Neuropsychiatric Effects in Workers with Occupational Exposure to Carbon Disulfide

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Abstract: Neuropsychiatric Effects in Workers with Occupational Exposure to Carbon Disulfide: Srmena KRSTEV, et al. Clinical Center of Serbia, Institute of Occupational and Radiological Health, Yugoslavia—In a cross-sectional study, prevalence of dysfunctions of the central nervous system was assessed in 134 male workers exposed to different levels of carbon disulfide (CS₂) in a rayon viscose plant and compared to 38 non-exposed workers. In three groups of workers from the same plant with different levels of CS₂ (heavy, intermediate, none) estimated by personal samplers, disorders in the central nervous system were examined by means of psychiatric examination and questionnaire 16 (Q16). Unconditional logistic regression was calculated adjusted for age, alcohol consumption and education. Psychoorganic syndrome was diagnosed significantly more often in workers with heavy CS₂ exposure, with adjusted OR of 17.9 (95% CI 2.18–146.73), and insignificantly in workers with intermediate exposure. Prevalence of workers with more than 6 positive answers on the Q16 was higher in the heavily exposed workers (OR=4.76; 95% CI 1.80–12.60). A similar result was found for almost all the questions in the Q16, and the most pronounced psychological symptom was of less interest in sex (adjusted OR=8.14; 95% CI 2.19–30.22). High correlation was found between symptoms recorded on neuropsychiatric examination and on Q16. Both neuropsychiatric exams and Q16 indicated disturbances in the central nervous system due to the long-term heavy exposure to CS₂. Disorders of the central nervous system were found more often in workers with heavy exposure to CS₂. Questionnaire Q16 is a valuable means for selecting workers for further neuropsychiatric testing.

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The problem of carbon disulfide (CS₂) intoxication is still present in Serbia, where a viscose rayon factory exists. In the production of viscose rayon fiber CS₂ is widely used as a solvent. Although CS₂ levels have decreased since the factory was established in 1958, they are still high and often exceed the Yugoslav Maximum Allowable Concentration (MAC).

Dysfunctions in the central nervous system are well known manifestations of adverse CS₂ effects. Today, developed psychiatric signs and symptoms are rare as a result of changes in technology and improved working conditions^{1, 2}. Instead, tiredness, sleepiness, affect lability, irritability, memory disturbances, decrease in intellectual capacity, as well as dizziness, headache and reduction in libido, are reported³. Psychological tests in workers exposed to long-term low levels of CS₂ have revealed different neurobehavioral changes, such as visual-perceptive, psychomotor or cognitive changes^{4, 5}. Despite progress in understanding the neurotoxicity of CS₂ exposure, some problems still exist. First of all, different terms are used for similar disorders, such as toxic encephalopathy, psychoorganic syndrome, dementia, neurobehavioral effects, chronic solvent syndrome, etc.⁶. Furthermore, the underlying pathological processes and the impact of long-term low-dose exposure are not fully understood. It is not clear enough whether neurobehavioral parameters are an adverse effect or should they rather be considered as indicators of a new level of adaptation of the central nervous system. The wide spectrum of psychological tests in use that are not always standardized can partly be responsible for some controversial results⁷.

The aim of our study was to establish the central nervous system dysfunction in workers exposed to different levels of CS₂ by neuropsychiatric check-ups and questionnaire 16 (Q16). Symptoms noted by neuropsychiatrists and recorded in questionnaire 16 were also compared.

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Materials and Methods

In a viscose rayon plant three groups of current workers were selected according to the CS₂ levels. The first group was composed of spinners in the spinning rooms where viscose rayon fibers were produced with a heavy CS₂ exposure (N=97). The second group of workers in the departments for viscose manufacturing were exposed to the intermediate CS₂ levels (N=37). The third, non-exposed comparison group were from the same plant but engaged in the department for processing cellophane, making cellophane products e.i., sacks, and packing them (n=38). The response rates were 93.3%, 61.7% and 79.2%, respectively. The criterion for selection was more than 5 yr of exposure for both exposed groups. For the second group with intermediate exposure to the criterion was added that those who had ever worked in the spinning rooms were excluded. In the comparison, non-exposed group, no one subject had ever been exposed to CS₂ or any other organic solvent. All workers were informed about the objectives of the study, and they agreed and signed to participate. At the end of check-ups they received detailed medical reports.

Selected groups were all males, and similar as to age, the length of time since first employed, and exposure duration for exposed groups (Table 1). Workers with heavy CS₂ exposure, i.e. spinners in the spinning room had less years of education than workers with intermediate CS₂ exposure, and particularly than the non-exposed group. Highly exposed workers were more prevalent among those with less alcohol consumption, but also among those with most alcohol consumption. Workers from all three groups were shift workers (including night shift), and were under similar physical strain while

performing their work tasks.

Exposure estimation was made by personal sampling and biological monitoring, and the procedure has been described elsewhere⁸⁾. Briefly, personal sampling of carbon disulfide was performed by means of passive diffusive charcoal badges on the second day of the morning shift. In the spinning rooms the TWA concentration was 57.7 mg of CS₂ in m³ of air (range 5.0–157.3 mg/m³), compared to 12.6 mg of CS₂ in m³ of air (range 0.2–50.8 mg/m³) in the viscose rayon manufacturing departments (Table 2). The average 2-thiothiazolidine-carboxylic acid (TTCA) readings in urine samples at the end of the day shift, as sensitive biological indicators of CS₂ exposure were significantly higher in spinners than in workers in viscose production (17.8 vs. 6.6 mg/g creatinine). Close correlation was found between TWA of CS₂ and TTCA in urine (R=0.89).

Neuropsychiatric examination was performed in a structured way by specially instructed neuropsychiatrists, who were aware of the workers' exposure status. The Hamilton Rating Scale for Depression⁹⁾, Coblenz Rating Scale for Dementia¹⁰⁾ and Benton's Visual Retention Test¹¹⁾ were used in all participants by neuropsychiatrists during the examination. At the end, psychoorganic syndrome was diagnosed when the following conditions were met: decrease in cognitive ability, impaired intellect, impaired memory and concentration, emotional liability, vegetative symptoms, sexual problems, vertigo and frequent headache.

The Swedish questionnaire Q16 for neuropsychiatric symptoms was translated by a number of experts, in order to preserve its original meaning and to be comparable to other investigations. The questionnaire was applied to all subjects, according to the proposed original method^{12, 13)},

Table 1. Demographic characteristics of examined groups

		Groups			Significance
		Heavy exposure	Intermediate exposure	Without exposure	p=
Age (yr)	Mean	41.7	44.2	42.3	0.288
	Range	26–59	26–61	27–63	
Length of employment (yr)	Mean	19.8	20.3	20.4	0.881
	Range	7–32	6–36	6–38	
Exposure duration (yr)	Mean	16.9	17.6	–	0.000
	Range	5–31	6–33	–	
Education (yr)	<8	53 (54.6%)	17 (45.9%)	7 (18.4%)	0.000
	8	37 (38.1%)	14 (37.8%)	7 (18.4%)	
	≥9	8 (7.2%)	6 (16.2%)	24 (63.2%)	
Alcohol consumption (g/wk)	≤25	31 (32.0%)	7 (18.9%)	8 (21.1%)	0.008
	26–90	17 (17.5%)	9 (24.3%)	15 (39.5%)	
	91–200	20 (20.6%)	14 (37.8%)	12 (31.6%)	
	≥201	29 (29.9%)	7 (18.9%)	3 (7.9%)	

Table 2. Exposure assessment of CS₂ by personal and biological monitoring (TTCA in urine) in exposed groups of workers

Measurements	Heavy exposure	Intermediate exposure
<i>CS₂ (mg/m³)</i>		
TWA concentration	57.7	12.6
Geometric mean	44.4	5.5
Median	45.7	8.2
Range	5.0–157.3	0.2–50.8
<i>TTCA in urine (mg/g of creatinine)</i>		
Arithmetic mean	17.8	6.6
Geometric mean	13.7	5.2
Median	16.0	5.2
Range	2.20–40.64	1.07–16.05

Table 3. Prevalence of diagnosed Psychoorganic Syndrome and adjusted ORs (for age, alcohol consumption and education) in selected groups

Psychoorganic Syndrome	Heavy exposure	Intermediate exposure	Without exposure
Number	26	4	1
Prevalence rate	26.8	10.8	2.6
Adjusted OR	17.87	3.24	–
95% CI	2.18–146.73	0.32–32.54	–

except that the interview was performed by a physician. The alteration was made because the workers generally had a low educational level and were not used to the self-administered questionnaires.

For crude odds ratios (OR) two-by-two-table statistics with 95% confidence intervals were applied. Unconditional logistic regression analysis was used to adjust for the following confounders: age (25–36, 37–43, 44–49, ≥50 yr), alcohol consumption (0–25, 26–90, 91–200, ≥201 g), and level of education (without or incomplete primary school, primary school for 8 yr, and more than 8 yr). The agreement between symptoms stated in the Q16 and symptoms found by neuropsychiatrists was also studied by means of the odds ratio. The PC statistical program Epi Info 2000 (Centers for Disease Control, Atlanta, GA, USA) was used for calculations.

Results

Psychoorganic syndrome was diagnosed in a quarter of workers with heavy exposure to CS₂, significantly more often than in two other groups (Table 3). In fact, it was diagnosed in only one subject without CS₂ exposure.

The percentage of workers with more than 6 positive

Table 4. Prevalence rates and adjusted ORs (for age, alcohol consumption and education) in workers with more than 6 positive answers on the Q-16

>6 positive answers	Heavy exposure	Intermediate exposure	Without exposure
Number	57	16	10
Prevalence rate	58.8	43.2	26.3
Adjusted OR	4.76	1.57	–
95% CI	1.80–12.60	0.52–4.76	–
Mean number of symptoms	7.0	5.2	3.8

answers was almost double in highly exposed workers compared to the intermediate exposure group and the non-exposed comparison group (Table 4). The risk of having more than 6 positive answers was high in the group of heavily exposed workers (adjusted OR=5.70; 95% CI 2.29–14.17), when age, alcohol consumption and education were put into the model. Similar findings were seen for the intermediately exposed workers, but were not significant (adjusted OR=1.39; 95% CI 0.47–4.13). The mean number of symptoms obtained from the questionnaire Q16 was 7.0 in the first, 5.2 in the second, and 3.8 in the third group (F=8.25; p=0.00065).

The crude ORs were increased for almost all questions on the Q16 in heavily exposed workers compared to those with intermediate exposure to CS₂ and non-exposed workers (data not presented). Similar results were obtained when adjusted ORs were calculated (Table 5). In the heavily exposed spinners the highest and significant adjusted ORs were seen for painful tingling in some parts of the body (adjusted OR=8.22), less interest in sex (adjusted OR=8.14), problems with concentration (adjusted OR=6.78), problems in getting the meaning in reading newspapers and books (adjusted OR=5.26), short memory (adjusted OR = 4.59), frequent headache (adjusted OR=3.71), frequent feelings of irritation (adjusted OR=2.90), and abnormal tiredness (OR=2.75). Adjusted ORs in the group of workers with intermediate exposure to CS₂ were also increased, but in no one case significantly. Categorized psychological symptoms from the Q16, e.g. forgetfulness (questions 7, 11, 13 and 14), absentmindedness (questions 6 and 10), and affect lability (questions 4 and 5) also showed highly increased adjusted OR for the heavily exposed group of workers (Table 6).

Close correlation was found between individual symptoms according to both sources (Table 7) for: headache at least once a week on the Q16 with frequent headache in the neuropsychiatric assessment (OR = 20.83; 95% CI 8.95–49.52), short memory on the Q16 and neuropsychiatric check-ups (OR=18.23; 95% CI 7.89–42.98), constant tiredness on the Q16 with tiredness immediately after sleeping according to neuropsychiatric

Table 5. Prevalence of positive answers to questionnaire Q16, adjusted ORs (for age, alcohol consumption and education) and 95% CI

Questions	Heavy exposure (n=97)		Intermediate exposure (n=37)		Without exposure (n=38)
	N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)
1. Tired	49 (50.5)	2.75 (1.12–6.75)	12 (32.4)	0.94 (0.32–2.72)	12 (31.6)
2. Palpitation	35 (36.1)	1.29 (0.52–3.17)	9 (24.3)	0.61 (0.20–1.85)	11 (28.9)
3. Tingling	75 (77.3)	8.22 (3.04–22.25)	13 (35.1)	0.66 (0.22–1.97)	15 (39.5)
4. Irritated	56 (57.7)	2.90 (1.19–7.05)	14 (37.8)	0.95 (0.34–2.67)	13 (34.2)
5. Depressed	30 (30.9)	2.73 (0.95–7.86)	13 (35.1)	2.62 (0.81–8.52)	6 (15.8)
6. Concentrated	39 (40.2)	6.78 (2.17–21.19)	8 (21.6)	1.23 (0.33–4.59)	6 (15.8)
7. Short memory	60 (61.9)	4.59 (1.69–12.44)	19 (51.4)	1.59 (0.51–4.98)	13 (34.2)
8. Perspire	35 (36.1)	2.68 (1.01–7.11)	13 (35.1)	2.25 (0.75–6.77)	8 (21.1)
9. Buttoning	4 (4.1)	–	–	–	–
10. Meaning	37 (38.1)	5.26 (1.62–17.15)	9 (24.3)	2.24 (0.59–8.54)	4 (10.5)
11. Relatives	35 (36.1)	2.40 (0.91–6.34)	14 (37.8)	1.85 (0.60–5.64)	9 (23.7)
12. Oppression	38 (39.2)	1.81 (0.73–4.49)	13 (35.1)	1.28 (0.44–3.70)	10 (26.3)
13. Make notes	42 (43.3)	1.49 (0.59–4.72)	14 (37.8)	0.84 (0.29–2.49)	12 (31.6)
14. Go back	40 (41.2)	1.45 (0.60–3.50)	19 (51.4)	1.82 (0.65–5.06)	13 (34.2)
15. Headache	60 (61.9)	3.71 (1.53–8.97)	16 (43.2)	1.48 (0.54–4.06)	12 (31.6)
16. Sex	39 (40.2)	8.14 (2.19–30.22)	8 (21.6)	2.53(0.58–11.03)	3 (7.9)

Table 6. Prevalence of categorized symptoms on questionnaire Q16, adjusted ORs (for age, alcohol consumption and education) and 95% CI

Questions	Heavy exposure (n=97)		Intermediate exposure (n=37)		Without exposure (n=38)
	N (%)	OR (95% CI)	N (%)	OR (95% CI)	N (%)
Forgetfulness	6 (71.1)	3.17 (1.23–8.20)	24 (64.9)	1.65 (0.5–4.92)	19 (50.0)
Absentmindedness	54 (55.7)	4.99 (1.87–13.36)	11 (29.7)	0.98 (0.31–3.08)	9 (23.7)
Affect lability	61 (62.9)	2.53 (1.04–6.17)	17 (45.9)	0.94 (0.33–2.63)	15 (16.1)

Table 7. Agreement of individual symptoms between the questionnaire Q-16 and findings on neuropsychiatric (NP) examinations

Symptoms at NP exams		Q-16		OR	95% CI
		Yes	No		
Headache	Yes	74	14	20.83	8.95–49.52
	No	17	67		
Short memory	Yes	79	13	18.23	7.89–42.98
	No	20	60		
Tired	Yes	65	8	11.49	4.69–29.12
	No	41	58		
Sex	Yes	37	13	10.01	4.39–23.20
	No	27	95		

assessment (OR=11.49; 95% CI 4.69–29.12), and less interest in sex than is normal on the Q16 with decreased libido on neuropsychiatric check-ups (OR=10.01; 4.39–23.20).

Discussion and Conclusion

In our study, psychoorganic syndrome was diagnosed by a neuropsychiatrist in 27% of the heavily exposed spinners, in 11% of workers with intermediate exposure, and in only one subject in the comparison group. The odds ratio was very high and significantly increased for the workers with heavy CS₂ exposure, even after age, alcohol consumption and education were adjusted for by the model. Adjusted odds ratio for workers with intermediate exposure was also increased, but insignificantly. The results indicated significantly increased risk of developing psychoorganic syndrome in the group of spinners that could be attributed to the long-term exposure to high CS₂ levels, and was not the result of age differences, high alcohol consumption or a low educational level. But we were not able to control the information bias due to the fact that the neuropsychiatrists were aware of the CS₂ status of the examinees. As the diagnosis of psychoorganic syndrome was established both by the neuropsychiatrist's examination and the abovementioned tests, we believe that possible bias could be neglected. Furthermore, all three psychiatrists included in the study were experienced in performing epidemiologic studies in working populations.

The development of neuropsychiatric symptoms due to high CS₂ levels, mostly in viscose rayon factories in Japan and Italy^{4, 5, 14–16}) were described in the 1960s and 1970s. An investigation in a viscose rayon plant in Norway, where concentrations of CS₂ were below 30 mg/m³ but with peak exposures of CS₂, showed that 4 yr after the cessation of exposure in 14 out of 16 workers toxic encephalopathy was diagnosed¹⁷). Most frequent symptoms were memory impairment, irritability, tiredness, and sleep disorders. Further examination of regional cerebral blood flow showed some cerebrovascular abnormalities after CS₂ exposure, but no significant difference from the control group was found¹⁸). But the study did not provide evidence that CS₂ was the main cause of toxic encephalopathy. Studies performed in Italy¹⁹), Poland²⁰) and Japan^{21, 22}) among workers with low levels of carbon disulfide exposure recorded different functional and subclinical changes in the central nervous system. In the viscose industry in Germany with similar exposure conditions, neither an increase in symptoms nor an increase in pathological findings in a clinical-neurological and neuropsychological examination was found²³). Exposure to CS₂ ranging from 3 mg/m³ to 147 mg/m³ in a viscose rayon factory in Belgium, had no significant effect on memory or attention⁷).

The Swedish questionnaire for neuropsychiatric

symptoms Q16 has been used in many occupational groups in different countries exposed to various hazards, mostly to organic solvents^{14, 24–33}), but also to lead^{31, 34}), welder's metals³⁵), styrene^{36–38}), pesticides³⁹) and manganese⁴⁰), etc. But in the literature we did not find any implementation of the questionnaire in workers exposed to CS₂, a well known neurotoxic agent.

The average number of positive answers on the Q16 in our examined groups (7.0 vs. 5.2 vs. 3.8) was much higher than in the majority of other published data for different occupational groups. Exceptions were workers with high exposure to styrene in a plant manufacturing polyester in Sweden among whom the mean number of positive answers in the Q16 was 10.4, and in the low exposed workers 5.3, but based on 9 vs. 8 examined workers³⁶). The mean number of positive answers on the Q16 was also higher in agricultural workers with acute pesticide poisoning in Nicaragua, i.e. 7.2 compared to 4.7 in the control group ($p < 0.01$)³⁹). In other studies with usually lower exposure to organic solvents, the mean number of positive answers was much lower, e.g., 1.9 in US workers exposed to a mixture of solvents³¹), 3.2 in English paintmakers³⁰), in 3.1 Swedish workers exposed to styrene³⁷), and 2.9 in Chinese printing and paint workers²⁵), etc. In the German study in which a slightly modified questionnaire was used—having 18 instead of 16 questions, the mean number of positive answers was 2.9 for 544 male painters⁴¹). Compared to the non-exposed group, they found more complaints in exposed painters, mostly cognitive deficits.

In our group of heavily exposed workers the odds ratios were significantly higher for almost all symptoms on the Q16. The results suggest that findings on the Q16 are related to high long-term exposure to carbon disulfide. Risks are still high and significant after age, alcohol consumption, and different educational level were included into the model. Regarding each symptom in the Q16, significantly increased risks have been found in the heavily exposed group of spinners for less interest in sex, memory impairment, absentmindedness, affect lability, tiredness, and neurovegetative disorders. Similar results have been found for workers with intermediate exposure, but adjusted ORs never reached statistical significance.

The report of low interest in sex in the 40% of spinners is of special concern. More than a half the workers in the heavily exposed group complained of impotence and reduced libido (55.7% and 53.6%, respectively) when examined by neuropsychiatrists. In Japanese workers in rayon manufacturing plants, mostly spinners and refining workers, reduced sexual desire was reported in 18.7% of all workers²²). Such a difference from our results can reflect the social and cultural differences i.e., hesitation to answer questions on sexual behaviour. It is difficult to find any clue to those disturbances in sexual life and to conclude that they are the consequences of organic

changes in the testes, reduction in some sexual hormones, or simply symptoms of neurobehavioral disorder. Nevertheless, so high a prevalence of confessed sexual problems, in a traditional social environment, as it is in Serbia, reflects a deep dissatisfaction with one's own health and deserves further investigation.

Our study found close agreement between some specific questions in the Q16 and the neuropsychiatric examination. In the Swedish study little agreement between the number of symptoms on the Q16 and the psychiatric diagnosis of chronic toxic encephalopathy has been established³². In the study performed in Italy, it was found that the answers to the Q16 questions regarding memory and attention-concentration were poorly related to the relevant neurobehavioral performance tests scores. The authors concluded that Q16 could not be recommended as a screening tool for workers occupationally exposed to neurotoxic chemicals, but could be used to monitor healthy rather than diseased persons³⁸.

In conclusion, our data suggest that high exposure to CS₂ is related to the disturbances in the central nervous system both according to neuropsychiatric examination and the Q16. According to our findings the questionnaire Q16 can distinguish occupational groups with different levels of exposure to CS₂. Furthermore, that difference is not a result of a different educational level, alcohol consumption, or age that exist between groups. We think that it is a valuable means for selecting subjects with behavioral complaints for further neuropsychiatric testing.

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