Cross sectional observation of the effects of carbon disulphide on arteriosclerosis in rayon manufacturing workers

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Abstract

Objective—A prospective cohort study was designed to clarify the relations between occupational exposure to carbon disulphide (CS₂) and its effects on arteriosclerosis in workers in 11 Japanese rayon manufacturing factories. This report is a cross sectional baseline observation in the first study year.

Methods—Study subjects were 432 male rayon workers (mean (range) age 35.5 (19.1–47.8); duration of exposure 13.4 (0.3–29.0)) and 402 male referent workers (age 35.8 (18.9–49.8)). Exposure to CS₂ was assessed by determining the concentration of 2-thiothiazolidine-4-carboxylic acid (TTCA) in urine. Mean (SD) TTCA was 3.42 (2.73) mg/g creatinine (Cr) (n=422). About a quarter of the urine samples were >5 mg/g Cr, a biological exposure index recommended by the American Conference of Governmental Industrial Hygienists. Health effects on arteriosclerosis were evaluated by measuring blood pressure, serum lipids, pulse wave velocity of the aorta, stiffness and blood flow of the carotid artery, and blood coagulation and fibrinolysis indices, and by use of brain magnetic resonance imaging, electrocardiogram (at rest and after exercise), ophthalmograph, and Rose's questionnaire. Information on potential confounding factors was collected by self administered questionnaire.

Results—Prevalence of microaneurysm of the retinal artery was significantly higher in workers exposed to CS₂ (8.1%) than in referent workers (3.4%), and increased with age. Other examinations did not show any differences between the two groups even after allowance for confounding factors.

Conclusions—Significant effects of CS₂ on arteriosclerosis were not found in current rayon manufacturing workers, with the exception of induction of microaneurysm of the retinal artery.

(Occup Environ Med 1998;55:468–472)

Keywords: carbon disulphide; arteriosclerosis; microaneurysm of the retinal artery

Since the introduction of industrial use of carbon disulphide (CS₂, CAS No 75–15–0) in the 19th century, several toxic effects of CS₂ have

been reported—at various exposure levels—on the psychiatric, neurological, neurobehavioural, cardiovascular, cerebrovascular, ophthalmological, endocrinological, nephrological, and reproductive systems.

In 1974, the Japan Society for Occupational Health (JSOH, formerly, the Japan Association of Industrial Health) recommended changing to a new occupational exposure limit (OEL) for CS₂ from 20 ppm to 10 ppm with skin notation, to reduce the risk of microaneurysm of the retinal artery, protein in urine, and a mild increase in blood pressure, all of which were found in Japanese rayon workers repeatedly exposed to around 20 ppm CS₂.¹

In the mid-1970s, a significantly higher mortality from coronary heart diseases was reported in Finnish rayon workers with an exposure duration to CS₂ of >5 years and exposure concentrations of 20–40 ppm in the 1950s and 10–30 ppm in the 1960s.^{2–4} The American Conference of Governmental Industrial Hygienists (ACGIH) concluded that a threshold limit value time weighted average (TLV-TWA) of 10 ppm would be appropriate based on the finding of the cardiovascular effects in workers exposed to air concentrations of CS₂ slightly >10 ppm.⁵

The aim of this study was to clarify by prospective cohort design the effects of current CS₂ exposure on workers' health in all 11 Japanese viscose rayon fibre manufacturing factories. The first year cross sectional study was conducted from autumn 1992 to winter 1993. The study design, CS₂ exposures, and effects on arteriosclerosis are presented in this report.

Subjects and methods

STUDY POPULATION

The study population was recruited from 11 factories manufacturing viscose rayon fibre and other synthetic fibres or plastic products. All were men and most of them worked three shifts. Workers aged ≥46 were excluded from the study population due to the difficulty of tracing them in the follow up study.

Workers exposed to CS₂ consisted of all workers from plants producing rayon staple fibre in seven factories and about half of the workers randomly selected from plants producing rayon filament fibre in four factories. Altogether 432 CS₂ workers were examined. Most of them wore protective masks when working in and around spinning machines.

In each factory, rough matching by age took place, and 402 workers with no or almost no

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Accepted 12 January 1998

Table 1 Characteristics of study population

	Workers exposed to CS ₂		Referents	
	n	Mean (SD)	n	Mean (SD)
Age (y)	432	35.46 (8.14)	402	35.77 (9.24)
Duration of exposure (y)	432	13.43 (8.19)	—	—
Height (cm)	426	168.68 (6.20)	384	168.26 (6.16)
Weight (kg)	426	63.58 (8.26)	384	63.68 (8.64)
Body mass index (kg/m ²)	426	22.33 (2.57)	384	22.49 (2.83)
Smoking (cigarettes/day):				
0	119		150	
<14	46		39	
15–24	196		139	
≥25	70		74	
Drinking (day/week):				
0	61		43	
1–3	151		153	
4–7	210		198	

history of exposure to hazardous chemicals were selected as a referent group.

Table 1 shows the characteristics of the study subjects. The CS₂ workers had a mean (SD) age of 35.46 (8.14) and had been engaged in their rayon manufacturing jobs for 13.43 (range 0.33–29.0) years. Referent workers were 35.77 (9.24) years old. Height, weight, body mass index (BMI), and weekly frequency of alcohol intake were similar between the study populations. The proportion of smokers was slightly higher in CS₂ workers.

EXPOSURE ASSESSMENT

From spring 1992, as a biological exposure monitoring variable, 2-thiothiazolidine-4-carboxylic acid in urine (TTCA) was measured twice a year with high performance liquid chromatography modified from the method of Ogata and Taguchi.⁶

In the first measurement in spring 1992, TTCA was not detected in the urine of rayon workers collected before starting their daily job or in the urine of any referent workers. Therefore, TTCA of workers exposed to CS₂ was measured only after the workers' shift, and no repeated TTCA analysis was performed on referent workers. From spring 1993, the urine was collected on the same day as the measurement of CS₂ in the worker's breathing zone. Annual average TTCA concentration was presumed to be a mean value of the spring and autumn values. In a worker whose TTCA was measured only once a year, the TTCA

concentration was assumed to be the average value. Because workers exposed to CS₂ who were not study subjects were included, the number of samples in table 2 exceeds the number of study subjects.

In 1992, the mean annual TTCA concentration was 3.36 mg/g Cr, lower than the biological exposure index (BEI) of 5 mg/g Cr recommended by the ACGIH, but in spring, the TTCA had exceeded the recommended BEI in about one fifth of workers, and by autumn it exceeded the BEI in >30% of workers. In 1993, TTCA decreased considerably, and the proportion of workers exceeding the BEI was <10% (table 2).

From spring 1993, the CS₂ concentration in the workers' breathing zone was assessed twice a year. A Perkin-Elmer diffusive sampler tube filled with CS₂ adsorbent (Tenax TA, GL Science) was attached to a lapel of each worker for an 8-hour shift. Desorption of the adsorbed CS₂ was achieved by heating the tube on a daily exposure limit test apparatus (DELTA, Sabre Gas Detection), and the concentration was measured with a CS₂ Kitagawa stain tube (Komyo Rikagaku Kogyo KK). Mean CS₂ concentrations in the breathing zone were < half of the OEL recommended by JSOH and ACGIH (table 2).

EFFECTS ON ARTERIOSCLEROSIS

Effects on arteriosclerosis were evaluated by blood pressure, stiffness of the aorta and carotid artery, electrocardiogram (ECG) at rest and after Master's double 2 step load, brain magnetic resonance imaging (MRI), ophthalmograph of the retinal artery, Rose's questionnaire, and clinical laboratory tests including measurement for serum lipids, blood coagulation, and fibrinolysis factors.

Blood pressure was measured by a doctor after at least 15 minutes rest with a sphygmomanometer in an air conditioned room.

The stiffness of the aortic wall was evaluated by measuring its pulse wave velocity (PWV-200, Fukuda Electric). The stiffness of the carotid artery and impedance of the brain arteries were assessed by ultrasound measurement of the blood flow rate, stiffness parameter, and maximal velocity of the blood (QMF-2000XA, Hayashi Electric).

The ECG at rest and after Master's double 2 step test were examined by an industrial physician, or under the supervision of an industrial physician in each factory, or, if no industrial physician was employed, by our research team. The electrocardiographic findings were read by two cardiologists and coded according to the Minnesota code.⁷

Brain MRI was examined in a hospital near each factory, with MRI equipment with 0.5 T in magnetic density. The MRI films of the first few workers were sent to a radiologist for quality evaluation. The radiologist offered some suggestions to the hospital technicians, and after the MRI quality had improved, the remaining workers were examined. One radiologist read all MRI films particularly to find definite or suspected microembolism (lacne) of the brain arteries and brain atrophy. Brain MRI

Table 2 Assessment of exposure to CS₂

	n	Arithmetic Mean (SD)	Geometric Mean (GSD)	Median	Range	Samples n
TTCA (mg/g Cr):						
1992:						
Spring	438	3.01 (3.22)	1.50 (3.76)	2.2	nd–22.3	98*
Autumn	437	3.82 (3.22)	2.50 (2.80)	2.8	nd–20.0	135*
Average	454	3.36 (2.75)	2.25 (2.69)	2.70	nd–17.85	115*
1993:						
Spring	416	1.74 (1.96)	1.05 (2.82)	1.2	nd–14.6	24*
Autumn	405	2.25 (2.46)	1.37 (2.88)	1.6	nd–20.0	38*
Average	427	1.99 (1.90)	1.36 (2.47)	1.48	nd–14.75	27*
CS ₂ (ppm):						
1993:						
Spring	220	5.21 (4.36)	3.78 (2.40)	4.1	nd–39.7	14†
Autumn	371	4.37 (3.63)	3.65 (2.25)	4.1	nd–39.0	15†
Average	411	4.48 (3.44)	3.36 (2.37)	4.10	nd–39.70	13†

*Number of samples >5 mg/g Cr (biological exposure index by American Conference of Governmental Industrial Hygienists).

†Number of samples >10 ppm (occupational exposure limit by Japan Society for Occupational Health and American Conference of Governmental Industrial Hygienists).

nd = Non-detectable.

Table 3 Blood pressure and stiffness of the carotid artery and the aorta

	Workers exposed to CS ₂ Mean (SD)	Referents Mean (SD)
Blood pressure:		
n	424	383
Systolic blood pressure (mm Hg)	121.1 (12.2)	120.1 (12.0)
Diastolic blood pressure (mm Hg)	70.7 (10.2)	70.2 (10.9)
Carotid artery:		
n	415	381
Blood flow (ml/s)†	10.84 (1.23)	10.75 (1.24)
Maximal blood flow rate (cm/s)†	63.64 (1.25)	64.61 (1.26)
Stiffness parameter†	7.76 (1.34)	7.73 (1.31)
Impedance of the brain arteries (mm Hg/blood flow)†	7.98 (1.26)	7.98 (1.28)
Aorta:		
n	417	371
Pulse wave velocity (m/s)	6.60 (1.13)	6.68 (1.14)
Pulse wave velocity adjusted by blood pressure (m/s)	6.98 (0.74)*	7.10 (0.84)

*p<0.05.

†Geometric mean (GSD).

could not be done on workers in one factory because none of the nearby hospitals used it.

A qualified doctor searched for microaneurysm, hypertensive or arteriosclerotic changes of the retinal artery, and retinal bleeding and exudate on colour slides of the ophthalmograph of both eyes. Because both or either site of the ophthalmograph were poor in quality and no microaneurysm was found in the one good quality ophthalmograph, 62 of 432 ophthalmographs in exposed workers and 108 of 402 in referent workers were excluded from analysis.

Clinical laboratory items examined were total cholesterol (TC), very low density lipoprotein (VLDL), low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride (TG), D-dimer, thrombin-antithrombin III complex (TAT), tissue plasminogen activator (t-PA), and plasminogen activator inhibitor-1 (PAI-1). All were analysed by a nationwide clinical laboratory which ran an internal quality control programme every day and participated in nationwide as well as worldwide external quality control programmes.

All of the health effect items were examined and diagnosed without knowledge of CS₂ exposure. Measurements of blood pressure,

and stiffness of the aorta and carotid artery—which were potentially affected by low temperature—were conducted in a room kept at about 28°C.

STATISTICAL ANALYSIS

Exposure status was categorised into two (exposed and referent) or three (two types of job titles, and referent) groups. Those working in the CS₂ fibre spinning or refining process were considered to be at higher exposure to CS₂ than those in other processes.

Differences in means of continuous variables between or among groups were tested by Student's *t* test, Welch's method, or one way analysis of variance (ANOVA) after appropriate transformation of the variables. Differences in prevalence of symptoms and signs were compared by the χ^2 test or Fisher's exact method. An increasing trend of prevalence was assessed by Cochran-Armitage test. For eliminating effects of possible confounding factors, a stratification method, multiple linear regression, or multiple logistic regression were applied. The confounding variables concerned were age or categorised age group (<29, 30–39, ≥40), BMI, smoking status (never or former, ≤14/days, 15–24/days, ≥25/days), and alcohol drinking habit (never or occasional, 1–3 times a week, 4–7 times a week).

Results

Neither statistical tests of differences in means nor 2x2 table or multiple contingency table analysis showed any effect between exposure to CS₂ and systolic and diastolic blood pressure, arterial stiffness indices, prevalence of ECG abnormalities at rest, ischaemic or other changes of ECG after Master's double 2 step load, prevalence or number of suspected or definite lacune and brain atrophy on MRI, blood coagulation and fibrinolysis factors, or prevalence of cardiovascular symptoms by Rose's questionnaire (tables 3–5). Some indices of serum lipids were more normal in workers exposed to CS₂ than in referent workers.

When multiple regression analysis or multiple logistic regression analysis was applied, exposure to CS₂ was not adopted as a significant contributive variable to any of the effect indices described (data not shown).

Prevalence of microaneurysm of the retinal artery was 8.1% in workers exposed to CS₂ and 3.4% in referent workers. The difference was significant. The difference in the prevalence of microaneurysm of the retinal artery between exposed and referent workers increased with age, and was significant in workers of the ≥40 year old age group (table 6). In exposed workers ≥40, although the prevalence of microaneurysm after a duration of exposure <10 years was similar to that of referent workers of the same age group, the prevalence of microaneurysm in exposed workers after durations of exposure of 10–19 years or ≥20 years was two or three times higher than that of those with shorter durations of exposure. The trend of the prevalence with duration of exposure was weakly significant (p=0.079).

Table 4 Effects on the coronary artery and brain arteries by ECG and MRI

	Workers exposed to CS ₂	Referents
ECG at rest:		
n	424	402
Myocardial infarction suspected	20	25
Abnormal QRS axis deviation	30	20
Left ventricular hypertrophy	103	84
Right ventricular hypertrophy	11	4
ST changes	12	9
Abnormal T wave	26	36
Atrioventricular block	2	6
Bundle branch block	23	24
Ventricular premature conduction	8	7
Supraventricular premature conduction	1	0
ECG changes after Master's double 2 step load:		
ST changes	8	17
Abnormal T wave	8	13
Bundle branch block	3	3
Ventricular premature conduction	2	3
Supraventricular premature conduction	4	1
Abnormal QT	0	1
Microembolism of brain arteries by MRI:		
n	383	379
Brain stem	16	17
Cerebellum	3	3
Cerebrum	131	117

Table 5 Effects on serum lipids, coagulation, and fibrinolysis factors

	Workers exposed to CS ₂		Referents	
	n	Mean (SD)	n	Mean (SD)
TC (mg/dl)	428	186.67 (31.81)	396	188.35 (35.69)
VLDL (mg/dl)†	428	119.94 (1.87)**	396	134.40 (1.85)
LDL (mg/dl)†	428	397.77 (1.30)	396	399.76 (1.31)
HDL (mg/dl)†	428	52.10 (1.29)*	396	50.00 (1.30)
TG (mg/dl)†	428	97.95 (1.77)**	396	109.38 (1.80)
D-dimer (ng/ml)†	244	33.92 (1.75)	200	34.77 (1.80)
TAT (ng/ml)†	216	2.67 (1.77)	178	2.88 (1.87)
T-PA (ng/ml)†	245	2.70 (1.57)	200	2.58 (1.41)
PAI-1 (ng/ml)†	237	30.96 (2.03)	199	29.53 (1.96)

*p<0.05, **p<0.01.

†Geometric mean (GSD). TC=total cholesterol; VLDL=very low density lipoprotein; LDL=low density lipoprotein; HDL=high density lipoprotein; TG=triglyceride; TAT=thrombin-antithrombin III complex; T-PA=tissue plasminogen activator; PAI-1=plasminogen activator inhibitor.

Table 6 Effect of CS₂ on the retinal artery

Prevalence of retinal microaneurysms by age group (%)				
	CS ₂ exposed workers**	Referents	Mean age	Prevalence (%)***
Age group:				
<30	2/101 (2.0)	2/90 (2.2)		
30-9	8/103 (7.8)	2/55 (3.6)		
≥40	19/156 (12.2)*	6/149 (4.0)		
Entire group	29/360 (8.1)*	10/294 (3.4)		
Retinal microaneurysms in ≥40 group by exposure duration:				
<10			43.2	1/20 (5.0)
10-19			43.4	5/51 (9.8)
≥20			43.7	13/85 (15.3)

*p<0.05 Between exposed workers and referents; **p<0.05 by test for trend (age); ***p=0.079 by test for trend (exposure duration).

Discussion

Past exposures to CS₂ are difficult to estimate accurately, but can be assumed to be higher than current exposure. Mean concentrations of TTCA and CS₂ in the breathing zone were lower than the recommended BEI and OEL. However, TTCA in about a quarter of workers exceeded BEI in 1992, which indicates the need for a greater effort to reduce the level of exposure to CS₂. After exposure assessment in the first cross sectional observation, some plants improved their work environments, which may be the main reason for the marked decline of the TTCA concentration in 1993.

The only exposure related effects on the vascular system was the prevalence of microaneurysms of the retinal artery.

In 1972, Hotta *et al* performed a cross sectional study on 289 rayon manufacturing workers with mean age of 42.1 years and mean exposure duration of 10.8 years, and 49 referent workers with mean age of 43.3 years.⁸ Prevalence of the "retinopathia carboxosulphonica" defined as microaneurysms, and haemorrhages or exudate on the retina was 30.8% in workers exposed to CS₂ and 4.1% in referent workers. Three or more microaneurysms, some dot or blot haemorrhages, or a few soft or hard exudates were found in about one third of CS₂ workers with retinopathy. No CS₂ exposure data were given. In 1976, Sugimoto *et al* reported retinopathy in 25.3% of 190 rayon manufacturing workers with a mean age of 35.5 years and mean exposure duration of 12.9 years.⁹ No exposure data were given. In 1978, Sugimoto *et al* compared the prevalence of the retinopathy in 420 workers exposed to CS₂ (mean age 41.3, mean exposure duration 17.0

years) to retinopathy in 390 referent workers (mean age 42.1).¹⁰ The prevalence of the retinopathy was 24.4% in workers exposed to CS₂ and 3.8% in referent workers. Environmental concentration of CS₂ in the rayon spinning room was stated to be 15-30 ppm before 1955 and 5-15 ppm after 1955.

In this study, the prevalence of retinal microaneurysm in the referent ≥40 year old group was similar to that in referent workers with almost the same mean age as in the past reports already described. This indicates that background prevalence of the retinal microaneurysm has remained unchanged in Japanese workers over the past 20 years. On the other hand, the prevalence of retinal microaneurysm was remarkably reduced in the CS₂ exposed ≥40 year old group, and overall prevalence was similar to that in current Belgian workers exposed to CS₂.^{11, 12} Unfortunately, we have no means of comparing ophthalmographs of the study population with those of past workers exposed to CS₂. To get information about the differences in the findings, we showed the ophthalmographs to a few retired and currently employed industrial physicians and asked them to make comments. All of them had had considerable experience of reading ophthalmographs of workers exposed to CS₂ in the 1960s and 1970s. They remarked on the small number and small diameter of the microaneurysms. Thus both the incidence and severity of the effects of CS₂ on the retinal artery seemed to be reduced.

The effects have, however, not entirely disappeared under the current levels of exposure to CS₂. Furthermore, we found a higher prevalence in older workers than in younger ones, and in workers exposed for longer in the ≥40 year old group, which would suggest that not only an interactive effect of long term exposure to CS₂ and aging, but long term exposure itself was the important factor for developing microaneurysms on the retinal artery. A follow up study will be necessary to assess the interactions between aging, exposure level, and exposure duration in the incidence of retinal microaneurysm.

Other effects related to exposure surveyed by various kinds of non-invasive clinical examinations for detecting arteriosclerosis were not disclosed, although several case reports, epidemiological studies, and animal experiments have reported effects of CS₂ on the cardiovascular system, cerebrovascular system, and lipid metabolism.¹³⁻²³ The biggest reason for this discrepancy may be the low level of exposure to CS₂. Because the exposure concentration of CS₂ was low, and the study subjects were young, we need to trace any changes in their reaction to exposure to CS₂ for as long as possible to confirm the relation between exposure to CS₂ and arteriosclerosis.

In conclusion, we failed to show significant effects of CS₂ on arteriosclerosis in current rayon manufacturing workers with a mean concentration of TTCA in urine of 3.42 mg/g Cr, with the exception of induction of microaneurysm of the retinal artery.

For their cordial cooperation, we thank the members of the Sub-committee for Carbon Disulfide in the Committee of the Occupational Health, the Japan Chemical Fibre Association, and the staff of the divisions of the occupational health and environmental control in 11 rayon factories surveyed. This study was supported mainly by a grant from the Japan Chemical Fibre Association, and in part by a Grant in Aid for Scientific Research from the Japan Ministry of Education (Project No 05454221).

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