SECTION VI

CASE STUDIES

CARDIOVASCULAR RISK ASSESSMENT OF CARBON DISULFIDE EXPOSURE

by
M. Tolonen

In the manufacture of viscose rayon, pulp is dissolved with carbon disulfide (CS_2) and hydrogen sulfide is formed as a by-product. Long-term exposure to CS_2 may cause or contribute to the development of, for example, behavioural deterioration, polyneuropathy, hormonal imbalance and vascular changes, such as coronary heart disease (CHD) or disturbed ocular micro-circulation. These conditions are promoted by several, perhaps many, factors which may act simultaneously and perhaps interact in influencing the development of the disease, particularly when a considerable time lag may occur between the beginning of the exposure and the manifestation of the disease. The many-fold syndrome of chronic CS_2 intoxication further complicates the diagnosis. More to the point, the problem does not appear approachable in a conventional, clinical way. Quantification of the risk - first assessed by the clinical acumen of doctors - is impracticable without epidemiology. This paper, drawing heavily on the Finnish experience, illustrates the evaluation of the various health risks associated with CS_2 exposure.

Cardiovascular Mortality

The Research Council's study of deaths resulting from CHD in British viscose rayon workers gave the first strong evidence for a causal relationship between long-term exposure to carbon disulfide and the increased risk of death from CHD (1). The proportional mortality rates and the calculations of observable death rates by type of exposure showed that men exposed for 10 years or more between 1933 and 1962, in a British viscose rayon plant, had a factor risk for death from CHD which was 2.5 times that of other workers. Over the 30-year period, 42% of all the deaths of rayon process workers were certified attributable to CHD. The proportion was 24% for other rayon workers and 17% for the other local men. The Registrar General's tables showed a national figure of 14%. This proportional mortality increased from 1943 but declined from 1958 to 1962, only slightly exceeding that

of other local men. The deaths indicated a strong dependence on the intensity of exposure, which had been more pronounced during wartime in the 1940s. Other cardiovascular deaths occurred in eight (3.3 expected) process workers aged 35–44 years.

In another British factory, the death rate from CHD for process operators was 6.1 (3.2 expected). Twice as many spinners died of CHD as had been expected (10 against 4.5). These numbers pointed to an occupational risk in the spinning section (1). Mowe (2) reported similar results from a viscose plant in Norway. The death rates from sudden death of exposed workers aged 35–54 years were three times those of the unexposed men. Hernberg et al. (3) observed a proportional mortality from CHD of 52%, against the expected 31.6%, among Finnish viscose rayon workers exposed to carbon disulfide for five years or more.

All of these mortality studies were retrospective. Thus, no control studies could be made of the confounding effects of the risk factors of CHD, such as cigarette smoking, physical activity and dietary habits.

The Finnish follow-up study on coronary mortality (4,5) has contributed to information on the causality of CHD and the quantity of the risk among workers exposed to carbon disulfide. The cohorts, comprising 343 exposed and 343 unexposed men, have been followed since 1967. During a 5.5-year period, 16 exposed men died from CHD against three unexposed workers, the odds ratio thus being 5.6. A comparison with national mortality figures showed that the risk of death due to CHD in the exposed cohort was two-fold whereas that of the unexposed group was one third (healthy worker effect).

In a continuation of the follow-up (6), the eight-year cumulative incidence rate for CHD mortality was 5.8% in the exposed group and 2.6% in the comparison group, the rate difference being 3.2%. The corresponding cumulative incidence rates for total mortality were 10.2% and 6.7%, respectively. This rate difference of 3.5% was almost identical to that for CHD alone. This result indicates that CHD was totally responsible for the excess mortality. However, during the last three years of follow-up, the same number of deaths, six from CHD, occurred in both cohorts and, during the eighth year, only one CHD death occurred in the exposed cohort against three

in the comparison cohort. Thus, a shift in the trend seems to have taken place.

Age-specific data indicate that the excess risk of CHD was strongest in the age range of 50–64 years. In all, 17 of the 20 coronary deaths of the exposed workers occurred in that age range compared with five in the comparison group. A more detailed analysis, together with a calculation of the life expectancy in different age categories, has been reported by Nurminen (7).

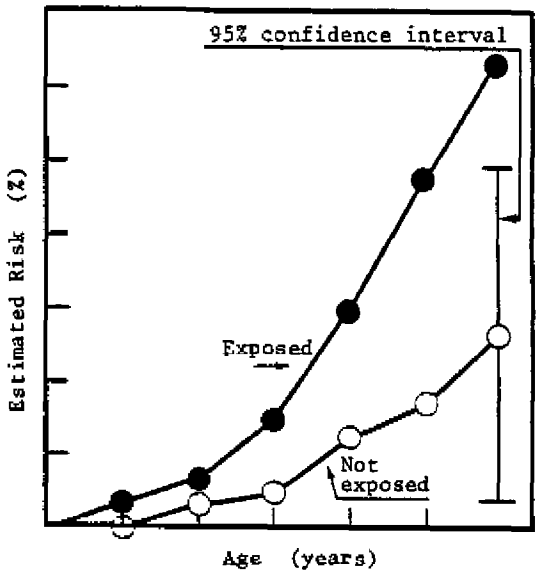
The ten-year follow-up (8) of the cohorts revealed that 14% of the exposed and 9% of the compeer cohort had died during the ten-year period. The difference in total mortality rates was on the verge of statistical significance ($p \leq 5\%$) whereas coronary deaths (11 cases) were over 2.5 times more frequent among the exposed group, the difference being statistically significant ($p < 1\%$). Other cardiovascular deaths occurred 5:1 in excess in the exposed group, but the difference did not attain the level of statistical significance. When the mortality data for CHD were divided into two successive five-year periods, the point estimate of the mortality rate ratio declined from the highly significant value of 4.7 during the first five-year period to a nonsignificant 1.9 during the second quinquennial interval. The age-specific estimated relative coronary death rates (exposed versus nonexposed) for the ten-year age intervals 40 to 49, 50 to 59 and 60 to 69 were 1.9, 2.7 and 3.4, respectively. For the entire age interval 40 to 69 years, the corresponding rate was 2.71 (95% confidence interval, 2.65–2.77).

The follow-up experience of both cohorts is summarized by the computation of their estimated (attrition) probabilities of death from CHD in Fig. 1. Thus, for example, the 20-year risk for a nonexposed 45-year-old person dying from CHD, assuming no competing risks from other diseases, was computed as:

$$1 - \prod_{i=45}^{60-64} (1 - M_i) = 8.5\%,$$

where M_i stands for the Frost estimate of death rate in the ith age interval. The estimation was based on the assumption that deaths occur uniformly throughout the five-year age intervals. For the age span 40 to 69 years, the death risk from CHD among exposed persons was 31.9% (± 4.3%) compared with 13.3% (± 5.8%) among the nonexposed.

Fig. 1. Estimated risk of death from coronary heart disease (estimated by assuming that the distribution of deaths is uniform or equivalent, i.e. that the survivor(ship) function is linear, within the five-year age intervals) (8)



The authors also studied whether or not the effects of CS_2 exposure, elevated blood pressure and older age could be quantitated (Nurminen, M. et al., unpublished manuscript). Long-linear models were fit predicting coronary deaths. The analysis identified the dual role of blood pressure in the potential mechanism of coronary death. Relative risks ranging from 2.2 to 12.8 were obtained for the joint effect of these three factors in the exposed group with reference to a subgroup of nonexposed, 40-year-old, normotensive men. The sole effect of CS_2 exposure magnified the relative risk by a multiplier of the order of 1.2 to 2.2 in various age/blood pressure cross-classifications.

Angina Pectoris, ECG Findings and Blood Pressure

Tolonen et al. (9) studied responses to a standardized angina and infarction questionnaire, the occurrence of coded resting and post-exercise ECG findings suggestive of CHD and blood pressure among 417 male Japanese and 237 Finnish workers occupationally exposed to carbon disulfide (CS_2) and their controls, 391 Japanese and 233 Finnish men without such exposure. All of the subjects were aged 35 to 54 years. Among the Japanese subjects, only seven exposed and one nonexposed worker had a history of angina, two exposed and no nonexposed men had typical angina and one had a history of possible myocardial infarction. In the Finnish exposed and nonexposed groups, the prevalence was 10% for total angina and 4% for typical angina, respectively.

No impressive differences emerged in the prevalences of "coronary" ECG items between the exposed and nonexposed groups. The presence of "coronary" ECG findings was no more frequent in those with a history of angina than in those workers without such findings. None of the exposed and nonexposed Japanese subjects with "coronary" ECG changes gave a history of angina or infarction. The "coronary" ECG prevalences for the Finnish exposed and nonexposed men were 30% and 24%, respectively. If a history of angina together with "coronary" ECG abnormalities were taken as evidence of probable CHD, the total prevalence among the Japanese was 0% for both the exposed and nonexposed groups and, among the Finns, 5% and 2%, respectively. Smoking history, obesity and blood pressure showed no marked differences in the Japanese groups. The diastolic and systolic blood pressures were significantly higher among the exposed Finnish workers than among their controls.

The study yielded no evidence for an increased occurrence of the examined parameters among the Japanese workers exposed to carbon disulfide whereas the exposure seemed causally associated with excess angina and high blood pressure among the Finns. The potential CHD induced by CS_2 seemed to be undetectable by means of electrocardiography. In the Finnish cohorts, anamnestic angina was more prevalent both in 1967-1968 and at re-examination in 1972 (Table 1).

Table 1. Prevalence (%) of reported chest pain in exposed and comparison cohorts in 1967/1968 and 1972. Probability of difference between the rates being due to chance and an estimate of the relative risk (9)

Classification	Prevalence in 1967/1968 (%)		Significance of the difference		Relative occurrence of the symptom, relative risk
	Exposed[a] (N = 343)	Nonexposed (N = 343)	z	p	
Typical	7.1	5.6	0.81	0.42	1.3
Probable	4.1	1.5	2.07	0.04	2.9
Possible	5.6	3.5	1.32	0.19	1.6
TOTAL	16.8	10.6	2.37	0.02	1.7

Classification	Prevalence in 1972 (%)		Significance of the difference		Relative occurrence of the symptom, relative risk
	Exposed (N = 316)	Nonexposed (N = 329)	z	p	
Typical	12.0	4.9	3.31	<0.001	2.8
Probable	4.7	3.0	1.14	0.25	1.6
Possible	7.9	5.2	1.41	0.15	1.6
TOTAL	24.6	13.0	3.84	0.00012	2.2

[a] In three cases, reported information was lacking.

Summary of Manifestation of CHD

Tolonen et al. (5) showed (Table 2) that the greatest effect of carbon disulfide on coronary arteries was on the production of fatal infarctions (relative risk 4.8), followed in reducing order by: all infarction, fatal and nonfatal (relative risk 3.7); nonfatal infarctions

(relative risk 2.8); angina (relative risk 2.2); and coronary ECGs (relative risk 1.4). In other words, the more serious the outcome, the greater the relative risk. Possibly, exposure to carbon disulfide not only worsens the prognosis of existing coronary heart disease but increases the incidence of new cases. However, this mode of action may not operate in countries where coronary heart disease is less common than in Finland. Coronary heart disease has a multifactorial etiology, and the pattern described above may be noticeable only when a sufficient number of other coronary risk factors are present at the same time.

Table 2. Estimates of relative risk and attributable risk (%) of CHD according to severity of manifestation (5)

Manifestation	Relative risk	Attributable risk
Fatal infarction	4.8	3.2
All infarctions	3.7	5.4
Nonfatal infarction	2.8	2.2
Angina	2.2	11.6
"Coronary" ECGs	1.4	6.1

Estimation of Individual Chronic Subclinical Effects of CS_2

At an individual level, risk estimation is difficult; in particular, the subclinical stage is difficult to identify. Yet the question of whether or not a disease has an occupational origin is frequently faced in industry. This situation exists because most occupational hazards manifest themselves with symptoms which are common, especially among middle-aged people. Chronic subclinical CS_2 poisoning is a typical example of such a syndrome. In 1974, an attempt to shed light on this problem was made by studying 97 men exposed to CS_2 and 96 controls (10). The mean age was 48 years (range 33-67 years), and the mean exposure time was 15 years (range 1-27 years). The group underwent many examinations, including examination of the heart

(positive = history of verified myocardial infarction and/or "Minnesota Codes" I_{1-3}, IV_{1-3}, V_{1-3}, VII_{1-3}, $VIII_3$, $XI_{1-3,5-7}$, and/or typical angina); psychological testing; measurement of the conduction velocities of eight peripheral nerves (polyneuropathy was considered to exist when two or more nerves showed reduced conduction velocities); and examination of the circulation of the ocular fundus (the criterion for disturbed circulation was delayed peripapillary filling - circumferential, segmental or both). The occurrence of disorders in the exposed and the control groups are shown in Tables 3-5.

Table 3. Observed number of disorders in the exposed and control groups and the estimates of the risk ratios (relative frequencies) (10)

Disorder	Group		Risk ratio[a]	p-value
	Exposed (N = 97)	Control (N = 96)		
Coronary heart disease	29	19	1.5	0.14
Polyneuropathy	49	23	2.1	0.00022
Disturbed ocular microcirculation	67	38	1.8	0.00011
Behavioural deterioration	39	24	1.6	0.035

[a] For example, the risk ratio 1.5 was calculated as (29/97)/(19/96).

Table 4. Total frequency of coronary heart disease in the exposed and control groups and the estimates of risk ratios (10)

Symptom and/or sign of CHD	Group		Risk ratio	p-value
	Exposed (N = 97)	Control (N = 96)		
Infarction	6	I	4.4	0.12
Angina pectoris	7	2	3.0	0.17
"Coronary" ECG plus infarction or angina	6	1	4.4	0.12
"Coronary" ECG without infarction or angina	16	16	1.0	1.00
Total CHD frequency	29	19	1.5	0.14

Table 5. Distribution of poor psychological test performances for the exposed and control groups and estimates of the risk ratios (10)

Behavioural change	Group		Risk ratio	p-value
	Exposed (N = 97)	Control (N = 96)		
Retardation (DS, BW speed, SA right)	31	16	2.2	0.02
Visual intelligence (PC, BD)	21	22	1.0	0.97
Idealization (Rorschach ink-blot test, adaptability)	35	24	1.8	0.13
Motor functions (Mira VI and VII)	40	31	1.3	0.25

No matter how clearly the exposed group showed significant excess morbidity rates of all disorders under study, the diagnosis at an individual level remains impracticable in these statistics. Therefore, the solitary and combined deviating findings in various organs of all individuals were analysed (Table 6).

Table 6. Prevalance (%) of coronary heart disease (CHD), delayed peripapillary circulation (EYE), polyneuropathy (PN) and behavioural symptoms (BS), their combinations in the subjects of the exposed and control groups, and the differences between the groups (10)

	Group		Difference = excess morbidity
	Exposed (N = 97)	Control (N = 96)	
Free of disease	5	31	
CHD only	4	9	-5
EYE only	19	19	0
PN only	6	6	0
BS only	7	6	1
CHD + EYE	4	4	0
CHD + PN	1	1	0
CHD + BS	1	2	-1
EYE + PN	12	5	7
EYE + BS	7	4	3
PN + BS	4	5	-1
CHD + EYE + PN	9	0	9
EYE + PN + BS	11	5	6
CHD + PN + BS	2	1	1
CHD + EYE + BS	2	2	0
CHD + EYE + PN + BS	6	0	6
Total	100	100	26

Only 5% of the exposed subjects, compared with 31% of the controls, were without any abnormalities. As many as 59% of the exposed and 29% of the unexposed men were affected by more than one disorder under study, but most combinations of disorders occurred more frequently in the exposed group. A combination of three abnormalities was three times more common in the exposed group than in the controls, and a combination of all four abnormalities occurred only in the *exposed* group. To detect the disorders responsible for the excess morbidity caused by CS_2, the data were summarized (Table 7). All excess morbidity was indicated by disturbed ocular microcirculation plus damage to either the peripheral or central nervous system or both.

Table 7. Combinations of disturbed ocular microcirculation (EYE), nervous or behavioural deterioration or both (NER), and coronary heart disease (CHD) in the exposed and control groups (from 10)

EYE	NER	CHD	Exposed	Controls	Difference
-	-	+	4	9	-5
-	+	+	4	4	0
-	+	-	17	17	0
+	-	-	19	19	0
+	-	+	4	4	0
+	+	-	30	14	16
+	+	+	17	2	15

With disturbances in the choroidal circulation present in all cases of excess "morbidity" (68% of the exposed), this abnormality apparently represents the earliest manifestation of carbon disulfide toxicity, at least of those considered here.

Thus, it can be postulated that in this material a positive diagnosis of carbon disulfide poisoning could only be made providing changes in the choroidal circulation have been observed and providing exposure has extended over 10 years or more, with an intensity of

magnitude of about 30-90 mg/m^3 (10-30 ppm). The estimated probability that a combination of findings is of occupational origin is computable as the excess morbidity over total morbidity. The results also showed that the etiological role of carbon disulfide could be demonstrated with greater probability, the greater the number of abnormalities present at the same time (in an examinee). This probability can be estimated for all the various combinations of the disorders. For example, the estimated probability that a syndrome of PN + BS + EYE (12-17) is an occupational disease is 70% and that of CHD + PN (or BS or both) + EYE is 100%.

REFERENCES

1. Tiller, J.R. et al. Occupational toxic factor from coronary heart disease. British medical journal, 4: 407 (1968).

2. Mowé, G. Coronary heart disease and occupational exposure to carbon disulfide, In: Djuric, D. et al., ed. Abstracts of the II International Symposium on Toxicology of Carbon Disulfide, Yugoslavia, 25-28 May 1971. Belgrade, Institute of Occupational and Radiological Health, 1971.

3. Partanon, T.S. et al. Coronary heart disease among workers exposed to carbon disulfide. British journal of industrial medicine, 27: 313-325 (1970).

4. Hernberg, S. et al. Excess mortality from coronary heart disease in viscose rayon workers exposed to carbon disulfide. Scandinavian journal of work, environment and health, 10: 93 (1973).

5. Tolonen, M. et al. A follow-up study of coronary heart disease in viscose rayon workers exposed to carbon disulfide. British journal of industrial medicine, 32(1): 1-10 (1975).

6. Hernberg, S. et al. Eight-year follow-up of viscose rayon workers exposed to carbon disulfide. Scandinavian journal of work, environment and health, 2(1): 27-30 (1976).

7. Nurminen, M. Survival experience of a cohort of carbon disulfide exposed workers: Life table analysis of an 8-year prospective follow-up period. Helsinki, Institute of Occupational Health (unpublished report).

8. Tolonen, M. et al. Ten-year coronary mortality of workers exposed to carbon disulfide. Scandinavian journal of work, environment and health, 5(2): 109-114 (1979).

9. Tolonen, M. et al. Angina pectoris, electrocardiographic findings and blood pressure in Finnish and Japanese workers exposed to carbon disulfide. International archives of occupational and environmental health, 37: 249-264 (1976).

10. Tolonen, M. Chronic subclinical carbon disulfide poisoning. Scandinavian journal of work, environment and health, 11: 154 (1974).