. Further 70-90% of CS_2 undergo biotransformation. The produced metabolites, together with less than 1% of unchanged CS_2, are excreted in the urine or exhaled (CO_2) (18,20).

Obviously great part of absorbed CS_2 is metabolized. The metabolism of CS_2 is not fully elucidated and a tentative scheme is presented on Figure 2(20).

The metabolism of CS_2 is very complex and it is basically performed by two pathways:

1. binding to: a) glutathione (GSH) to produce thiazolidine-2-thione-4-carboxylic acid and 2-oxothiazolidine-4-carboxylic acid, b) amino acids to produce dithiocarbamates and 2-thio-5-thiazolidione,

2. oxidative desulfuration performed by microsomal mixed function oxidases (MFO) producing partially CO_2 as a final product.

The quantity of metabolites produced by first pathway (including thiourea) is relatively small. Therefore, from the quantitative, as well as of toxicological point of view, the second pathway represents the most important way of CS_2 conversion.

Recently a large amount of evidence has been accumulated to support the concept that microsomal function oxidases (MFO) are the most important enzyme systems involved in biotransformation of xenobiotics in mammalian and other species liver and other organs (23,24). These processes include oxidation, hydroxylation, desulfuration, dehalogenation etc.

The oxidative desulfuration of CS_2 is performed by MFO probably in two stages. In the first stage a sulfur atom is liberated and carbonyl sulfide, as an intermediate, is formed. In the second stage the second sulfur atom is liberated to produce CO_2 as a final product. Unstable intermediates are also producing thiourea under the influence of cytosolic carbonic anhydrase.

Due to unspecificity of MFO, several other sulfur-containing compounds, like disulfiram (Antabuse), diethyldithiocarbamates, thiocarbonyl, thiourea are also undergoing oxidative desulfuration.

Reactive sulfur atoms liberated during this process may become bound to the cellular components and initiate toxic changes in the liver and other tissues.

Recent studies (18, 20, 21) indicate that the apoprotein of cytochrome P-450 (which is the central enzyme molecule of MFO), may be the primary target of the toxic action of liberated sulfur atoms.

It is supposed that a portion of the S atoms released during oxidative desulfuration of mentioned compounds, reacts with the - SH groups of cysteine residue in the cytochrome P-450 apoprotein, ~~to form a high molecular weight~~. That means that the protein moiety of cytochrome P-450 represents the main target of the toxic action of CS_2. However, the lesion of apoprotein would cause a decrease of affinity and/or a decrease in the number of binding sites for heme inside the microsomes. As a consequence a loss of heme will occur, as well as a decreased utilization of newly formed heme by apoprotein, with more heme degraded to the bile pigments.

In such a way, the denaturation of cytochrome P-450 molecule, peroxidation of lipids, and, finally, destruction of the cytochrome P-450 and cytochrome P-488 will follow (18, 20, 21, 22, 23). All these studies are suggesting that the liberated sulfur atom is primary toxic agent in liver toxicity due to the exposure to CS_2 and, probably, other sulfur containing compounds.

Small concentration of CS_2 will probably produce an inducing effect on MFO, like numerous other toxicants in similar concentration. However, higher CS_2 concentrations will exert an inhibitory effect on MFO.

For biologically active toxicants a small increase in the dose can produce much larger than expected, elevation in tissue concentration of subjects with reduced capacity for metabolic detoxification.

In our case we assume that subjects with greater metabolic capacity of MFO represent the resistant group. When this subgroup is exposed to higher concentrations of CS_2 they are able relatively quickly to perform detoxifying process, in spite of partial inactivation of cytochrome P-450 enzyme. The decrease of metabolic capacity of impaired MFO is still over the critical threshold enabling continuous detoxification of CS_2.

According to this hypothesis subjects with a lower metabolic capacity of MFO represent the susceptible subgroup, in whom the destruction of enzyme molecules will cause a decrease in the rate of metabolism below the critical threshold, so that the intoxication will be developed (24, 25).

The group of "invalids", removed from CS_2 exposure for many years after intoxication, represented a surprise for us due to persistent low metabolic capacity of MFO. This can be explained by an irreversible disturbance of MFO. It would be interesting to find out the exact nature of this phenomenon and develop an adequate explanation. An irreparable liver injury could be a rational explanation.

Increasing evidence is suggesting that interindividual toxicokinetic (pharmacokinetic) variations are mainly based on differences in the MFO activity, rather than on differences in absorption, distribution or excretion of the toxicant (1, 26, 27). The synthesis, capacity and function of enzymes are under genetic control and these characteristics are inherited. Therefore, genetic factor can be the main cause of large interindividual variations in toxicokinetics.

We can suppose that the capacity of MFO for oxidative desulfuration of sulfur containing compounds represent inheritable variations of genetic nature. As a consequence the "Antabuse test" could represent a predictive test of individual susceptibility of workers to CS_2 and other sulfur containing compounds.

It seems that applying this test we can establish at least metabolic capacity of the MFO form responsible for metabolism of sulfur containing compounds, if not of the complete MFO system.

The "Antabuse test" represents an attempt to identity distinguishing biochemical characteristics associated with the specific susceptibility of each subject to the sulfur containing chemicals (phenotyping).

The next step would be to develop a, "pedigree analysis" of individuals and their families to reveal the role of genetic factor in controlling interindividual variations in the MFO system responsible for metabolism of sulfur containing compounds. Using family studies the Mendelian mode of transmission of this condition can be established.

Also, it would be interesting to study the rate of metabolism of Antabuse on the same subjects parallel with an other chemical, which is not sulfur containing, to find out if Antabuse test is revealing only the metabolic capacity of the enzyme form responsible or sulfur containing compounds, or of the complete MFO.

Summary

Author describes development of the "Antabuse test" as a preemployment predictive test of individual susceptibility of workers to the carbon disulfide exposure.

In discussion the hypothesis explaining this phenomenon is presented.

Procedure for the "Antabuse test"

During the pre-employment medical examination of new workers for work in the viscose factory with CS_2 exposure it is advisable to perform also the "Antabuse test".

After oral application of 0,5 g. of Antabuse /Disulfiram, TETD/ to the worker it is necessary to sample the urine fraction during the first 6 hours. In this urine sample determine the concentration of diethyl- dithio-carbamate /DDC/ as well as creatinine. Calculate the excretion of DDC in mcg/g creatinine.

All healthy individuals showing a DDC excretion over 150 mcg/g creatinine could be proposed for work in the operations with the CS_2 exposure. Individuals with the DDC excretion under the mentioned value may be susceptible to CS_2 and could be accepted for work outside the CS_2 exposure.

It is necessary to stress that all individuals after oral application of Antabuse must strictly avoid any alcohol consumption. In the opposite case alcohol will provoke very unpleasant and even dangerous "Antabuse syndrome".

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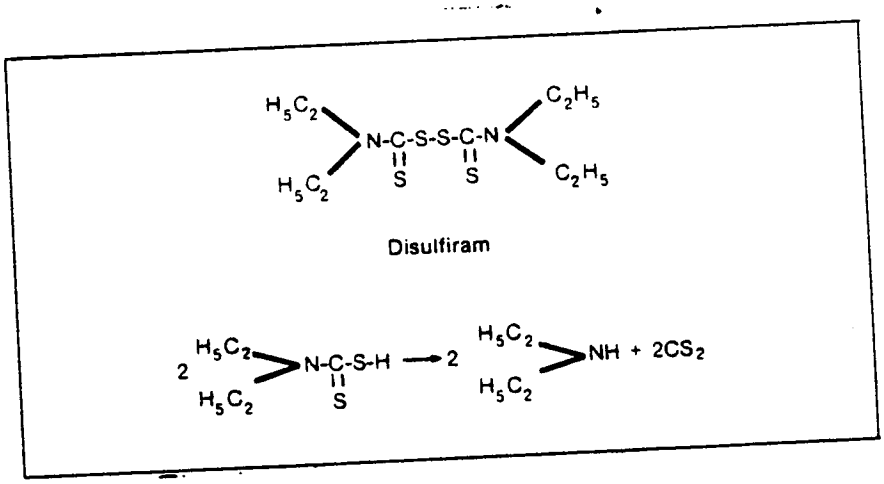

Figure 1 . Disulfiram and metabolites .

Table 1.—Determination of DDC in Urine After Oral Administration of 0.5 gm Disulfiram

Group	No. of Workers	Duration of Exposure, yr	DDC, μg/mg of Creatinine		
			Minimal Value	Maximal Value	Mean Value
Control group from viscose rayon yarn production	18	11 to 15	50	564	160.50
Resistant group from staple-cell rayon production	21	7 to 14	35	130	90.04
Susceptible group disabled (invalids) from staple-cell rayon production	33	. . .*	30	110	49.70

*Removed from CS_2 exposure of five to ten years.

Table 2.—Statistical Evaluation of Results

Group	No. of Workers	Mean Value of DDC, μg/mg of Creatinine	Standard Deviation	Statistical Significance
Control group	18	160.50	130.7	$t = 2.356$ $P < .05$
Resistant group	21	90.04	39.3	
Control group	18	160.50	130.7	$t = 4.714$ $P < .001$
Susceptible group	33	49.70	29.0	
Resistant group	21	90.04	39.3	$t = 4.337$ $P < .001$
Susceptible group	33	49.70	29.0	

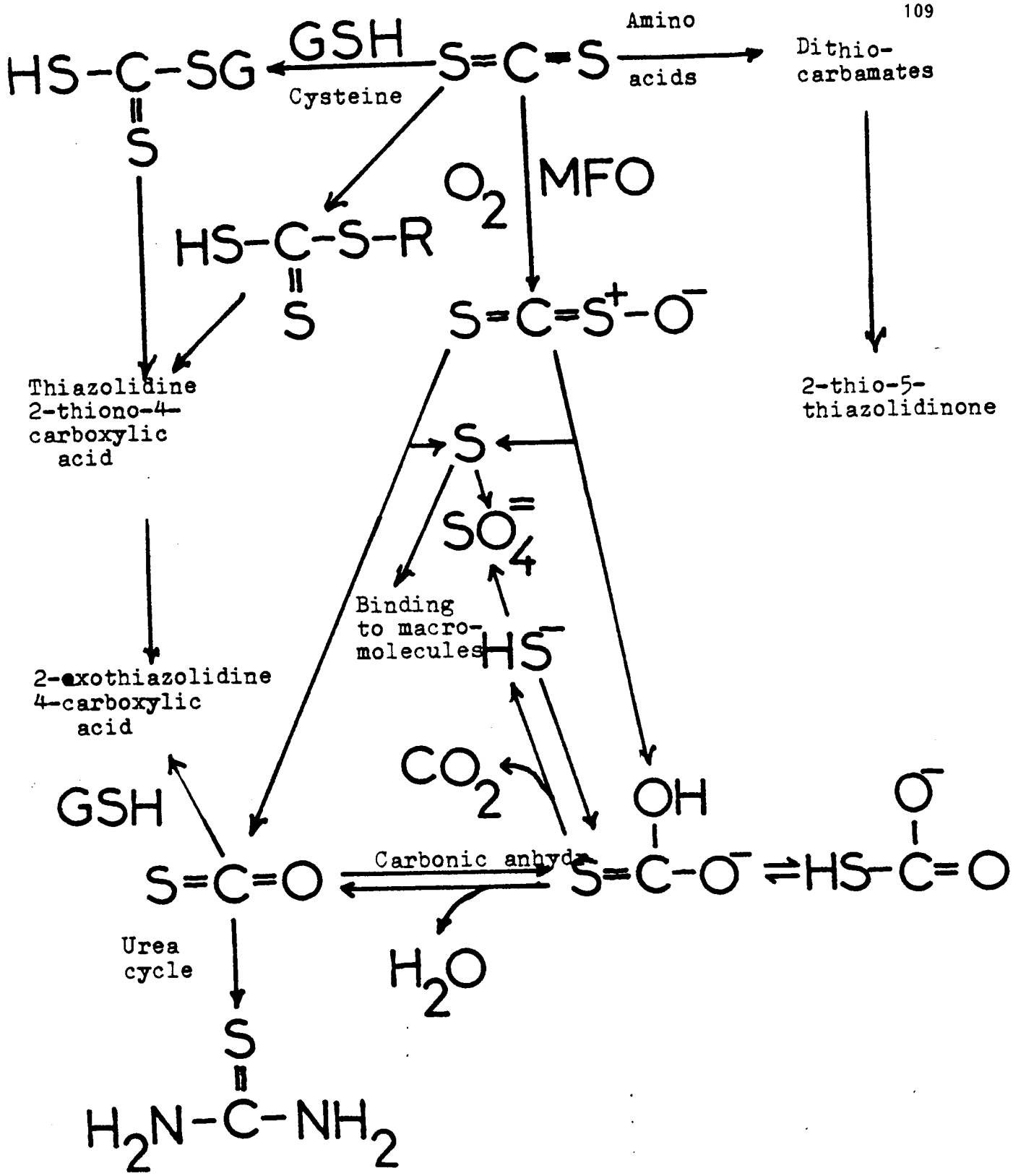

Figure 2. Scheme of CS_2 metabolism.

"Clinical Picture, Chronic Symptoms, Prognosis".

Lecture on Swedish-Jugoslavian seminar. Malmö 14 june 1990.
by Palle Ørbæk M. D.

For at least 15 years the diagnostic entity solvent induced chronic brain damage has been in use in the Scandinavian countries. However, large inter Scandinavian variation in diagnostc criteria has always been the case but the recognition of the problem is in common.

1985, in Copenhagen, it was suggested that the solvent induced neurasthenic-depressive syndromes could be stratified in three levels of degree of severity (1). My presentation today of the clinical picture confine to Swedish practice, and thus include cases of mild and severe chronic toxic encephalopathy having definite, psychometrical deviations from standardized Swedish reference materials.

The clinical picture leads the the conceptual tool of a syndrome which is very common in most areas of medicine. I feel that is important to clarify the distinction between the monothetic assumption, that the term syndrome represents fixed groups of findings that is both sufficient and necessary, and the polythetic assumption that a common but not invariant, set of findings defines the syndrome.

More specifically I would like to cite Beckner's definition of a diagnostic syndrome (2):

1. Each individual possesses a large numbers of characters in a certain set.

2. Each character in the set is possessed by a large number of individuals.

3. No character in the set is possessed by every individual.

Clinical picture

The subjective feelings of cases, later diagnosed as chronic toxic encephalopathy, can be seen as combinations of asthenia - depressive feelings - and anxiety. The verbal expression of such thoughts and feelings is obviously very individual, and varies between social groupings and countries (figure 1).

Between countries the ways of expressing such states of mind might show large variation. Thus some methods used for screening and diagnosis might only be international on the conceptual level.

Furthermore the clinical picture of chronic toxic encephalopathy includes, the intellectual decline essential the concept of a chronic brain damage. Another

important component of the clinical picture is the individuals' reduced social functioning capacity.

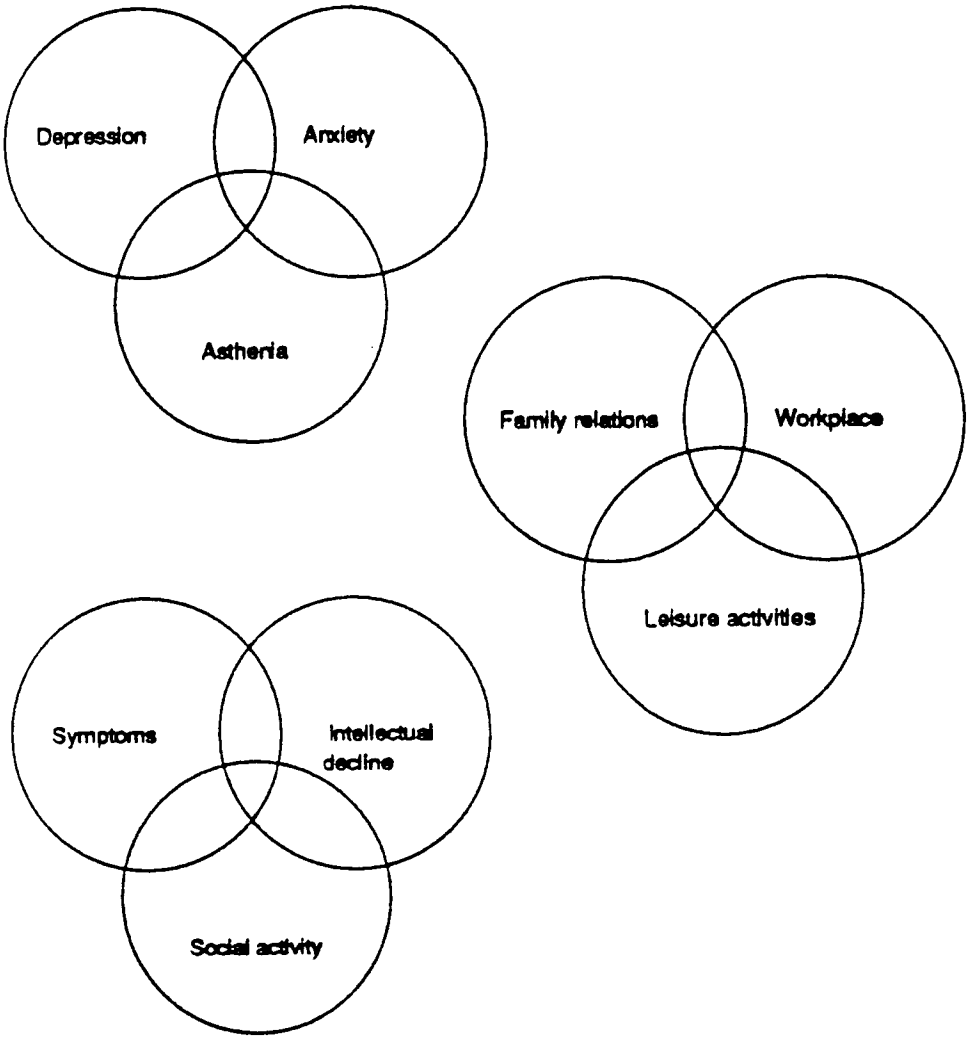

Figure 1. Various system views on toxic encephalopathy related phenomena.

The severe influence on the subjects' various social systems is very important to focus when we conceptualize the clinical picture of chronic toxic encephalopathy. My experience is that leisure activities is renounced long before working incapacity drives the subjects to their physician. Family relations have often been tense for a long time before seeking help.

Examination programme

The wide variation of clinical picture, and the many possible reasons to experience symptoms similar to chronic toxic encephalopathy, makes a comprehensive examination program nescessary.

Our clinical routine includes medical, social and neuropsychological examinations, on all new suspected cases, referred to our department (figure 2).

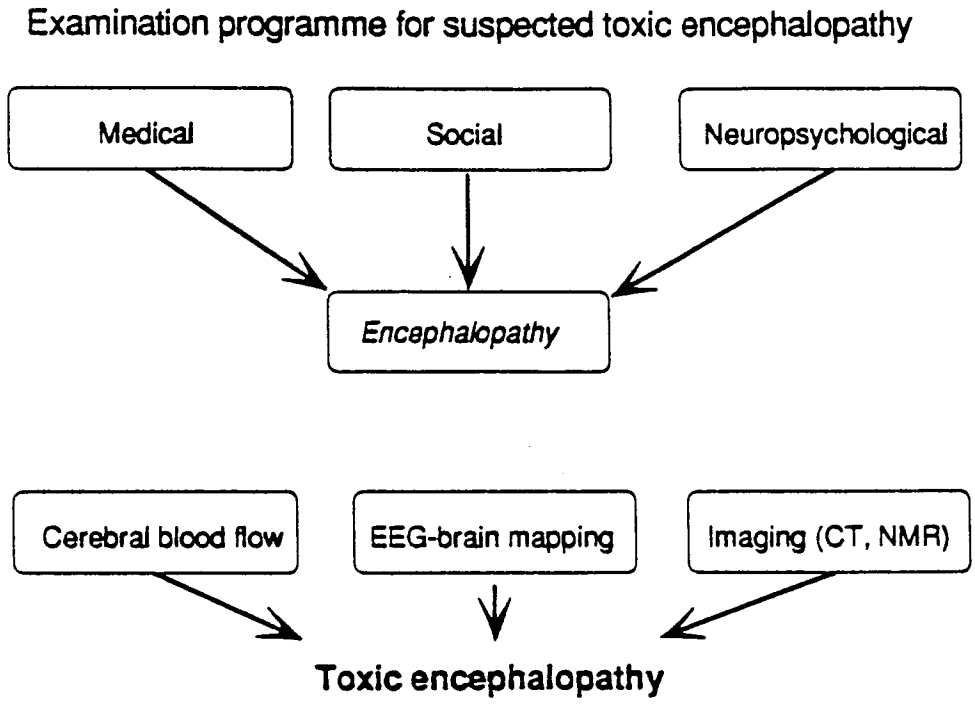

Figure 2. Examination programme for suspected encephalopathy.

If this procedure turns up with a consensus among the physician, social worker and neuropsychologist, that an encephalopathy syndrome is present, further examinations are made to elucidate possibly treatable diseases or other known causes to brain dysfunction such as various forms of dementia in their early stages. Great care is taken to evaluate possible alcohol abuse before we finally end up with diagnosing chronic toxic encephalopathy.

Symtoms and clinical findings

In a group of men, which we followed for 2 to 7 years after they were given the diagnosis chronic toxic encephalopathy, the dominant symptoms when they were examined for the first time were -recent memory failure - fatigue - problems with concentration - irritability and headache (3). Similar symptoms are reported from exposed subjects in cross-sectional studies (4, 5).

In the neuropsychological examination the cases of toxic encephalopathy performed between unexposed controls, and the first test results of a group of men, that later on was diagnosed as multi-infarction dementia (figure 3). An exception from this pattern was verbal memory test, in which the chronic toxic encephalopathy and multi-infarction groups had similarly reduced capabilities.

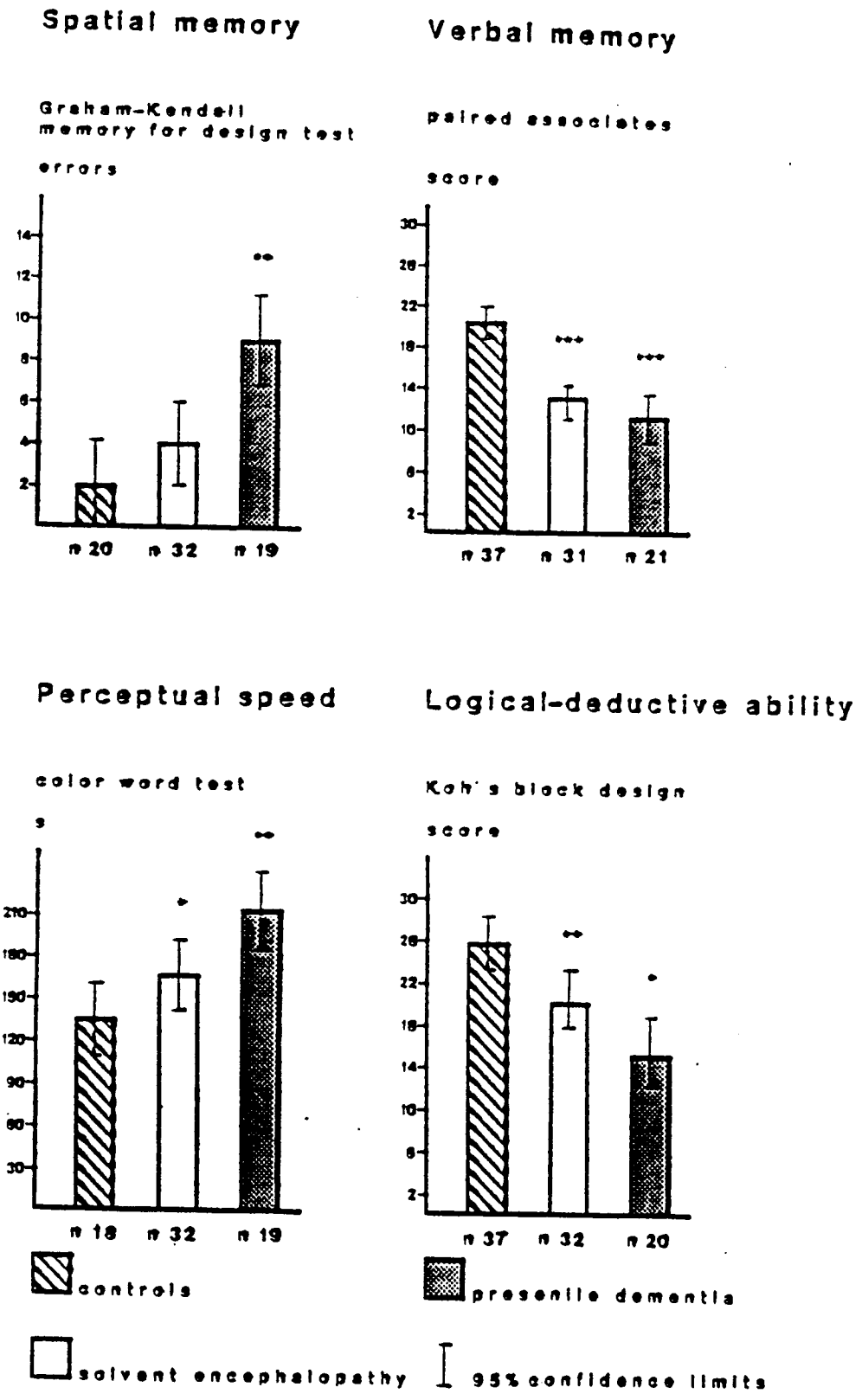

Figure 3. Test results of referents, toxic encephalopathy cases and early stage of multiinfarction presenile dementia.

Physiological examinations at diagnosis

On the EEG we found one third having increased *beta*- as well as *theta*-activity, one third had either increased *beta*- or *theta*-activity (3,6).

On computed tomography only a few had signs of cortical atrophy, and none of central atrophy. Compared with an age matched reference group the patients did not deviate in linear measurements on the CT-films (7).

Cerebral blood flow was at the lower reference limit for one third of the subjects. No dementia specific pattern was included in this group (8).

In addition to the CNS dysfunction signs, the group also frequently displayed signs of peripheral nerve dysfunction (9).

Social network changes

When we re-examined the subjects, 2 to 7 years after, they were given the diagnosis chronic toxic encephalopathy, a large social evaluation including home visits an family interviews was made.

Among other things, the subjects were found to be very restricted in social participation, and many experienced very large changes following the disease. But usually the process had started long before they seeked medical care. Leisure activities and other social participation were reduced before working was given up (table 1).

	%
Negative influence on daily family activities	86
Reduced leisure activity	81
Reduced participation in organizations	64
Fewer contacts with friends	55
Fewer visits to relatives	52
Less contact with neighbors	29

Table 1. Social activity and network changes in cases of toxic encephalopathy.

Follow-up

With the exception for memory and mood lability problems, the tendency was toward slight improvement after cessation of exposure. However, this does not imply that the symptoms had disappeared, but the mean number of core symptoms went down from 7 to 5 (3).

On psychometric testing, we found a tendency of further decline of verbal memory, but otherwise no change of test performance after cessation of exposure (6, 8, 9).

In the various physiological examinations the clinically observable tendency was toward improvement but not to complete normalization (6, 8, 9).

Conclusions

In conclusion, the clinical picture of chronic toxic encephalopathy is a syndrome, including a number of characteristic symptoms, signs of intellectual decline and reduced social participation.

Cessation of exposure may imply slight relief of symptoms, but will not by any means cure the patients. However, the cessation of exposure stops progression of the brain disorder. Thus denoting positive expectations for appropriate rehabilitation schemes.

Preliminary results, from our ongoing study on rehabilitation of chronic toxic encephalopathy cases, support the possibility of improving the patients subjective feelings, as well as their objective functioning.

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BONE MARROW RESPONSE IN CHRONIC EXPERIMENTAL BENZENE POISONING

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Benzene has been known as a hematopoietic toxin since the nineteenth century (1,2). Chronic benzene exposure results in a progressive depression of bone marrow function which leads to a reduction in the number of all circulating blood elements in both man and animals (3,4). Toxic effects on the bone marrow are dose dependent and range from the production of mild peripheral blood cytopenias to fatal aplastic anemia (3). Benzene is also a known human leukemogen (5,6) and its carcinogenic potency has recently been confirmed in experimental toxicological studies (7,8).

Early detection of minimal hematopoietic damage in biological monitoring of benzene exposed workers is still unsatisfactory (9). To date, increased red cell mean corpuscular volume (MCV) indicative of macrocytosis (10), decreased phagocytic function (11) and increased alkaline phosphatase activity of leukocytes (12), chromosomal aberrations and sister chromatide exchange abnormalities of circulating lymphocytes (13), altered serum immunoglobulin levels (14) and prolonged red blood cell glycerol hemolysis time (15) has been used with varying success.

In this study we chose a different method for detecting the toxic effects of benzene. It is well

known that the administration of certain substances such as endotoxin, etiocholanone or glucocorticosteroids will produce an increase in the peripheral blood polymorphonuclear neutrophil count and thus reflect the size of the marrow reserve pool of granulocytes (16). The method proved useful in clinical practice for evaluation of the myelotoxic effects of chemotherapy in patients with inflammatory and neoplastic diseases, and in various granulocytopenic diseases (17, 18, 19). The method has never been used for assessing the effects of acute or chronic exposure to toxic chemicals and benzene in particular. The aim of this work is to study granulocyte reserve response as an indicator of bone marrow function in experimental benzene poisoning.

MATERIALS AND METHODS

Forty-eight three months old male albino rats weighing 250-300 g. were randomly divided into four experimental groups of twelve animals each. The animals were housed in plastic cages, covered with stainless steel mesh, with three animals per cage. They were fed standard laboratory rat diet (Biotehnološki fakultet, Ljubljana, Yugoslavia) and drank tap

water ad libitum. The Control group received no treatment at all. Rats in the second group (Oil) were administered subcutaneously (s.c.) 1 ml of olive oil ("Ljekarne Zagreb", Zagreb, Yugoslavia) five days per week over the three weeks, i.e. 15 doses in all. The third group (B 440) and the fourth group (B 880) were administered s.c. 440 mg/kg (vol 0.5 ml/kg) and 880 mg/kg (vol. 1.0 ml/kg) of benzene in olive oil respectively. Chromatoquality grade benzene ("Kemika", Zagreb, Yugoslavia) in olive oil (50% v/v) was administered.

At the end of the treatment all animals received a single i.v. dose of 1 mg dexamethasone-Na ("Krka", Novo Mesto, Yugoslavia). Blood samples were obtained from the tail vein and white blood cell and differential counts were performed before administration of dexamethasone and at 2, 4 and 6 hours thereafter. The total white cell count was determined in Bürker-Türck chambers after dilution with Türck solution 1:10.

Peripheral blood smears were prepared and stained using a May-Grünwald-Giemsa stain and two hundred cells counted under oil immersion.(20) The number of leucocytes, lymphocytes and granulocytes was expressed in S.T. units ($x10^9/L$). The individual granulocyte responses were determined by subtracting the number of

granulocytes before the administration of dexamethasone (initial) from the maximum number of granulocytes observed thereafter (maximal response).

The results were expressed as arithmetic means with standard deviation of the mean and the significance of the difference was assessed by Student's t test at $P < 0.05$ level.

RESULTS

Chronic benzene poisoning was followed by a decreased number of leukocytes in the peripheral circulation in relation to control animals ($P < 0.05$). The impairment was more prominent with a higher dose of benzene (B 880) than with a lower dose (B 440) ($P<0.05$) indicating the dose dependent effect. Two animals on high benzene dose (B 880) died before the end of the experimental treatment indicating that the sublethal dose/rate had been reached.

Peripheral lymphocytes appeared more sensitive to benzene poisoning than granulocytes. Olive oil vehicles had a stimulating affect upon both lymphocytes and granulocytes in peripheral circulation probably due to inflammatory response. Considering the fact that the

same olive oil was used as a vehicle in benzene poisoned rats the deleterious effect of benzene on white cells is even more significant (Table 1, Fig. 1).

Apparently no response, assessed by an increase in granulocytes in peripheral blood, was observed in both groups of benzene treated rats, i.e. B 440 and B 880. ($P < 0.05$ for both groups) respectively, if compared to the Control and Oil group. The number of granulocytes in the Control group increased by more than double, indicating a normal response of bone marrow to dexamethasone. The response of granulocytes in the olive oil group was about twice the normal response also (Table 2, Fig. 2). The peak values of granulocytes in peripheral circulation were observed four hours after the administration of corticosteroids in the control and oil group respectively (Fig. 3).

DISCUSSION

The study of experimentally induced benzene toxicity has traditionally been concentrated on evaluation of quantitative and qualitative charges in recognizable hemic elements (4). In this study a dose dependant decrease in a number of circulating leukocytes - mostly lymphocytes - was observed in benzene treated animals. Similar reports demonstrated peripheral

cytopenia accompanied by a variable marrow profile in poisoned animals (4).

In this study we determined granulocyte increment at three different time intervals after glucocorticoid stimulation, as a measure of marrow function. The principal mechanism of this phenomenon is a mobilization of granulocytes from the bone marrow reserves (21,22). In benzene treated rats there was a statistically significant reduction of mean granulocyte responses as compared to controls ($P < 0.05$), but no significant difference was observed between the two benzene dose levels.

These preliminary results indicate that bone marrow granulocyte reserve response is seriously affected in chronic experimental benzene poisoning. Further studies on experimental models at different dose regimens and in comparison with other methods indicating early benzene hemotoxicity are necessary. This assay should also be evaluated in human benzene exposure, in individuals with suspected benzene hemotoxicity and in preemployment and periodic medical examinations of benzene workers.

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Table 1. White blood cells in chronic benzene poisoning ($\times 10^9$/L)*

Group	Leukocytes	Lymphocytes	Granulocytes
Control	$9,51 \pm 2,29^{a}$	$4,94 \pm 1,69^{a}$	$3,58 \pm 1,39^{a,b}$
Oil	$13,08 \pm 3,38^{b}$	$9,00 \pm 3,65^{b}$	$5,69 \pm 3,32^{a}$
B 440	$6,59 + 3,06^{c}$	$2,05 \pm 1,51^{c}$	$3,86 \pm 1,68^{a,b}$
B 880	$3,49 \pm 3,00^{d}$	$0,87 \pm 0,85^{d}$	$2,26 \pm 2,05^{b}$

* Mean ($\overline{X}_{12}$) $\pm$ SD except for B 880 where Mean ($\overline{X}_{10}$) as two animals had died before the end of treatment

$^{a-d}$Means bearing various superscript in the same column differ significantly ($P < 0,05$)

Table 2. The granulocyte response in chronic benzene poisoning

Group	Granulocyte count * ($\times 10^9$/L)	
	Initial	Maximal response
Control	$3.58 \pm 1.39^{a,b}$	10.97 ± 4.7^{a}
Oil	5.69 ± 3.32^{a}	10.90 ± 6.59^{a}
B 440	$3.86 \pm 1.68^{a,b}$	3.12 ± 3.58^{b}
B 880	2.26 ± 2.05^{b}	2.73 ± 3.90^{b}

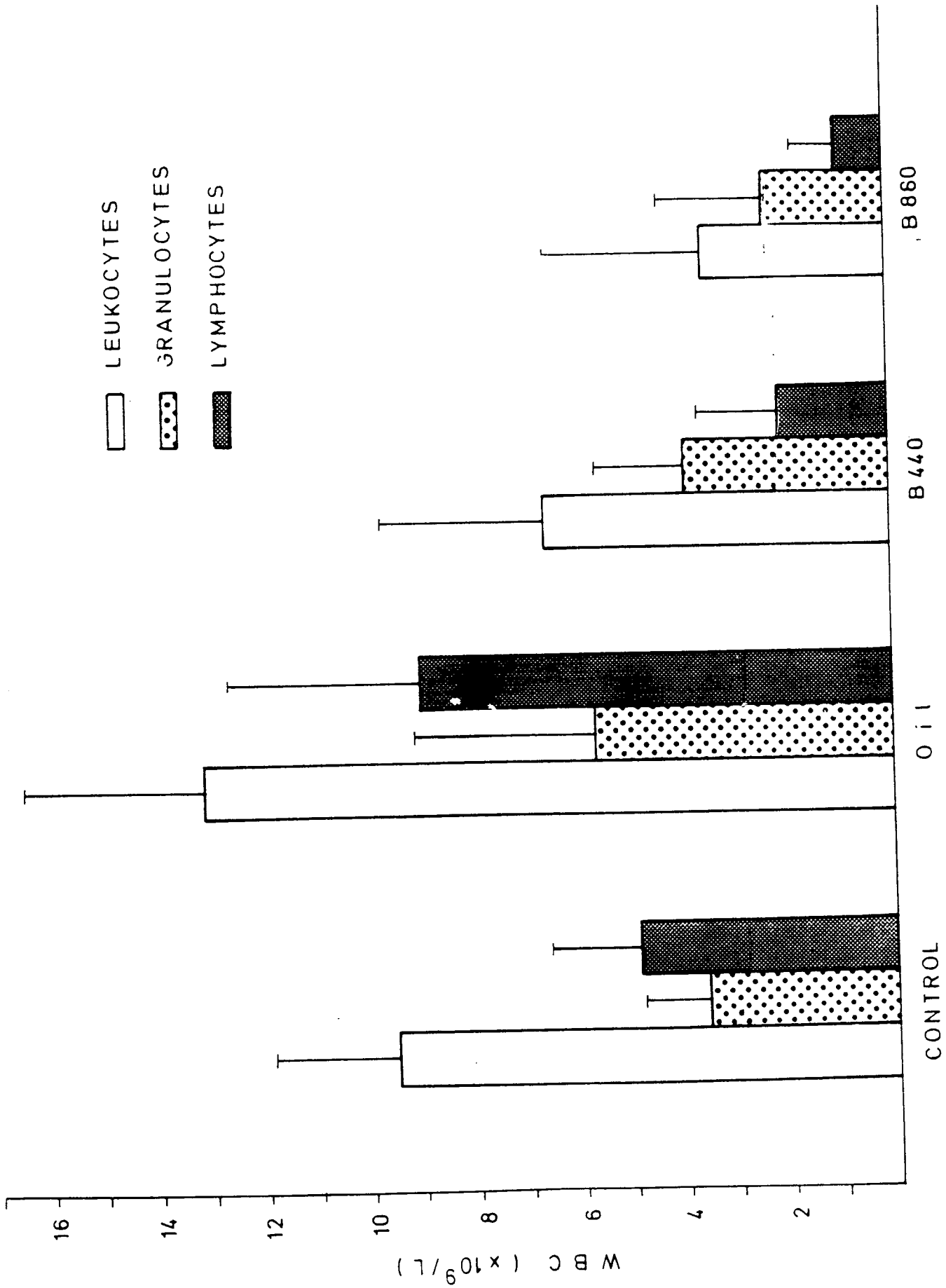
* Mean ($\bar{X}_{12}$) $\pm$ SD except for B 880 where Mean ($\bar{X}_{10}$) as two animals died before the end of treatment.

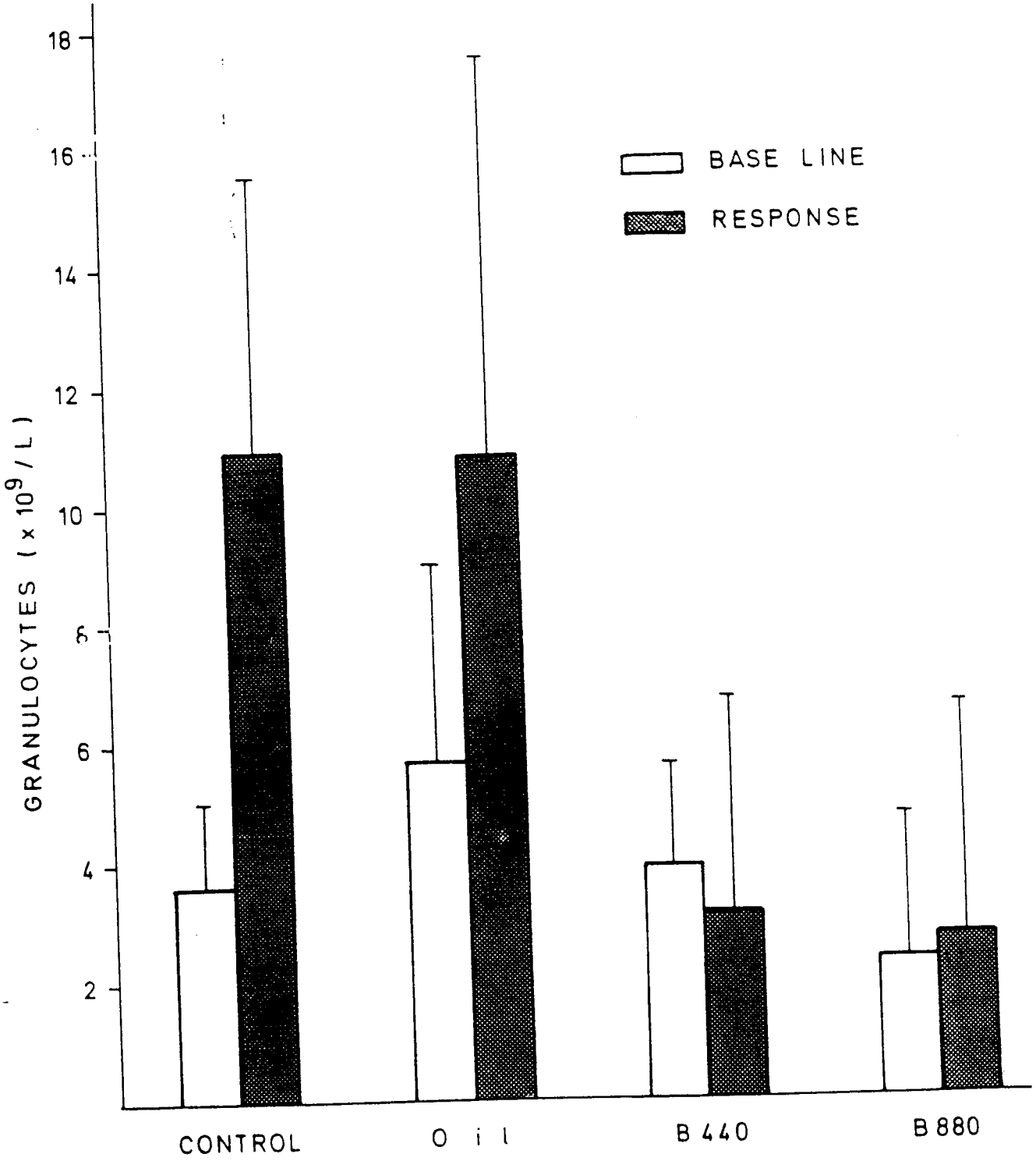
a-b Means bearing various superscript in the same column differ significantly ($P < 0.05$)

Figure 1. Peripheral white blood cells (WBC) in chronic benzene poisoning (Mean ($\bar{X}_{12}$) $\pm$ SD except for B 880 where $\bar{X}_{10}$)

Figure 2. Granulocyte response to i.v. dexamethasone in chronic benzene poisoning (○ Control, △ Oil, ● B 440, ▲ B 880)

Figure 3. Maximal granulocyte response to i.v. dexamethasone in chronic benzene poisoning


LEUKOCYTES
GRANULOCYTES
LYMPHOCYTES
WBC (x10⁹/L)
16
14
12
10
8
6
4
2
CONTROL
Oil
B 440
B 860


18
16
14
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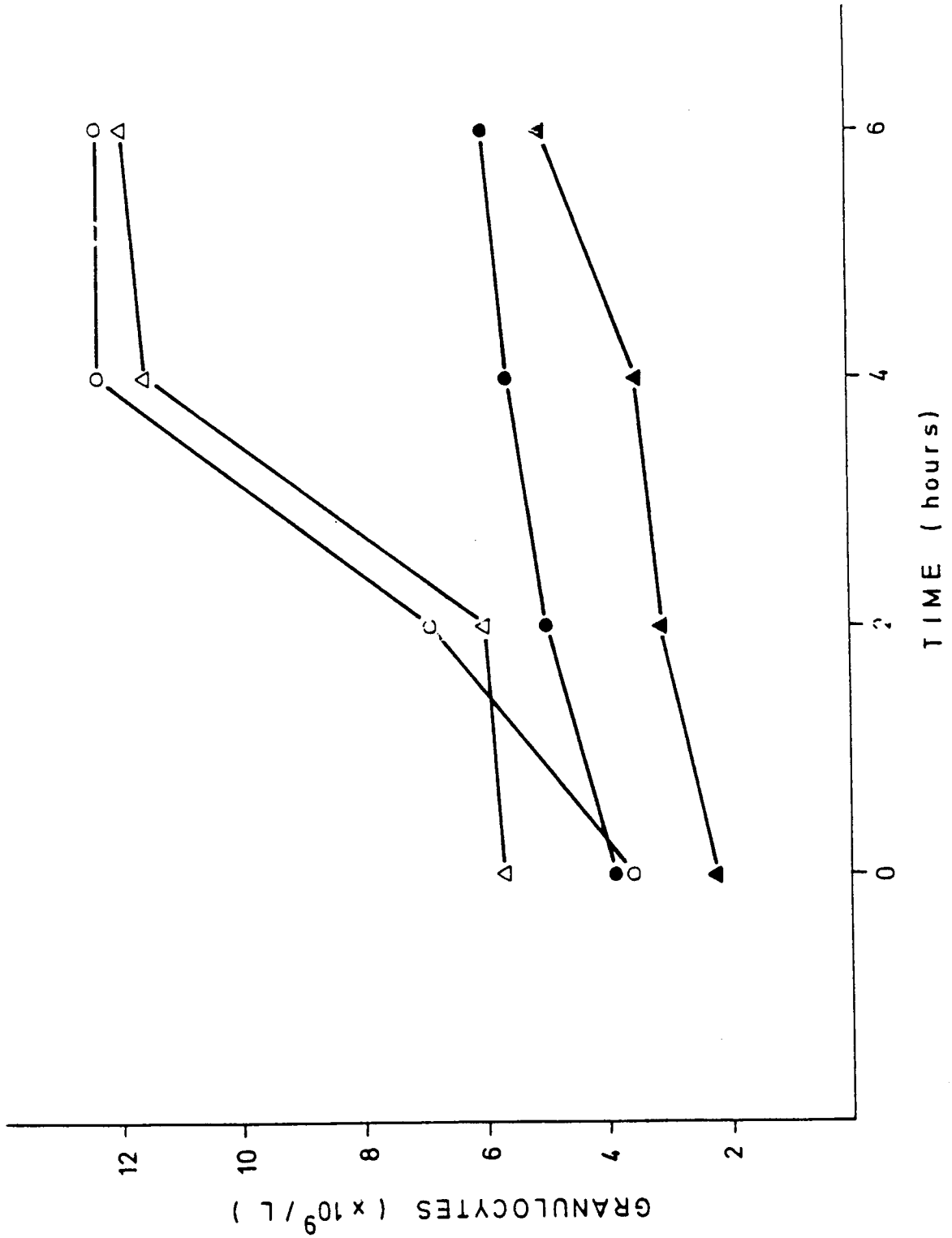
10
6
4
2
GRANULOCYTES (x 10^9 / L)
BASE LINE
RESPONSE
CONTROL
O i l
B 440
B 880


CONTROL
Oil
B 440
B 880
GRANULOCYTES (x 10⁹ / L)
12
10
8
6
4
2
0
2
4
6
TIME (hours)

Bone Marrow Response in Chronic Experimental Benzene Poisoning

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Glucocorticosteroid administration induces transient leukocytosis by releasing granulocytes from the bone marrow in man and animals. The bone marrow reserve of granulocytes is a critical element of normal host defences against infection and it has been used in clinical practice to evaluate the myelotoxic effects of chemotherapy in patients with inflammatory and neoplastic diseases, and other granulocytopenic diseases. The aim of this study is to estimate bone marrow granulocyte reserves in chronic benzene-poisoned rats as an indicator of benzene hematotoxicity.

Three months old male albino rats were randomly divided into four experimental groups of 12 animals each: (1) Control, (2) Oil, (3) B 440 and (4) B 880. The Control group was fed standard laboratory rat diet and drank distilled water ad libitum only. The Oil group was administered 1 ml of olive oil which served as a vehicle s.c. five days per week over the three weeks, totalling 15 doses. The third group (B 440) and the fourth group (B 880) were administered in the same way 440 mg/kg (0.5 ml/kg) and 880 mg/kg (1.0 ml/kg) of benzene in olive oil respectively. At the end of the treatment all animals received a single i.v. dose of 1 mg dexamethasone-Na ("Krka", Novo Mesto, Yugoslavia). Blood samples were

obtained from the tail vein and white blood cell and differential counts were made before administration of dexamethasone and at 2, 4 and 6 hours thereafter. The results are expressed as an arithmetic mean with standard deviations and the significance of the difference was tested by Student's t-test.

The initial leukocyte counts ($x\ 10^9/l$) were, in decreasing order, 13.08 ± 3.38 (Oil), 9.51 ± 2.29 (Control), 6.59 ± 3.06 (B 440), 3.49 ± 3.00 (B 880) ($P < 0.05$ for each group). The leukocyte count was mostly suppressed by the highest benzene level which appears sublethal as two animals had died during the treatment. The peak values of leukocytes after dexamethasone administration, were higher for the Control (7.6 ± 5.79) and Oil group (5.89 ± 5.85) of animals as compared to the B 440 (2.34 ± 3.81) and B 880 (2.19 ± 3.19) groups. (Control = Oil > B 440 = B 880) ($P < 0.05$).

The results show that bone marrow response in rats is seriously affected by experimental chronic benzene poisoning.

Lecture 900614.

MORTALITY AND CANCER MORBIDITY IN TOLUENE EXPOSED ROTOGRAVURE PRINTERS.

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Reports from some epidemiological studies indicate an association between exposure to organic solvents and risk for malignant tumours. There are, however, also studies, which have failed to confirm these results. Further, the positive studies are not consistent as to type of tumour.

Most of these epidemiological studies concern populations with exposure to a mixture of different organic solvents. One of the most used solvents is toluene, and toluene is often a part of the "mixed solvent exposure", common in many trades. Therefore, toluene is of special interest. Also, toluene has a chemical structure which is very similar to that of benzene, which, as you know, is an established human carcinogen.

We therefore felt a need to study cancer morbidity in a population for which toluene is a dominant exposure, and not just one of many others in a solvent mixture.

Rotogravure printing industries use toluene as a major solvent, and, therefore, workers from these industries can be used for epidemiological cohort studies of this kind.

At the time of the study there were nine rotogravure plants in Sweden, and they were all invited to participate. Eight responded positively and are included in the study.

From each company´s records relevant informations were obtained for all workers who had been employed for three months or more from the time of the start of rotogravure printing in each company to 1985.

There were 1020 cohort members. Rotogravure printing started between 1920 and 1961 in the eight companies. The company G have used some other solvents beside toluene in their printing (Table 1).

Vital status was determined up to 31 December 1986 (Table 2). Ten subjects (about 1%) were lost in follow up. When considering subjects employed for five years or more, only two (0.4%) were not found.

Death certificates were obtained for all subjects who died between 1952 and 1986 from the National Swedish Central Bureau of Statistics. These certificates were based on aoutopsy in 71% of the cases. Further, information on all tumours diagnosed from 1958 to 1985 was obtained from the Southern Swedish Regional and the National Swedish tumour Registers.

Expected **mortality** for the period 1952-86 was calculated using rates specific for each geographical area, where we had a factory (Malmö, Stockholm and the county of Malmöhus), and also specific for sex, calendar-year, cause of death, and five year age group.

Similarly, yearly **morbidity** rates for cancer were obtained and used. Only deaths or tumours before the age of 80 have been included.

Cause specific standardised mortality or morbidity ratios (SMRs) and 95% confidence limits (CLs) have been calculated.

EXPOSURE

Gun Nise has done a great work and made special efforts in estimating the past exposure. Exposure history has been evaluated for the six major rotogravure printing plants where toluene was the dominant solvent used.

The method used in these evaluations is in principle: a) visits to all the plants to get a picture of the present conditions; b) measurements of toluene concentrations in air in some of the plants; c) determinations of toluene concentrations in biological samples (blood and subcutaneous fat) from workers

in the same plants; d) collection and detailed study of all written material about the plants´ occupational environments, and e) interviews with workers with a long employment period in rotogravure printing.

ad b) and c): In three plants (C,D,F) Gun made extensive studies of the present concentrations of toluene in air by personal monitoring. The workers were followed for seven weeks in all. At the same time samples of blood and subcutaneous fat were collected and analysed for toluene.

ad d) As to earlier measurements, sporadic reports on toluene in air wre found from 1969 on. There were some informations on air levels as far back as 1943. Since 1975 more extensive measurements have been made in all plants.

ad e) All workers in plants C;D and F have been interviewed about their past and present working conditions. Some had more than 40 years experience of rotogravure printing.

After collecting and studying all information thoroughly, Gun made the exposure evaluation, beginning by estimating the average toluene air concentration of oday in each plant. Then, locking backwards stepwise, the exposure levels were revised whenever there was any improvement in occupational hygiene. (The estimates are summarised in Figure 1).

RESULTS

Mortality

129 deaths were observed vs. 125 expected (Figure 2). There were no excess in some **non-malignant** diseases of special interest.

There was an increased risk of dying from **malignant** disease (Figure 3) with SMR=1.36. However, the lower 95% CL was =.99. There were statistically significant increases in deaths from tumours in the gastro-intestinal tracts (SMR=2.06), including both stomach (SMR=2.72) and colon/rectum (SMR=2.18); the later, however, not significant.

When a minimum time of at least 5 years of exposure and 10 years latency time was applied, there still was an increase in deaths from tumours of the gastro-intestinal tract (SMR=2.09).

Tumour morbidity

During 1958 - 1985, 68 malignant tumours were registered in the cohort compared to 54 expected (SMR=1.26; Figure 4). Among the specific cancers, only those of the respiratory tract were significantly increased (SMR= 1.76). The increase in respiratory cancers was, however, no longer seen when 5 years exposure time and 10 years latency time was demanded.

There were no associations between cumulated dose of toluene and SMRs for all tumour sites (Figure 5), gastrointestinal, or respiratory tumours respectively.

DISCUSSION

Validity

a) No selection
b) Small loss in follow up
c) Rather high diagnostic accuracy
d) Reference rates
e) Confounding (life-style factors)
f) Exposure estimates

ad a) Health examinations before starting work have been done in some of the plants during recent years, for most of the accumulated time there has been no active selection of healthy workers.

ad b) The loss in follow up is small.

ad c) 71% of the death certificates were based on necropsies and the cohort members lived near big hospitals, well equipped for diagnosing tumours.

ad d) The workers in the cohort come from different parts of Sweden. The common procedure in this kind of epidemiological study is to use national rates. If such rates had been used for reference the SMR for deaths from respiratory cancer would have been significantly raised to 2.72. About half the cohort came from plants in Stockholm area, where the incidence of lung cancer is about twice that for all Sweden. We have thus chosen reference rates from different regions corresponding to the locations of the plants, which must be more appropriate.

ad e) We have no information on possible confounding lifestyle factors, such as smoking and alcohol consumption. However, deaths from diseases related to smoking or alcohol were not increased.

Mortality and morbidity

The "healthy worker effect", often seen in epidemiological studies of working populations was not seen. In fact, the total number of deaths was a little higher than expected, which might indicate an increased mortality.

There was an increase in deaths from stomach cancer. However, the statistical significance in this finding was lost when exposure- and latency-time was considered, and there was no no dose-response relation. Thus conclusion must be somewhat guarded.

For some periods, the workers in our cohort have been exposed to bensene, which is an established cause of acute myeloic leukaemia. Also lymphomas and myelomas have been reported after exposure to benzene. These tumors were not increased in the present cohort. These tumours are rare. The power to detect a SMR of at least 3.0 in this study, based on given expected values have been calculated to 71 % for lymphomas and only 50% for leukaemias. There is also reason to believe that metabolic transformation of benzene to reactive metabolites is inhibited by simultaneous toluene exposure.

So, this toluene exposed cohort did not reveal any dramatic increases in tumour risks. We could not confirm that toluene is a human carcinogen.

However, most malignant tumours have a long latency time and the effects of a harmful working environment often appear late. As the major part of our cohort is still young, further follow up is necessary and the cohort will therefore be under continued observation.

REFERENCE: Svensson, Nise, Englander, Attewell, Skerfving, Möller: Deaths and tumours among rotogravure printers exposed to toluene. Br J Ind Med 1990; 47:372-379.

LEGENDS

Figure 1. Median (thick line) and range (thin lines) of estimated average toluene concentration at six factories using toluene as dominant solvent between 1920 and 1985.

Figure 2. Observed (O) and expected (E) mortality in a cohort of rotogravure printers. SMRs and 95% confidence intervals given.

Figure 3. Observed (O) and expected (E) mortality in tumours in a cohort of rotogravure printers. SMRs and 95% confidence intervals given.

Figure 4. Observed (O) and expected (E) cancer morbidity in a cohort of rotogravure printers. SMRs and 95% confidence intervals given.

Figure 5. SMR for all malignant tumors, gastrointestinal, and respiratory tumours according to cumulated dose of toluene acquired up tp ten years previously. Thin lines indicate 95% confidence intervals.

Table 1. Number of cohort members from the different plants and first year of rotogravure printing.

Plant	Cohort members	Start of rotogravure printing, year
A	228	1920
B	74	1932
C	94	1956
D	60	1948
E	132	1961
F	231	1935
G	190	
H	11	
Total	**1020**	

Table 2. Vital status of the cohort, 1986.

Vital status	All N	%	> 5 years employment > 10 years latency N	%
Living	839	82	397	80
Dead	131	13	92	19
Emigrated	43	4	5	1
Unknown (insuff. identity)	7	1	2	-
Total	1020	100	496	100

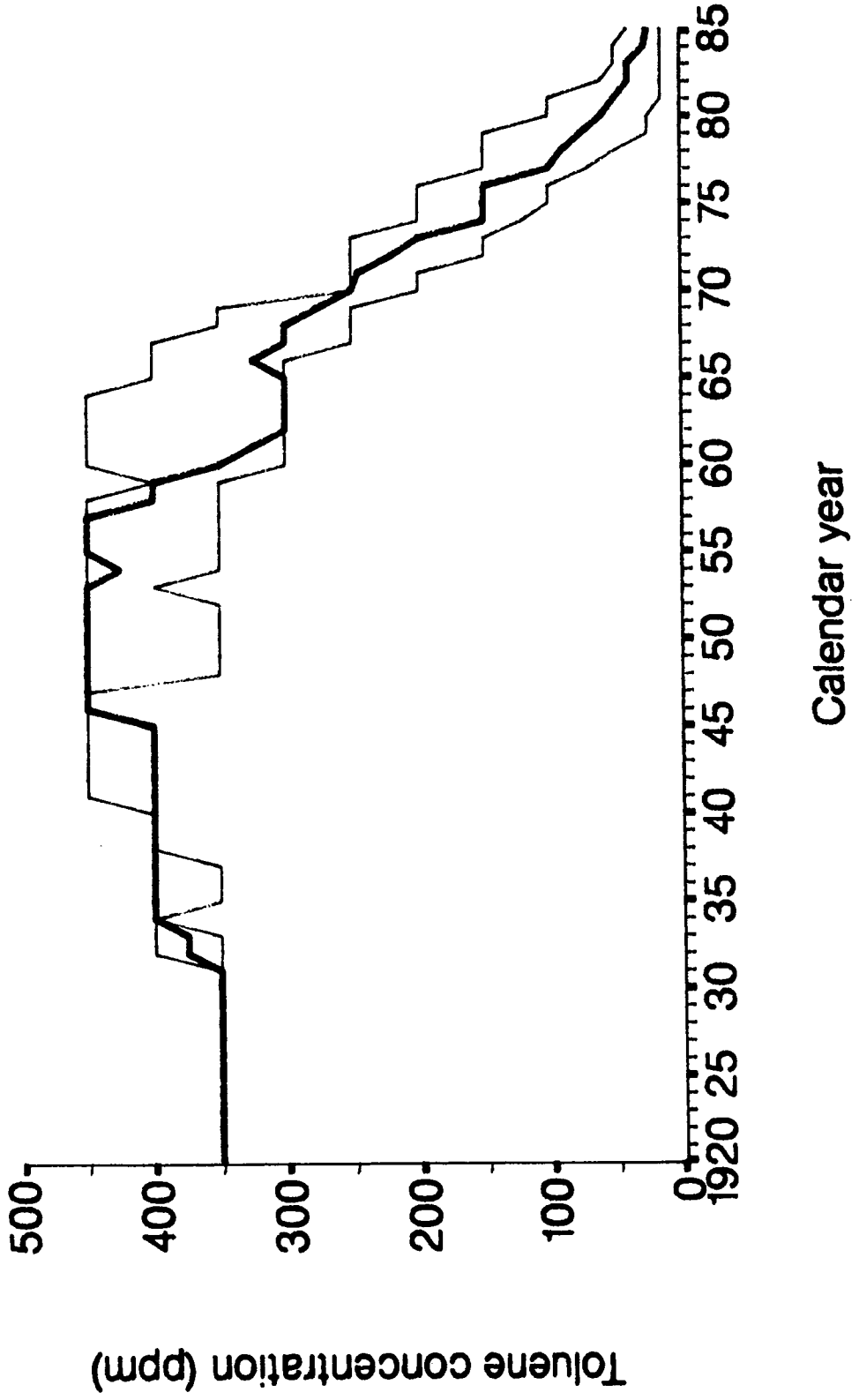
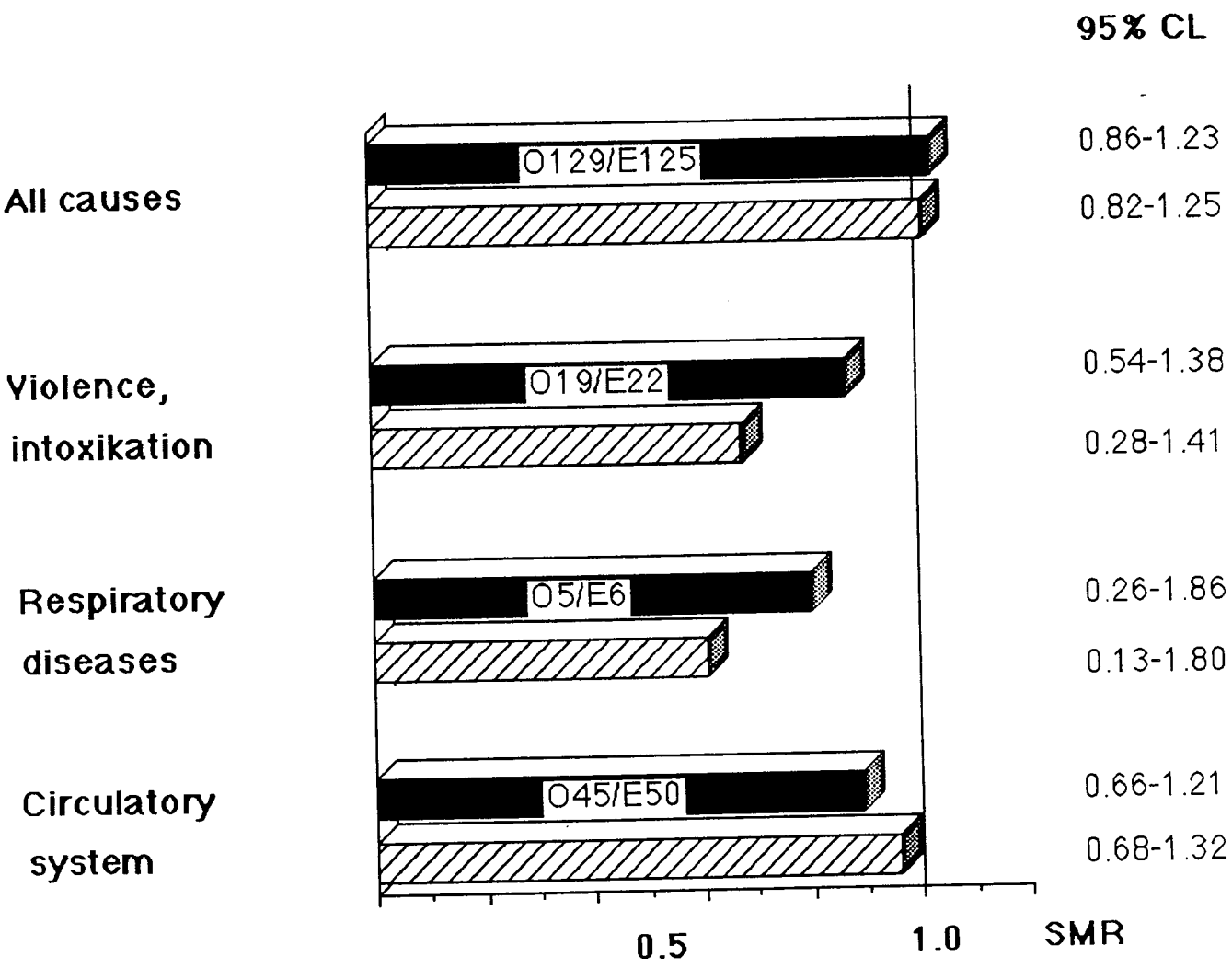

Toluene concentration (ppm)
500
400
300
200
100
0
1920 25 30 35 40 45 50 55 60 65 70 75 80 85
Calendar year

Figure 1

Mortality. Non – malignant diseases.



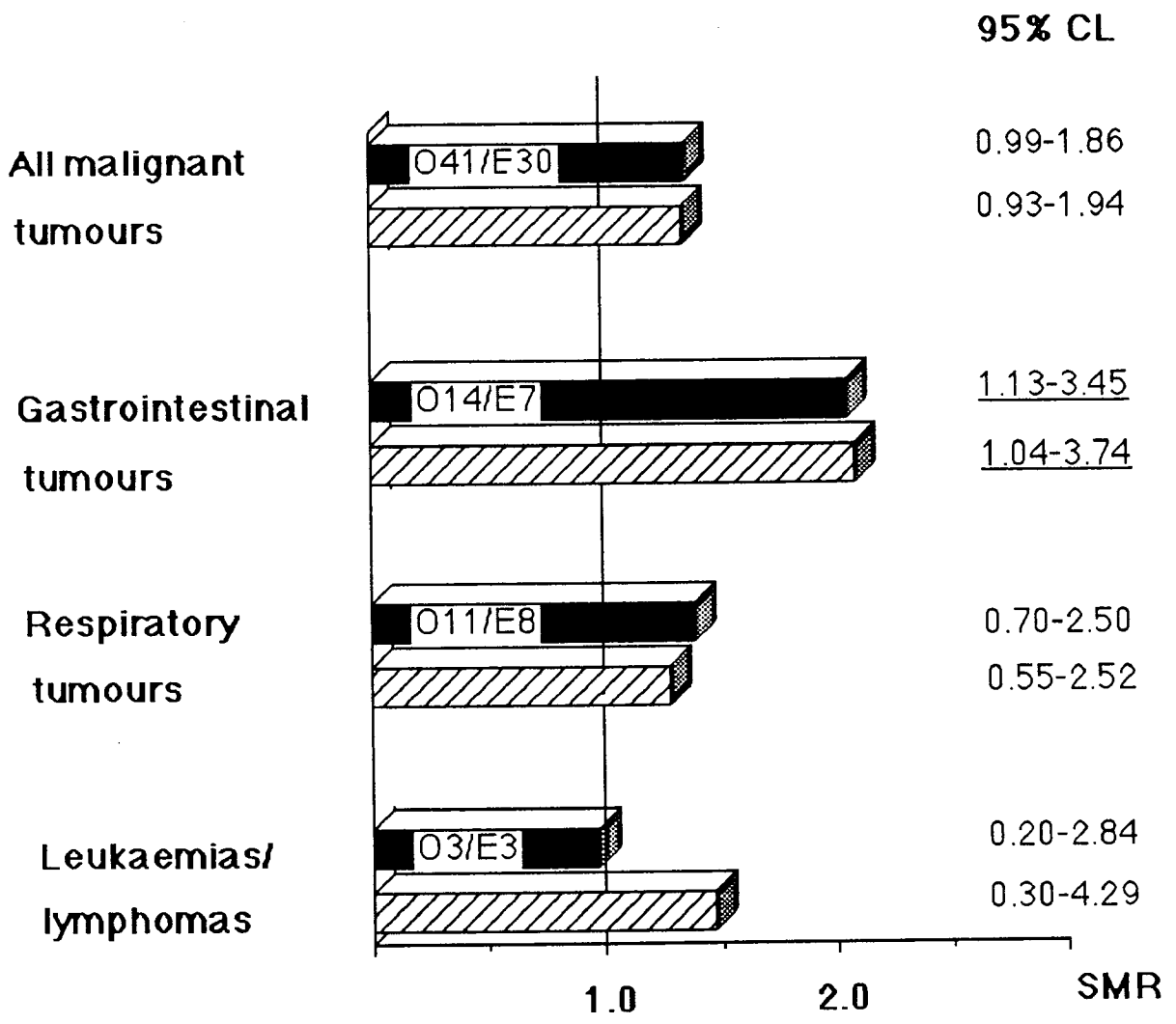
All. 1,013 subjects. 21,373 subjects under obs.

> 5 years exposure. > 10 years latency time.

506 subjects. 8,615 person-years under obs.

Figure 2

Mortality. Malignant neoplasms.



All. 1,013 subjects. 21,373 person-years under obs.

> 5 years of exposure. > 10 years latency time.
506 subjects. 8,615 person-years under obs.

Figure 3

Tumour morbidity 1958 - 1985.

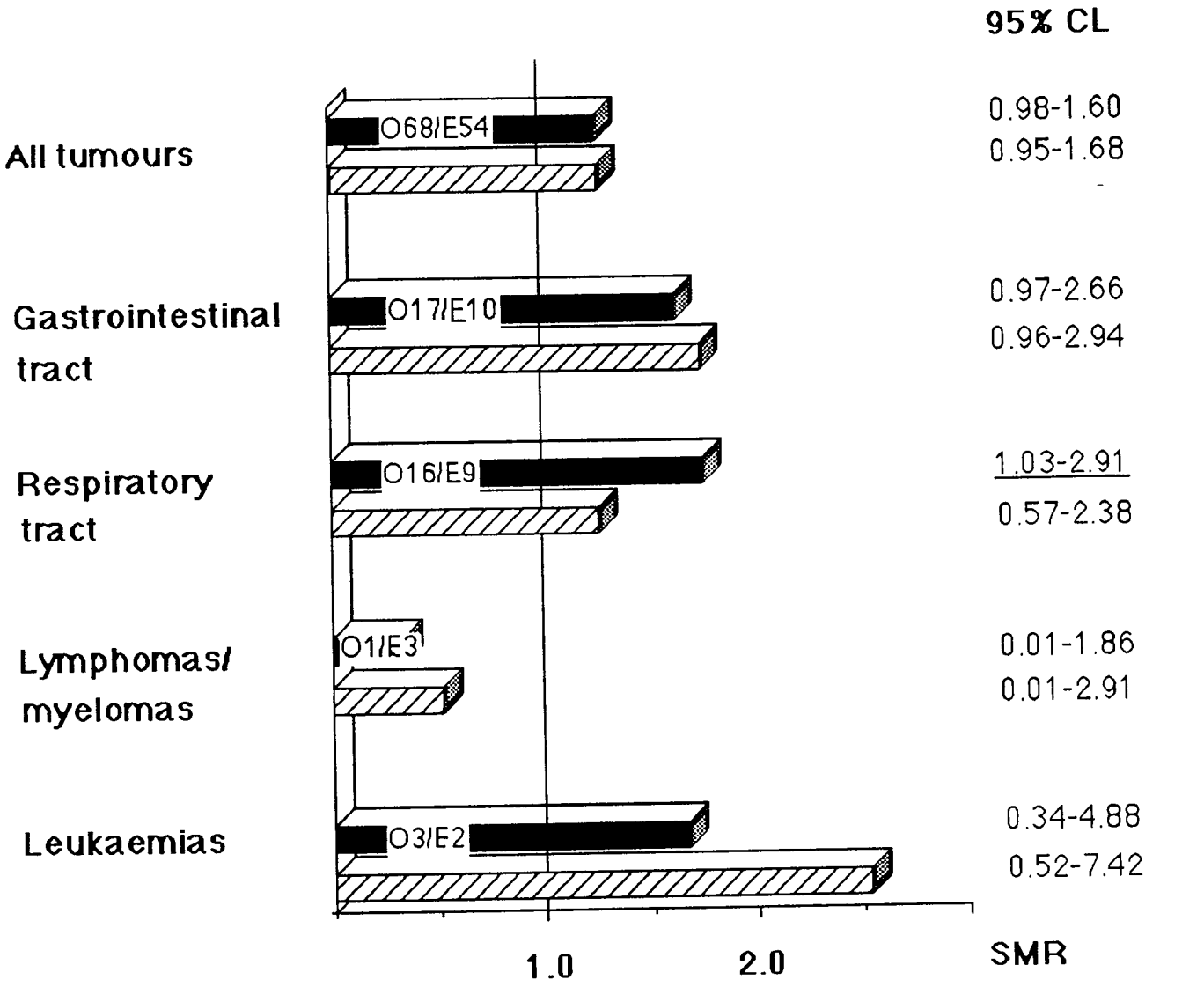


Figure 4

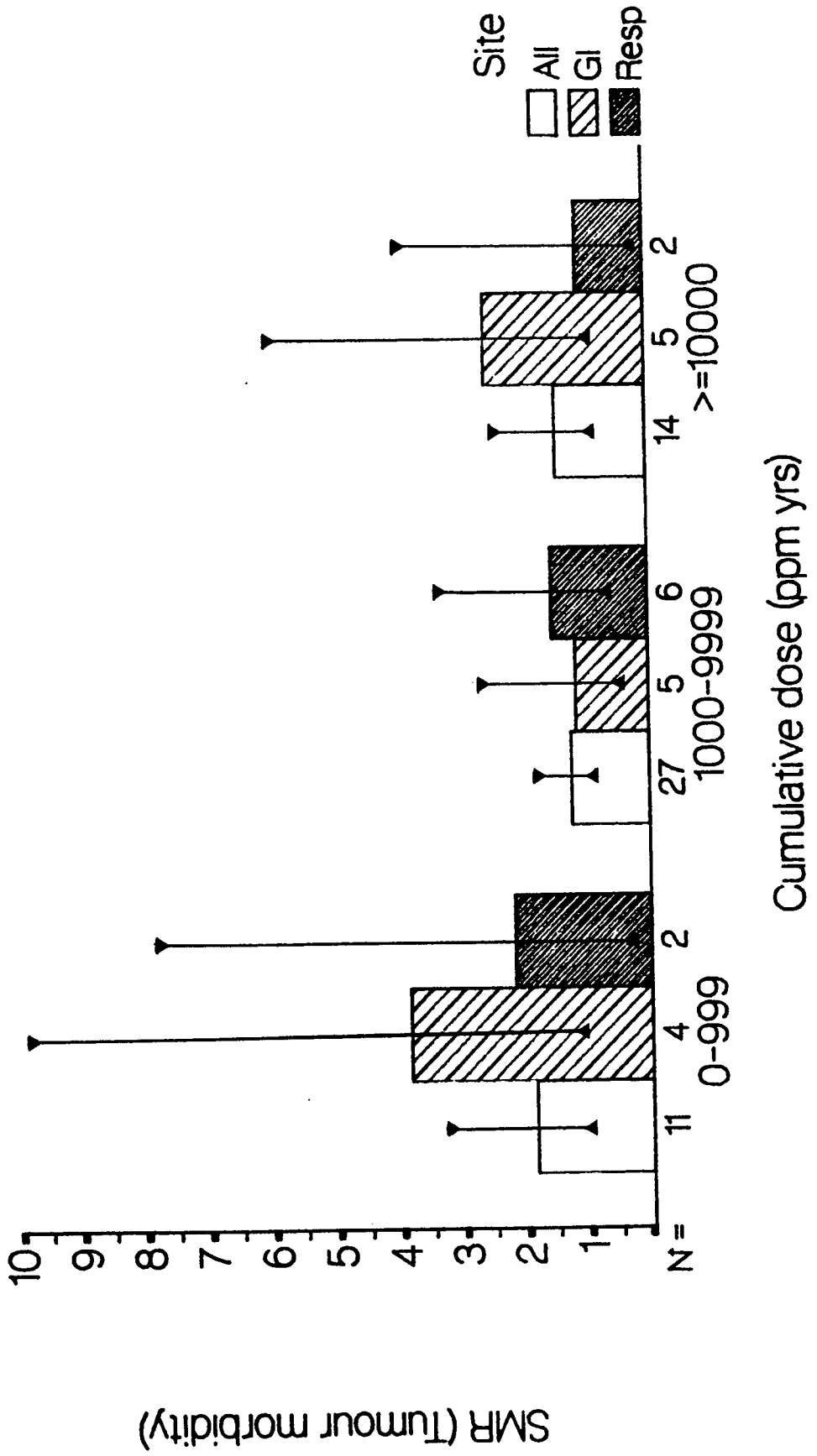

SMR (Tumour morbidity)
10
9
8
7
6
5
4
3
2
1
N =
11
4
2
0-999
27
5
6
1000-9999
14
5
2
>=10000
Cumulative dose (ppm yrs)
Site
All
GI
Resp

Figure 5

A SELECTION OF BIOLOGICAL INDICATORS IN OCCUPATIONAL EXPOSURE TO TOLUENE AND XYLENE

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In order to select the most appropriate biological indicators in biological monitoring of toluene and xylene absorption in conditions of occupational exposure, a comparative study of themselves and their metabolites in the blood and urine of workers occupationally exposed to toluene (N=5) and xylene (N=19) was carried out. It was found that toluene in blood after work is the best indicator of toluene exposure and both xylene in blood and its only major metabolite methylhippuric acid in urine are good indicators of xylene exposure. The still conflicting results on the validity of hippuric acid and o-cresol, as toluene exposure indicators were also confirmed.

Neurotoxicity of solvents represents one of the most important issues in occupational health. Damage to the central nervous system by solvents is potentially irreversible and for development of an adequate programme of prevention it is essential to define the early effects of solvents on any target organ. Simultaneously the establishment of the relationship between early clinical signs of exposure and the levels of solvents and/ /or their metabolites in biological samples is of the same importance. Up to now such integral investigations have not been carried out in our country. Ascertainment of possible chronic CNS damage in occupational exposure to toluene and the comparatively small number of papers on chronic xylene toxicity have brought to light the need for establishing the most reliable indicators in biological monitoring. Our objective was to perform a comparative study of toluene and xylene absorption in actual conditions of occupational exposure by determining toluene and xylene in blood and their metabolites in urine. It was anticipated that the results obtained would be a realistic basis for recommendation of the most appropriate indicator in biological monitoring of occupational exposure to toluene and xylene.

SUBJECTS AND METHODS

The study was performed in 24 workers employed in a paint factory. Among them five were exposed to toluene and 19 to xylene. The occupational and health histories of all subjects, all male, were recorded as were data on medical treatment, chronic diseases, smoking habit and alcohol consumption. Their characteristics are presented (Table 1). Toluene and xylene in the working atmosphere were measured twice a year. Their concentrations showed a very wide range (toluene 6-350 mg m^{-3}; xylene 16-185 mg m^{-3}) sometimes even higher than MAC for Yugoslavia (200 mg m^{-3} for toluene; 50 mg m^{-3} for xylene). Since biological indicators were the first aim of this study, ambiental monitoring was less important.

The exposed subjects were examined three times: on Monday morning before work (a) and on Wednesday before (b), and at the end of, the work-shift (c). Each time venous blood and urine samples were taken. Blood was analysed on the same day and urine samples were frozen at -20 ^{o}C until analysed. Toluene and xylene in blood were determined by head-space method described by Angerer et al. with own modifications[1], hippuric and m-methylhippuric acids in urine by extraction method of Buchet and Lauwerys[2], and o-cresol in urine by Sherwood's and Carter's extraction method[3]. All applied methods were gas chromatographical and are in accordance with the accepted criteria for reliability. It should be mentioned that having no standards of o- and m-isomers only m-xylene in blood and m-methylhippuric acid in urine were analysed. It does not significantly influence the objective of the study since m-xylene is predominant isomer in a typical xylene mixture.

The results for toluene, m-xylene, hippuric and m-methylhippuric acids and o-cresol are presented as median and range values since the distribution of results is skewed. The significance of the differences between the three periods for all examined parameters within the group was tested by paired Student's t-test. The correlation analyses were done by standard statistical method.

RESULTS AND DISCUSSION

Neither m-xylene nor m-methylhippuric acid were detected in any sample of the blood and urine of five workers exposed to toluene, which confirms that they were not exposed to xylene. Therefore in Table 2 only toluene, hippuric acid and o-cresol results are presented.

In all blood samples from Monday before the start of work toluene was found and its concentration increased significantly during the working week. Hippuric acid in urine was higher on Wednesday after work in comparison with both concentrations before work but no difference was statistically significant. Median values of o-cresol were very similar on Wednesday before and after work although both higher than the median value on Monday. Such a result is difficult to explain and similar investigations are planned with a greater number of workers exposed to toluene. Owing to a small number of subjects the correlation analyses between indicators were not done.

In a very detailed and well elaborated study on toluene by Nise and Ørbaek[4] the relation between toluene in the working atmosphere and toluene in blood after work was established. Exposure to 300 mg m^{-3} corresponds to a post-shift toluene in blood of 0.75 mg L^{-1} which is comparable with the biological limit value set by ACGIH of 1.0 mg toluene per liter of blood at 375 mg m^{-3} toluene in air[5]. In the presented study only one subject had such a high toluene concentration in blood (1.004 mg L^{-1}). The Yugoslav maximal allowed concentration of toluene in the working atmosphere is 200 mg m^{-3} [6]. According to the upper relation this concentration could cause an average blood toluene concentration of 0.54 mg L^{-1}. Since we found a higher median concentration of 0.66 mg L^{-1} it could be roughly estimated that workers were exposed to toluene concentration above 200 mg m^{-3}.

Table 3 presents the results of m-xylene and m-methylhippuric acid in the blood and urine respectively, of workers exposed to xylene. Both parameters were on a similar level in two investigations before work. After work they increased and the difference between both morning concentrations and afternoon concentration was highly significant for both parameters. Biological tolerance value for xylene in blood after work is 1.5 mg L^{-1}.

In this investigation only one subject had such a high m-xylene concentration (1.544 mg L^{-1}). m-Methylhippuric acid did not achieve biological tolerance value of 1.5 g g^{-1} creatinine set by ACGIH[5].

In the same table the results of the correlation analyses are presented. Better correlation between m-xylene and m-methylhippuric acid could possibly be obtained after determination of all three xylene isomer relations to all three methylhippuric acids. Another improvement could be blood sampling at 2-3 h post exposure when the solvent releases at a more uniform rate. Namely, the concentration of xylene decreases quite rapidly in the course of 1-2 h and thereafter more slowly. In conditions of actual exposure it is, however, quite impossible because workers go home immediately after work.

In workers exposed to xylene toluene was also detected in all blood samples in all three periods of the investigation except in one subject on Wednesday before work when toluene concentration was less than the detection limit i.e. < 0.003 mg L^{-1}. Thereafter concentrations of toluene in blood and hippuric acid and o-cresol in urine are presented (Table 4). These blood toluene concentrations were much lower in comparison with the concentrations in subjects exposed only to toluene. However, statistically significant differences were found between both morning concentrations and the toluene concentration after work. Our previous assumption was that toluene is present as a contaminant of industrially used xylene. This was not confirmed because the correlation between toluene and xylene was insignificant. Hippuric acid concentrations in the morning urine samples were even higher than in the urine samples of workers exposed only to toluene. This could be a sign of unreliability of hippuric acid as an indicator of toluene exposure.

The o-cresol concentrations increased during the working week and the difference between both morning concentrations and afternoon concentration was highly significant. However, the correlation between toluene and o-cresol in all periods of investigation was insignificant.

On the basis of the results obtained in this study which was performed in conditions of actual occupational exposure it could be concluded that:

- Through biological monitoring using the adequate indicators the exposure to toluene and simultaneous exposure to xylene and toluene, respectively has been confirmed.

- Toluene in blood after work is the best indicator of toluene exposure.
- The still conflicting results on the validity of both hippuric acid and o-cresol – as toluene exposure indicators – are also confirmed in this study.
- Xylene in blood as well as its only major metabolite, methylhippuric acid, normally not present in urine, are good indicators of xylene exposure.

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(2) Buchet JP, Lauwerys RR. Measurement of urinary hippuric and m-methylhippuric acids by gas chromatography. Br J Ind Med, 1973; 30: 125-8.

(3) Sherwood RJ, Carter FW. The measurement of occupational exposure to benzene vapour. Ann Occup Hyg, 1970; 13: 125-46.

(4) Nise G, Ørbaek P. Toluene in venous blood during and after work in rotogravure printing. Int Arch Environ Health, 1988; 60: 31-5.

(5) American Conference of Governmental Industrial Hygienists. Threshold limit values and biological exposure indices for 1986-1987. Cincinnati: ACGIH, 1986.

(6) Maximum allowable concentrations (MAC) of toxic gases, vapours and aerosols in working premises atmosphere. Službeni list, 1971; 35: 1 (in Croatian).

Table 1. Characteristics of the exposed subjects

	Workers exposed to toluene (N=5)	Workers exposed to xylene (N=19)
Age (years)	36.8 ($\bar{X}$) R=31-49	37.4 ($\bar{X}$) R=33-49
Duration of exposure to solvents (years)	13.0 ($\bar{X}$) R=10-18	12.6 ($\bar{X}$) R=2-20
Alcohol consumption	3 - moderate 2 - none	16 - moderate 3 - none
Smoking status (smokers/nonsmokers)	3/2	9/10
Medication	none	none

Table 2. Median (M) and range (R) values of toluene in blood and hippuric acid and o-cresol in urine of workers exposed to toluene on Monday before work (a) and on Wednesday before (b) and after work (c)

Biological indicator	Statistical parameter	a	b	c
Toluene (mg L^{-1})	M	0.011	0.081	0.660
	R	0.005-0.026	0.017-0.121	0.092-1.004
	N	5	5	5
		t=3.291; p<0.05		
			t=3.546; p<0.05	
		t=3.683; p<0.05		
Hippuric acid (mg g^{-1} creat.)	M	340	250	610
	R	180-450	230-440	390-1890
	N	5	5	5
		t=1.143; p>0.10		
			t=1.808; p>0.10	
		t=1.784; p>0.10		
o-Cresol (mg g^{-1} creat.)	M	0.57	1.17	1.26
	R	0.09-2.53	0.45-4.90	0.68-1.53
	N	5	5	5
		t=1.431; p>0.10		
			t=1.027; p>0.10	
		t=0.876; p>0.10		

Table 3. Median (M) and range (R) values of m-xylene in blood and m-methylhippuric acid in urine of workers exposed to xylene on Monday before work (a) and on Wednesday before (b) and after work (c)

Biological indicator	Statistical parameter	a	b	c
m-Xylene ($mg\ L^{-1}$)	M	0.048*	0.077**	0.388***
	R	0.020-0.236	0.022-0.313	0.138-1.544
	N	19	19	18
		t=1.847; p>0.05		
			t=5.129; p<0.0001	
		t=5.148; p<0.0001		
m-Methylhippuric acid ($mg\ g^{-1}$ creat.)	M	36*	40**	364***
	R	14-129	12-121	26-1232
	N	17	17	19
		t=0.498; p>0.50		
			t=4.891; p<0.001	
		t=4.934; p<0.001		

* r=0.602; p 0.02
** r=0.690; p 0.01
*** r=0.530; p 0.05

Table 4. Median (M) and range (R) values of toluene in blood, hippuric acid and o-cresol in urine of workers exposed to xylene on Monday before work (a) and on Wednesday before (b) and after work (c)

Biological indicator	Statistical parameter	a	b	c
Toluene ($mg\ L^{-1}$)	M	0.005	0.006	0.015
	R	0.004-0.014	0.0-0.013	0.006-0.238
	N	19	19	18
		t=0.724; p>0.10		
			t=2.130; p<0.05	
		t=2.121; p<0.05		
Hippuric acid ($mg\ g^{-1}$ creat.)	M	450	530	490
	R	40-1320	70-1670	80-1580
	N	17	17	19
		t=0.412; p>0.50		
			t=0.559; p>0.50	
		t=0.180; p>0.50		
o-Cresol ($mg\ g^{-1}$ creat.)	M	0.29	0.44	1.18
	R	0.09-0.75	0.14-1.37	0.26-2.05
	N	17	17	19
		t=0.802; p>0.10		
			t=7.244; p<0.001	
		t=5.535; p<0.001		

Lecture: Jan-Erik Karlsson

Föredrag 1990-06-21

EXPOSURE TO SOLVENTS IN A SWEDISH OFFSET-ROTATION PRINTINGSHOP AND NEURASTHENIC SYMPTOMS AMONG THE PRINTERS

Ladies and gentlemen!

I would like to report on a study personal from the clinic made last year in an offset-rotation printingshop and which we in fact may continue this year.

First a little about the background. The local trade union of the printers contacted the clinic because they had received complaints from their members working with offset-rotation, especially from those working with machines where they use alcohol in the dampingwater. The alcohol in question is isopropanol, which is mixed with the water in a concentration sometimes reaching 20 % in order to improve the quality of the print. The most common complaints concerned headache, fatigue and irritation of mucous membranes.

After a couple of meetings which also included the employer of the company in concern and representatives from the local safety and from the occupational health service the outlines for the study was laid down. We decided to divide the study in two parts - a medical and a technical. The first is structured around a questionnaire distributed to all the employees at the plant, the latter consists of measurements of solvents in workplace air and biological monitoring.

Before I carry on, a few words about the plant. The number of employees is about 170, which makes it one of the largest of it's kind in Sweden. The company is specialized in offset-rotation print and the plant housed by the time of the study five printing machines, three of which with alcohol damping. Four machines were situated in the big printing hall (40 x 50 m), the fifth has its own room. The premises are adequatly ventilated and each machine has its own local exhaust system. Besides printing the company has departments for repro, bookbindery and administration.

Methods

The questionnaire was distributed to 168 persons and contained questions regarding neurasthenic symptoms possibly related to toxic effects of solvents and symptoms from the respiratory tract and mucous membranes, as well as questions about psycho-social topics and ergonomics. From hereon I will concentrate on the neurasthenic part, where questions selected from two questionnarires, the so called Q15 (15 questions) and SCL (Symptom Check List) (12 questions), were used for creation of indices. The answers were statistically evaluated and comparisations were made between subjects exposed (printers) and not exposed to solvents (referents).

The technical study started up with measurement of isopropanol in ambient air of the personal (N=31) working at the machines with alcohol damping. The sampling equipment, which consisted of motorized glassyringes, was carried by each worker during the workshift (8 h) and samples were analyzed on a portable gaschromatograph every half hour. The whole operation lasted for three weeks and about 400 samples were analysed. During this period we also collected urine samples before and at different

times after exposure to determine the concentration of acetone, which is the main metabolite to isopropanol. The aim was to establish a possible dose-exposure relationship and to find out if there was a rise in concentration at the end of the workingweek.

Whilst analysing the airsamples we found some high peaks which we know originated from solvents used by cleaning the printing rollers. However we could not identify these peaks on the small portable instrument, so at a later occasion we sampled air on active charcoal during cleaning works. The samples were brought to our laboratory and analysed on a stationary GC.

Results

In the technical study we found that the main problem was not exposure to isopropanol during normal operation, but to solvents (including isopropanol) during the cleaning operations. As is seen in table 1 the so called additive effect, which takes in account the interacting influence of the individual solvents, might by a wide margin exceed 1, which is the permitted limit. This is especially true when using benzine. The operations are rather shortlasting (max 20 min), but recurrent. Besides regarding the white-spirit products, which has different names e g Typo-clean, the contents vary from one deliverance to another.

The exposure to isopropanol during normal operation was moderate as can been seen in diagram 1. It varied between 15 and 90 mg/m^3 which corresponds to 4-25 % of the Swedish treshold limit value. A peculiar note is that one of the highest values was measured in the control room of one of the machines!

In spite the moderate exposure to isopropanol there is a slight rise of the acetone content in urine at the end of the week as is seen in diagram 2. It is also obvius that the alcohol metabolizes rather fast in the body as the maximum content of acetone seems to be around eight hours after finished exposure. Sometimes even earlier if there has been peaks of exposure early in the workingshift. Due to acetone being an endogenous substance, there is no zero value.

As it shown in diagram 3 we could not establish any dose-response relationship between the uptake of isopropanol and content of acetone in urine, probably because the levels of concentration of the alcohol was low. The conditions had probably been worse at the time the complaints were brought to the union, as the company since then had lowered the mixture of isopropanol in water from 20 to less than 10 %.

Now it would be interesting to see if the findings to some extent was reflected in the answers of the questionnaire.We found an increase of neurasthenic problems among the printers compared to the referents, especially memory problems (56 %), mood lability (40 %) and concentration difficulties (31 %). Indexes, which were created by summation of answers to the questions from the check-lists mentioned earlier, with great specificity separated the exposed group from the referents as is shown in table 2. It is recommened that persons with seven or more positive answers should be examined with concern to toxic encephalopathy. A very important note is that the reported symptoms is spread equally among the printers despite their age.

Conclusions

It is not possible to classify the symptoms of the printers as chronic effects of exposure to solvents. In fact - the age distribution makes it look more like acute effects probably above all from cleaning works. Another possible explanation is the fact that the company planned to reorganize the working shifts at the time of the study. A neuropsychological testing could have suggested the correct explanation more precisely. Anyway such high incidence of neurasthenic symptoms indicates that there is a great risk of psychic ill-health among the printers and the company is recommended to improve above all the methods of cleaning the rollers.

1990-07-17

Jan-Eric Karlsson
Occupational hygienist

KHS

Table 1

Timeweighted averages for solvents in air during cleaning works

Machine	White spirit (mg/m^3)	Benzine (mg/m^3)	Isopropanol (mg/m^3)	Additive effect
1	28	828	148	3.6
2	80	-	140	0.4
3	200	-	140	0.6

Table 2

Number of persons with seven or more symptoms of twelve included in SCL-index

	Exposed	Referents
Total	12/52	1/36
-30 year	3/17	0/2
31-50 year	5/18	1/20
51- year	4/17	0/13

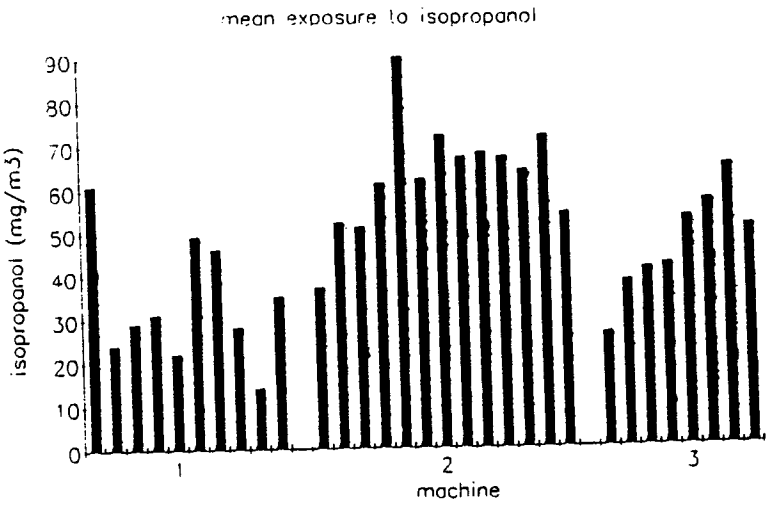

Diagram 1

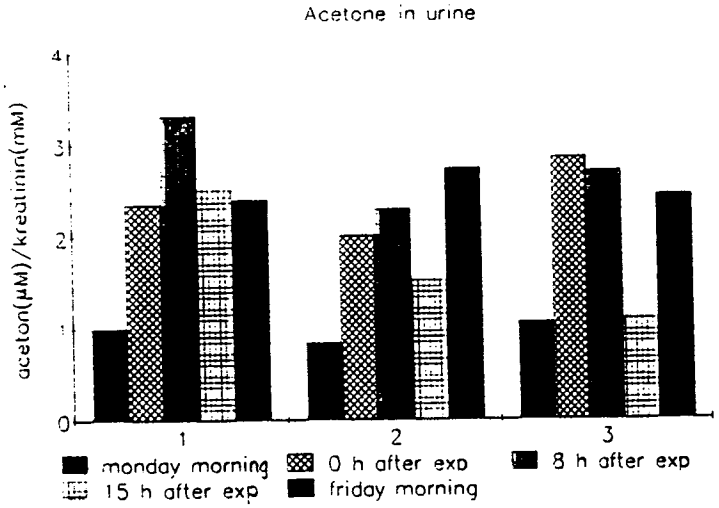

Diagram 2

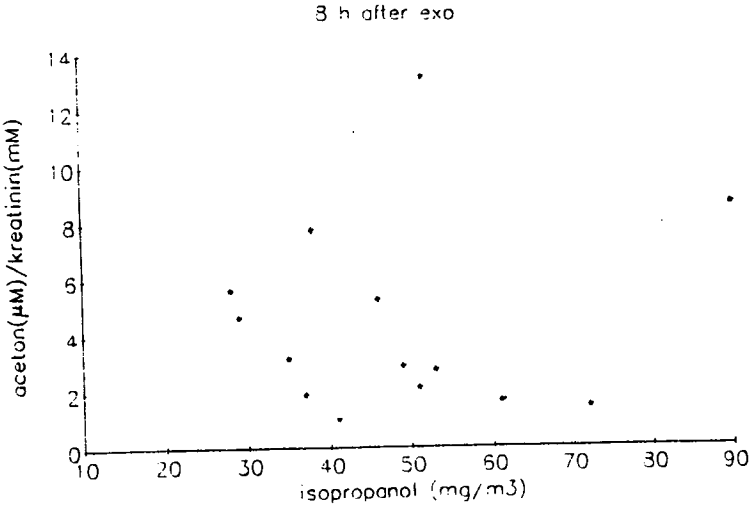

Diagram 3

HAND FINGERS' SKIN HISTOPATHOLOGICAL STUDY OF WORKERS WITH VIBRATION SYNDROMA AND CLINICAL SIGN OF EMTY FINGERS PHENOMRNON - "PRINT IN DOUGH" (+)

K. Tričković, D. Ilić, G. Penev, Lj. Petrović, D. Stojanović, Č. Kutlešić and V. Tričković.

In 35 workers occupationaly exposed to vibrations with "empty fingers phenomenon-print in dough" earlier reported (3), biopsy of hand' skin finger has been made. Hyperkeratosis and papilomatosis of epiderm was found in 97 %, oclusive and suboclusive changes of blood vessels in 86 %, skin sclerosis in 57 % and kolagenisation in subdermal part in 66 %. Histo-chemical and histo-ensimatic investigations are in progress.

INTRODUCTION

Vibrations are undoubtedly an actual occupational hazard causing a complex of disorders and changes known as vibration disease, or vibration syndrome (1,2). To the wellknown and described clinical simptomatology it is added, not long ago, a newly described sign "empty fingers phenomenon or print in dough"(3). The most frequent and the most famous form of vibration disease is certainly neuro-vascular one, with well known Raynaud phenomenon reported in 1911 by Lorige and later on by many other authors. But, beside more or less clearly described condition, we are still in dillemma till which point are only functional changes, are they exclusivevely of functional nature, when organic changes have commenced and do they exist?

MATERIAL AND METHOD

Histopathological examination of volar side of skin, usually of the 4-th hand finger at 35 workers exposed to vibration, with

(+) Investigation is partially financed by Science Community of Serbia.

vibration disease and manifested sing of "WHITE - DEAD FINGERS", with Raynaud syndrome respectively, including clinical sign of "empty fingers phenomenon - print in dough" have been studied. Otherwise, by our study the total of 1014 workers, miners, metal industry and chain saw workers have been examined.

After local anesthesia, a biopsy was performed of 4 th finger, of its proximal part by volar side. Hematoxilin-eosin, Wan-Gieson, Foot and PAS technique of specimen dyeing is applied (4,5).

RESULTS

All examined workers of various occupation have exibited signs of vibration disease in the range of 20-56 %. It has been mainly neurovascular symptoms with prevalence of the onset of white fingers (digiti mortui, fig. 1). Within the whole number of vibration diseases diagnosed cases, there 10,1 - 32,5 % oheases with trophhic changes, which, by our knowlendge, was not reported before in the current scientific literature. Such changes are exiibited as a slack, non-elastic skin,with a tactile feelin lacking of dermal and subdrrmal substrete, with a print like in dough, long lasting, all having given an impression of empty fingers(Fig. 2,3). Therefore, we have named the clinical symptom "EMPTY FINGERS PHENOMENON OR PRINT IN DOUGH". We have cosidered this sign only as a clinical manifestation of deeper and more serious damages of the skin. That is why have performed histopathological study, up to now on 35 workers with vibration disease with above described signs. All examined workers voluntarily accepted skin biopsy. The resultats of study are shown in Fig. 4, 5, 6 and 7.
On controle skin specimens (N=12), taken elswhere, no changes were observed.

Fig. 4

- MORE CHARACTERISTIC CHANGES OF FINGER SKIN HISTOPATHOLOGY IN PATIENTS WITH CLINICAL SIGN OF "EMPTY FINGERS"

F I N D I N G S	N	%
HYPERKERATOSIS AND PAPILOMATOSIS OF EPIDERMIS	33	97,1
OCCLUSION AND SUBOCCLUSION OF BLOOD VESSELS FIBROSIS OF ADVENTITIA, MIDDLE COAT AND HYALINOSIS OF INNERMOST	30	86,0
SKIN SCLEROSIS	20	57,0

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Fig. 4

MORE CHARACTERISTIC CHANGES OF FINGER SKIN HISTOPATHOLOGY IN PATIENTS WITH CLINICAL SIGN OF "EMPTY FINGERS"

(N = 35)

FINDINGS	N	%
HYPERKERATOSIS AND PAPILOMATOSIS OF EPIDERMIS	33	97,1
OCCLUSION AND SUBOCCLUSION OF BLOOD VESSELS FIBROSIS OF ADVENTITIA, MIDDLE COAT AND HYALINOSIS OF INNERMOST	30	86,0
SKIN SCLEROSIS	20	57,0
ATROPHY AND NEURON DEMYELINISATION	13	37,0
SUBDERMAL COLAGENISATION	23	66,0
RETICULIN FIBRES REDUCTION OF SUBDERMIS	9	27, 0

DISCUSSION

There is no doubt that vibration disease occurs in workers using various vibration tools and are exposed to vibration. Mani reports in this countri and abroad have consent in this regard and confirmed by many references (6,7,8,9,10,11 and 12). Our Clinical examination have established vibration disease in 56 % of cases with indicative signs for this condition 63,10). In the range of 10,1 % to 32,5 % trophic changes were detected doughy impresion of the finger's skin, entiteled, as already mentioned "PHENOMENON OF EMPY FINGERS". The presumption was that trophic condition of the relevant tissue area is deranged, what finaly caused an alteration of the skin nutrition. In current literature there was only a few histopathological studies of the skin in vibration disease patients, but similar study to ours with the same scope we found nowhere (11,12). The problem of small number and unadequate histopathological investigation, have beeh particullarli emphasized by Andreeva and Galinina, Karpova and M. Smaidman (6, 7, 8),

Experimental histopathological studies on laboratory animals, can not adequatelyrepresent tissue response of human organism.

Therefore, our investigation could be of a particular significance, because they have been performed on workers chronically exposed to the effect of local vibration in various occupation and for a period of many years. The obtained results are convincible suggesting organic nature of detected changes. By tkis, on the walls of dermal blood vessels discovered morphologic changes are of separate

meaning. They have beholden as oclusion and subocclusion blood vessels because of fibrotic changes of adventitia and middle coat and hyalinosis of innermost. However, there were present also blood vesseles thrombosis, their narrowing similar to endarteritis, capillary increasing with distracted and swalen surroundings and arterioles hyalinosis. Such reduction of arterial netting, must lead to weaker arterialization of the given areas and to local tissue hunger. Trophic derangement hand to influence also other parts of the skin, including neural atrophy. That is why some reduction of the skin substrate occured, what have clinically manifested as a loose, non-elastic skin, without fulleness and vigor, with an impression like in dough and empty fingers. This we consider as a consequence of tropho-vascular changes in the skin and histopathological substrate of described clinical manifestation, respectivelly. This clinical sign with convincing morphologic changes, histopathologicaly proved, is clearly suggesting that vibration disease is not any more one the level of functional disorder, but in an advanced phasis of disease characterized now with organic and irreversible changes.

Such a manifestation one can find also in other cases where exist the problem of vascular disorders and skin tissue trophic problem, as for example in arteriosclerosis of older poeple. But changes accompanying vibration disease do appear in exposed workers in thier full vital work abilityleading in many cases toward disablement.

CONCLUSION

1. Numerous clinical symptoms indicating vibration disease are verified in workers occupationally exposed to vibration by our clinical examination.

2. Within the frame of clinical manifestation, trophic changes of hand fingers with "PRINT IN DOUGH", loos skin, without fullness and vigor, giving an impression that fingers are empty and therefore this clinical occurence is named "PHENOMENON OF EMPTY FINGERS).

3. Up to now hand fingers skin biopsy in 35 workers with vibration disease has ve been performed combined with histopathological investigation. Organic changes in the walls of the small blood vessels more established in 86 % cases, as occlusion, subocclusion, etc, because of adventitial and middle coat fibrosis and hyalinosis

of blood vessels innermost have been found. Other epidermal, dermal and subdermal changes are diagnosed, as well.

4. All described histopathological changes do represent a substrate for clinical sign called "PHENOMENON OF EMPTY FINGERS" arose as a result of tropho-vascular changes in the skin of fingers in vibration disease patients.

5. Clinical appearance of "PHENOMENON OF EMPTYF FINGERS" one should comprehend as a sign indicating that vibration disease is not any more in the phase of functional disorders, but in on advanced state when the patient il faced with organic irreversibile changes.

6. Besides histopathological changes, described in this paper, our further study is in progress on histo-chemistry, histo-enzimology and some others aspects aiming toward more comprehensive ivestigation and understanding of vibration disease ethiopathogenesis.

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SUMMARY

The histopathologic examination were made skin of hand fingers for 35 workers of various occupations using vibration tools, with vibration disease and with previously descibed "PHENOMENON OF EMPTY FINGERS - PRINT IN DOUGH". The results show organic changes on neurovascular system on the skin of hand fingers. They are histopathologic substrate of this phenomenon and evidence that they are not only functional but also organic, irreversibile changes. Dermal sclerosis, hyperceratosis, changes of epidermis, occlusion and subocclusion of arteriolas, colagenisation and hyalinosis of damaged areas were also evident.

Medical Faculty, Niš, Yugoslavia.

EXPLANATIONS FOR ENCLOSED PHOTOGRAPHS (Not reproduced)

Fig. 1. Onset of White - Dead Fingers" (Collection of K. Tričković).
fig. 2. "Print in Dough, Phenomenon of Empty Fingers" of saw chain wood-cutter with vibration disease (Collection of. K. Tričković).

Fig. 3. Same as photograph in Fig. 2.

Fig. 4. Tabella
Fig. 5. Hematoxylin-Eosin 20 x 10, Subocclusive changes of blood vessel, neural fibres atrophy and dermal oedema(Collekt.of K. Tričković).
Fig. 6. H. E., 20 x 10 Arterioles with subocclusion. Neural atrophy. (Collection K. Tričković).
Fig. 7. H. E., 10 x 10, Atrophy muscular fibres with uneven oedema and separated colagenous fibres in dermis (Collect. K. Tričković)

Lecture: Ulf Hjortsberg

Tactile sensory dysfunction following vibration exposure

Dear colleges and friends from Yugoslavia!

The topic of my speech is tactile sensory dysfunction following vibration exposure. This is a specialized field within the broad concept hand-arm vibration syndrome. We have previously mainly concerned ourself with the well known vascular dysfunction in vibration induced disease and much of interest have previously been focus on this particular aspect of the vibration syndrome.

However, in later years attention has been directed toward the neurological aspects of vibration induced injury. This new interest has been preceded by basic increase of knowledge about nerve physiology within the hand. In Sweden the basic physiological nerve research by Roland Johansson and Åke Vallbo at the University of Umeå have increased our knowledge about the tactile sensory system in the glabrous skin the human hand. This basic knowledge about peripheral nerve function within the hand is essential to this knowledge about tactile sensory system within the hand.

I will give you a short review of the current knowledge. The vibrotactile sensation within the hand is received by several so called mechano-receptor systems. It is estimated that there are up to twenty thousand so called mechanoreceptive units innervating the skin of human hand. Due to the properties of adapt to a constant pressure one can divide receptors between two population - one is a slowly adapting receptor type called the SA-receptor - the other is a fast adapting type called FA-receptor. A further subdivision within both slow adapting and fast adapting receptor fields are if or not they respond to small objects with sharp borders or whether they react to large objects with obscure borders. By definition receptors reacting to small objects having sharp borders are of type one. These type one receptors have been linked to both the Merkel cell neurite complex and the Meissner complex. On other hand receptors responding to a big objects with diffuse obscure borders are called the type two receptors. These receptors have been linked to the Parcinian corpuscles and also to the Ruffini nerve

endings. One must however bear in mind that these receptor systems are greatly overlapping and at high energy or accelerations levels all receptor systems eventually will be activated. There are however certain differences between the receptors ability to react to low-frequency vibrations, that is vibrations up to about 60 Hz. They are received mainly by the SA-receptors but on the other hand when you come over 60 Hz the FA-II receptors are firstly activated.

It is also clear that the Pacinian corpuscles or the FA II receptor system will react to the displacement of skin far away from the area where they are situated. The fast-adapting receptors of type 2 seems to be more potent since even one single signal from a FA-2-receptor can give rise to a neurological sensation. On the other hand there are needed from a summation of impulses several FA-1-receptors to make a up a neurological sensation. In the slowly adapting receptor system seems that slowly adapting receptors of type 1, that is those who react for small sharp borders, can react both to objects with sharp borders and to vibro-tactile perception. The SA-1-receptors are also active in the manipulative dexterity. The rather crude clinical examination called two point discrimination test is directed to an evaluation of the SA-1-receptor function. There seems to be a good correlation between defective two point discrimination and a pathological so called vibrogram in the lower frequencies.

It must however, be stated that the skin is most sensitive in the vibrations range between 250 and 350 Hz. The hand finger system it seems is created in such a way that the mechanical properties of a skin are such that there is an optimal vibration of the skin tissue at about 250 to 350 Hz. Therefore receptors most active at the vibration range will first discover any vibration displacement. It has been found that Parcinian corpuscles at this frequency are able to find a displacement of the skin at the amplitude of only about 1/10000 mm.

It has been stated that by using so called vibrogram or tactilogram at different vibration frequencies one may detect the function of separate receptor system. It is however, not clear whether there does exist such isolate dysfunction of one or two receptor systems. On the other hand it seems that the vibro-tactile sense is constructed in a way that it is most reactive or

sensitive within the range of 250 to 350 Hz. There has not been any report or statements of any specific dysfunction or disease solely in any particular tactile receptor system.

During later years new instruments has developed to test vibro-tactile sensory system within the hand. One commercially available instrument is called Sometic® and consists of a hand held device giving vibration at 250 Hz. The function of this instruments is however not optimal since it is not possible to control the pressure of the needle on the skin surface.

A better way of testing the vibro-tactile sense is by applying a known pressure of the vibrating needle to the skin thus eliminating the difference in pressure of a needle on the fingertip. Some investigators have also previously used the Sometic vibrations device on the dorsum of a finger which is not optimal procedure since the mechanoreceptors are mot densely located on the volar surface of the finger.

Another drawback is that there seems to be great overlap when using different methods to study the vibrotactile sense. One therefore has difficulties in interpreting the results of other investigators when testing for the vibrotactile sense. There is also a great overlap between individuals being disable from a defective vibrotactile sensation and those who are symptom free. At the present time there also seems to be no agreement whether vibrotactile testing should be done on any large scale basis for the purpose of screening vibration exposed workers. Another difficult question is to decide when the vibrotactile sensation becomes abnormal or if it is possible to use an abnormal testing as a basis for legal medical injury compensation.

My own interest in this research field came from a number of patients being exposed to high frequency vibrations from dental drilling at grinding. A number of dental technicians visited our clinic due to sensory disturbances in the hand. These patients had been exposed to high frequency vibrations for many years. Their main complain was tingling and numbness in the hand and a loss of manual dexterity. We examined ten men between 36 and 62 years of age, (mean age 44). Eight of them had various sensory hand disturbances and four of them also

had vascular spastic reactions. We compared them with ten age matched healthy men lacking symptoms from the hands. Our exposure group had been exposed to vibrations to the hand-arm system. Measurements of vibration levels on the tool and of work piece revealed that there was a considerable amount of vibration above 1000 Hz. Our patients were examined with measurements of sensory conduction velocity of the median nerve measured fractionally over the forearm and over carpus and from carpus to the middle finger by use of antidrom nerve conduction technique.

We measured also threshold for warming and cooling by the Termotest®, and measured the vibration threshold at the fingertip by use of a vibrating probe placed at the volar surface of each finger tip. This examination was also done using measurements at seven different vibration frequencies from 8 Hz to 500 Hz by a new technique developed here in Malmö by Dr Lundborg.

In an addition to these measurements we also measured the so called tactile-electric difference on the 3rd digit meaning the difference between electrical and tactical stimulation time done by stimulation on the distal part of the finger and measured nerve response over the volar surface over the carpus. By using this set up for time delay measurement we cold detect a slight tactile-electric difference in the dental technicians as compared to the matched referents. This could indicate a delay in the conduction of vibration impulses from the distal part of a finger. In combination with the pathological perception of vibration and cooling thresholds it could indicate that the damage was situated in the distal part of a finger presumably in a very near area of the mechanoreceptors. This could indicate that mechanoreceptors were somehow damage but it could also indicate that the nerve connection to the receptor system was damaged since we also found pathological threshold for cooling and warming sensations which are carried by free nerve endings and are not relying on any special receptor system. The results of our results are summarized (table 1, 2 and 3).

I must also point to the fact that high frequency vibrations are mainly damped within the skin due to the physical gelatinous properties of skin in the distal fingers. It's also known that high

frequency vibrations will be damped within very short distance of the skin, maybe only 1 mm or less. Our results pointed to a clear pathological functions of the mechanical receptors and/or distal nerve endings in dental technicians exposed to high frequency vibrations. There is at the present time need for further investigations in this field. I think one can also state that there is a need for new standards to be set for vibrations above the present ISO/DIS norm 5349 at the present relevant only to vibrations in frequency 6,3 - 1250 Hz.

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EFFECTS OF DAMPING OF VIBRATIONS BY ANTIVIBRATION GLOVS, LEVERS AND VIBRO-ABSORBENS AND THEIR APPLICATION IN PERSONAL AND GENERAL TECHNICAL WORK PROTECTION(+)

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INTRODUCTION - General technical measures for protection from harmful effects of local vibration used up to now, have failed to give satisfactory results. Devices for personal protection almost do not exit. That is the reason vibrational disease is quite common professional illiness. The need arises for furthe research and application of general technical devices, as well as personal protective devices. This work contains the results of damping of vibrations by original of divices of personal and tecnical protection.

OBJECTIFS - We developed antivibration protective glovs YU-PAT 150/81-85, M-373/82-85, antivibration lever with same characteristics and vibroabsorber M 1993/89. Hundred and twenty workerss withs vibrogeneus professions have been specially interogated for their personal estimation of use of antivibration gloves and other devices.

METHODOLOGY - For the survey of vibrations and the relevent parameters, suitable measuring kit of firm BRÜL and KJAER has been used. Surveyng under laboratory conditions during the exploatation has also been done. Vibroisolatory characteristics of gloves, levers and vibroabsorbers were recognized under the ifluence of sine signals, accidental vibrations and realistic time analysis. Personal estimation of comforts of antivibration gloves has been done by poll system.

RESULTS - Obtained by mentioned methods of research convincingly chow the efficiency of damping of vibrations at all

frequencies, event low - frequencies, specially when anti-vibration gloves are concerned. Personal estimation of the majority of workers is positive and justifies their request for the wide use of gloves. Building of vibroabsorbes in between main jounts, of varius machines and appliances, specially in motocultivators M-506 S, produced by the factory IMT Knjaževac as well as the application of antivibration gloves and levers, makes the work these tools more comfortable and much safer.

CONCLUSION - The vibration producede spcially by hand vibrating tools are still a problem in general and personal technical protection of the exposed workers. The results obtained by our original means and solutions which we patented, give possibilities for a significant damping of vibrations and reuce their bad influence on health and workinng ability of workers. Exceptionally good results were reached with antivibration gloves and levers, both in objective and subjective estimation. That is the reason for their assemblyline production and mass applocattion. Thei are also excellent protection from other professional harms and injuries at work. Therefove, their standardisation is justified in Yugoslavia, as well as in Sweden and other countries.

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