Exposure to carbon disulphide and ischaemic heart disease in a viscose rayon factory

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ABSTRACT The cohort of viscose rayon workers previously described by Tiller *et al* has been reconstructed and followed up to the end of 1982. The pattern of mortality at ages 45 to 64 for the extended period 1950-82 is similar to that described by Tiller *et al* for 1950-64. The spinners, the workers most heavily exposed to carbon disulphide, have a significantly higher mortality from all causes than the least exposed group. The excess mortality is largely accounted for by ischaemic heart disease (IHD) for which the spinners have an SMR of 172. When mortality is related to an exposure score in the same group, both all cause ($p < 0.01$) and IHD ($p < 0.001$) mortality increase with increasing exposure level. When this analysis is repeated covering all ages these trends become much less strong and only that for IHD remains significant ($p < 0.05$). Over the age of 65 there is a tendency for mortality to decline with increasing exposure. This is contrary to expectation under the usual hypothesis that carbon disulphide promotes atherosclerosis. Instead it suggests that carbon disulphide has some type of reversible, direct cardiotoxic or thrombotic effect. This is supported by the findings that there is a strong trend ($p < 0.01$) for IHD mortality to increase with increasing exposure in the previous two years. Further, both IHD ($p < 0.001$) and total ($p < 0.01$) mortality show highly significant trends with exposure among current workers but no such trends among workers who have left the industry.

The hazards of exposure to high concentrations of carbon disulphide (CS_2) have been known since the nineteenth century when it was used in the vulcanisation of rubber. Carbon disulphide is a neurotoxic poison, exposure to concentrations of the order of 1000 ppm can cause acute psychosis and exposure to around 5000 ppm is rapidly fatal.

In this century the main industrial use of carbon disulphide has been in the viscose rayon industry. Cellulose produced from wood pulp is converted, after treatment with caustic soda, into cellulose xanthate by the addition of carbon disulphide. The cellulose xanthate is dissolved in dilute caustic soda giving a solution called viscose. At times viscose process workers are exposed to carbon disulphide. The viscose solution is pumped through a jet into a warm sulphuric acid bath where the original cellulose is precipitated as a continuous thread. This is cut into short lengths, washed, and dried. Men working in this spinning department may be exposed to both carbon disulphide and hydrogen sulphide.

In 1954 Vigliani described 100 cases of poisoning from carbon disulphide that occurred in five viscose

rayon plants in Piedmont during 1940 and 1941. Polyneuritis was seen in 88% of these cases. Under the wartime conditions these men were exposed to concentrations ranging from 60 to 500 ppm. After the war conditions in rayon plants improved and exposures were considerably reduced.

Vigliani describes how, on moving from Turin to Milan in 1942, he began to see cases with "a vascular, diffused encephalopathy." From 1943 to 1953 he saw 43 such cases, 15 of whom were aged under 50. He advanced the hypothesis that "prolonged exposure to CS_2 can lead to a favourable situation for producing atherosclerosis." He also described vascular lesions in animals exposed to CS_2 . Later workers report atherosclerosis in animals exposed to CS_2 .²

In 1968 Tiller *et al* produced the first evidence relating the development of coronary heart disease to exposure to carbon disulphide among viscose rayon workers.³ They began with a proportional mortality study in an area containing three rayon plants and found that 42% of deaths among viscose and spinning process workers were certified to coronary heart disease. The corresponding proportion among other non-process, rayon workers was 24%, whereas for non-rayon workers it was 17%. They then conducted

a cohort study among the men employed at the most modern of the three factories. The cohort was followed up from 1950 to 1964. Among men employed in the rayon industry for more than 10 years, those exposed to carbon disulphide had death rates from coronary heart disease more than twice that of other rayon workers. The findings of Tiller *et al* have since been supported by Hernberg and co-workers.^{4,5} They found that coronary mortality over a ten year period was more than twice as high in a cohort of 343 viscose rayon workers exposed for at least five years to CS₂ as it was in a cohort of 343 paper mill workers matched for age and district of birth.

The viscose rayon industry has greatly diminished in size in Europe in the face of competition from other yarns. It is, however, a source of employment in many developing countries. Levels of exposure to CS₂ have undoubtedly declined since the 1940s and 1950s, although few objective data are available. In the United Kingdom the threshold limit value (TLV) was 20 ppm in the 1960s and has since been reduced to 10 ppm. The cohort study of Tiller *et al* is still much the largest that has been reported.³ An extension of the period of follow up of that cohort should yield important additional information, particularly in relation to the lower exposures to CS₂ in the 1970s. We report here a follow up of that cohort to the end of 1982.

Subjects and methods

The population studied by Tiller *et al* was defined as all men who were employed at one factory for at least one year between 1 January 1945 and 31 December 1949.³ They followed up this cohort from 1 January 1950 to 31 December 1964. Therefore, to be a member of the defined population the man had to be still alive on 1 January 1950. We reconstructed the cohort from records preserved by Tiller. Without his invaluable help the study would not have been possible because company records before 1960 were incomplete.

Records were found for 3098 men. Of these, 128 men had worked for less than one year between 1945

and 1949 and a further 31 had died before 1950. Thus 2939 men were eligible for the study. These men were traced through company records and through the National Health Service Central Registry. A positive tracing as alive or dead at the end of 1982 could not be made for 91 (3.1%) men. Seventy of these were known to have emigrated. The analysis reported here is thus based on 2848 men. Tiller *et al* largely restricted their analyses to men with at least 10 years experience in the viscose rayon industry and we have done likewise. A total of 1664 men had 10 or more years experience in the industry. For these men the actual date of study entry is either 1 January 1950 or the date of achieving 10 years experience in the industry, whichever is the later.

For each man, the data collected included date of birth, date and cause of death, and the description and dates of every job that he had had in the viscose rayon factory. All causes of death were coded to the ICD classification by one experienced coder. The revision used was that in force at the time that the death occurred. Thus a death may have been coded to the 6th, 7th, 8th, or 9th revisions of the ICD.

We tried to follow Tiller *et al* in classifying men into one of six occupational groups, according to their worst exposure to CS₂. Men of foreman grade and above were classified as "staff" and the remainder as "operatives." Operatives were classed as:

- process workers who had worked in the spinning department (highest exposure to CS₂)
- process workers who had worked in the viscose making department but not in spinning (low to moderate exposure to CS₂)
- non-process fitters (some exposed at times to high levels of CS₂ while maintaining machinery)
- other non-process workers (little or no exposure to CS₂).

Staff were simply divided into two groups as process workers (with some exposure to CS₂) and non-process workers (with no exposure to CS₂). Table 1 gives the distribution of men by occupation group and length of time in the industry.

An exposure score was also calculated for all oper-

Table 1 Number of men by occupation group and period spent in the viscose rayon industry

Occupation group	Period spent in viscose rayon industry		Total
	< 10 years	≥ 10 years	
Operatives:			
Spinner	343	661	1004
Viscose	204	257	461
Non-process fitter	75	55	130
Other non-process	508	373	881
Staff:			
Process	12	192	204
Non-process	42	126	168
Total	1184	1664	2848

Table 2 Codes used for specific causes of death under different revisions of the ICD

Specific cause of death	Codes used with ICD revision		
	6th and 7th	8th	9th
Ischaemic heart disease	420,422	410-414	410-414
Other circulatory disease	330-334	390-458	390-459
	400-468	excluding	excluding
	excluding 420,422	410-414	410-414

atives. Measurement of doses by means of personal monitors has been carried out only during the past six years. Before this, measurements of environmental levels of CS₂ were done on an area basis. Taking into consideration personal monitoring results, previous area measurements, and the nature of the work, each job was allocated a CS₂ rating. This task was performed by one of the authors (ST) together with an experienced senior member of staff who had been employed at the factory since 1946. The CS₂ ratings ranged from 0 (no exposure to CS₂) to 4 (highest exposure to CS₂). There is no doubt that those highest exposed on a continuous basis were the spinners who were allocated a rating of 4. The next highest were the wash operatives (working within the spinning department) who were allocated a rating of 3. A rating of 2 was allocated to most viscose operatives. They were exposed to intermittent high levels over a shift every third or fourth week since the majority of them rotated their job and spent much of their time in areas with no exposure to CS₂. Likewise fitters, pipefitters, and their mates intermittently exposed to high CS₂ levels were given a rating of 2. All other operatives were given a rating of 1 (little exposure) or 0 (no exposure). The exposure score was then the product of this CS₂ rating with the number of months spent in the particular job, summed over all jobs. This exposure score could be calculated over any chosen period. Exposure scores were not calculated for staff

because of the difficulty of allocating a CS₂ rating to many of the staff jobs.

The results are presented as standardised mortality ratios (SMRs). Man-years at risk were calculated using MYCL⁶ in five year age groups within quinquennial calendar periods. Expected deaths were obtained by applying the England and Wales death rates to the man-years at risk. The England and Wales rates used were the average annual age specific rates for the appropriate quinquennial calendar period. SMRs were calculated for total mortality, for ischaemic heart disease mortality, and for other circulatory diseases. Table 2 shows the ICD codes used to define these specific causes under the different ICD revisions.

Significance tests were calculated using the usual assumption that the observed deaths follow the Poisson distribution whereas the expected deaths are based on such large numbers that they may be taken as without error.⁷

Results

There was some uncertainty over the accuracy of our reconstruction of the original cohort. The best means of dispelling this uncertainty was to repeat the analysis performed by Tiller *et al* and to compare our results with their published figures. They restricted all their analyses to the age range 45 to 64 years.² Of the 1664 men with more than 10 years experience in the industry, 1334 were aged between 45 and 64 at some time between entry and the end of 1964. Table 3 shows the comparison for man-years at risk and for ischaemic heart disease (IHD) deaths. In general the two sets of results compare well. It seems that we have classed as spinners some of the men that Tiller *et al* classed as viscose workers. This reflects the difficulty of job classification. The only discrepancy of any size is in the observed deaths from IHD among the other non-process workers and this is partly explained by

Table 3 Man-years and observed and expected deaths from IHD. The current reconstructed cohort compared with the original published results

Occupation group	Tiller <i>et al</i> analysis			Current analysis		
	Man-years at risk	IHD deaths		Man-years at risk	IHD deaths	
		Observed	Expected		Observed	Expected
Operatives:						
Spinner	4585	28	14.6	4924	28	16.9
Viscose	2221	5	7.2	1815	5	6.2
Non-process fitter	*	6	1.8	413	6	1.8
Other non-process	1997	6	8.0	2258	11	9.8
Staff:						
Process	1502	9	4.3	1482	9	4.5
Non-process	752	3	2.3	768	3	2.6

*Not given.

Follow up to 31 December 1964; ages 45 to 64; men with 10 or more years experience in the industry.

Table 4 Observed and expected deaths and SMRs by cause and occupation group; ages 45 to 64. Period of follow up 1950-82

Occupation group	IHD			Other circulatory			All causes		
	Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp	SMR
Operatives:									
Spinner	73***	42.5	172	33**	20.0	165	183***	134.6	136
Viscose	19	17.1	111	5	8.0	63	53	53.8	99
Non-process fitter	9**	3.1	290	0	1.6	0	13	10.3	126
Other non-process	22	18.4	120	16	9.5	168	62	61.1	101
Staff:									
Process	20	13.2	152	5	6.1	82	44	41.3	107
Non-process	10	7.4	135	4	3.4	118	20	23.0	87

Observed deaths significantly greater than expected: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

the difficulties in job classification. Of the 11 men that we classed as other non-process workers who died of IHD, one was classed by Tiller *et al* as a viscose process worker and two as spinners. Overall, we found seven more deaths among our cohort than did Tiller *et al* and of these, five were certified to ischaemic heart disease. The comparison is, however, sufficiently close to conclude that the original cohort has been successfully reconstructed.

Table 3 also shows the high mortality from ischaemic heart disease among the spinning operatives (SMR = 166) and the process staff (SMR = 200) as reported by Tiller *et al*. When the period of follow up is extended to the end of 1982 this pattern is maintained (table 4). All cause mortality among spinning operatives is significantly ($p < 0.001$) higher than expected and the SMR of 136 is also significantly ($p < 0.05$) higher than the SMR of 101 found among the other non-process operatives, the least exposed group of operatives. The excess total deaths among the spinners are almost entirely accounted for by an excess of deaths from circulatory causes, most being due to IHD for which the SMR is 172 ($p < 0.001$). There is no evidence of any excess mortality among the viscose process workers. The overall pattern of mortality in the extended period of follow up from 1965 to 1982 is similar to that seen in the period 1950-64.

Classification by occupation group indicates the highest level of CS₂ that a worker will have been exposed to but takes no account of the duration of

that exposure. In table 5 mortality from all causes, from IHD, and from other circulatory causes is related to exposure score. Staff have been excluded because of the difficulty of allocating them an exposure score. As in tables 3 and 4, the analysis is limited to men with at least 10 years experience in the industry and it is restricted to ages 45 to 64. There is a significant ($p < 0.01$) trend for all cause mortality to increase with exposure, and a pronounced and highly significant ($p < 0.001$) trend for IHD mortality to increase with exposure. Mortality from other circulatory causes is generally high but shows no association with exposure. In this instance the exposure score has been calculated up to the point of study entry. This avoids the bias that is introduced when the periods over which exposure is measured and mortality is analysed are permitted to overlap.⁸ When exposure is calculated up to 1960 and mortality analysed from 1960 to 1982 a similar pattern emerges.

The main hypothesis put forward to explain the excess mortality from IHD is that CS₂ promotes atherosclerosis.¹⁻³ If this is so then we should expect IHD mortality to remain high after exposure to CS₂ ceases. In particular, there is no reason to limit analysis to ages 45 to 64. In table 6 mortality is again related to exposure score but the age restriction is removed. There are still trends for total and IHD mortality to increase with exposure but they are much less strong than those seen at ages 45 to 64. For IHD mortality the trend is just significant at the 5% level whereas that for total mortality is not statistically

Table 5 Observed and expected deaths and SMRs by exposure score among operatives; ages 45 to 64. Period of follow up 1950-82

Exposure score	IHD			Other circulatory			All causes		
	Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp	SMR
0-99	4	8.1	49	6	4.0	150	20	26.2	76
100-199	25	26.3	95	21	12.4	169	87	82.9	105
200-299	47	25.4	185	9	11.9	76	106	79.9	133
≥ 300	47	21.4	220	18	10.8	167	98	70.6	139

Test for trend: all causes χ^2 (1 df) = 8.1; $p < 0.01$.
IHD χ^2 (1 df) = 18.4; $p < 0.001$.

significant. In fact, above age 65 there is no trend of total mortality with exposure, and IHD mortality tends to decline with increasing exposure. This finding suggests that any hazard may cease when exposure ceases and hence that the effect is some type of reversible, direct cardiotoxic or thrombotic effect.

The measure of exposure used in tables 5 and 6 is the exposure-months score calculated up to the point of study entry. This is not necessarily a good measure of current or recent exposure. To test better the hypothesis of a reversible direct effect, mortality was then related to the exposure-months score in the previous two years. Each man year from the anniversary of study entry was allocated to the appropriate five year age group and calendar period and to one of five exposure-months groups (0, 1–23, 24–47, 48–71, and 72–96) according to the exposure in the immediately previous two years. Thus any one man might contribute man-years to all five exposure groups. Two years after having left his last CS₂ exposed job a man's exposure score would be 0 and would remain so. Thus most of the experience after age 65 would have a zero exposure score.

Mortality in relation to exposure to CS₂ in the previous two years is shown in table 7. Again the analysis is restricted to operatives with at least 10 years experience in the industry. There is no convincing evidence that all cause mortality varies with exposure in the last two years (χ^2 (4 df) = 7.8, $p = 0.10$, NS) and the variations that do exist show no evidence of a consistent trend with exposure. There are highly significant ($p < 0.01$) differences in IHD mortality between the different exposure score groups and in particular

there is a trend ($p < 0.01$) for IHD mortality to increase with exposure in the last two years. The most pronounced increase occurs in workers with exposure scores greater than 48. The only workers who could obtain such scores are spinners, wash operatives, fitters and pipefitters and their mates, and viscosite operatives. They are all at risk of having been exposed to high levels of CS₂. As in other analyses (tables 4 and 5) mortality from other circulatory diseases shows an unusual pattern. In general it is high with SMRs of the order of 150 to 170 but there is one exposure score group in which it is very low. There is, however, no suggestion of any trend with exposure.

In table 7 nearly two thirds of both observed and expected deaths occur in the group with no exposure to carbon disulphide in the previous two years. This group is a mixture of current workers with no exposure and workers who have left the industry maybe many years before. In table 8 mortality related to interval since last employment and exposure score up to the time of study entry. The group described as current workers are those still in employment or who have left the factory within the past year. This latter group were included with the current workers to get over the problem of workers who leave the industry because they are ill.

Total mortality varies significantly (χ^2 (2 df) 12.3, $p < 0.01$) with interval since last employment. It is lowest among the current workers and highest one to nine years after leaving employment. Within the current workers total mortality increases significantly with exposure (χ^2 (1 df) = 8.8, $p < 0.01$). There is some suggestion of a similar trend one to nine years

Table 6 Observed and expected deaths and SMRs by exposure score among operatives; all ages. Period of follow up 1950–82

Exposure score	IHD			Other circulatory			All causes		
	Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp	SMR
0–99	28	28.1	100	28	20.0	140	94	95.5	98
100–199	79	68.1	116	68	42.5	160	261	223.0	117
200–299	80	58.1	138	48	34.4	140	236	188.4	125
≥300	80	55.7	144	57	35.8	159	227	186.7	122

Test for trend: all causes χ^2 (1 df) = 2.7, NS.
IHD χ^2 (1 df) = 4.0; $p < 0.05$.

Table 7 Observed and expected deaths and SMRs by exposure score in the last two years; all ages. Period of follow up 1950–82

Exposure score in previous 2 years	IHD			Other circulatory			All causes		
	Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp	SMR
0	149	129.4	115	149	89.4	167	528	429.0	123
1–23	12	11.3	106	10	6.7	149	44	36.4	121
24–47	30	28.9	104	26	15.7	166	93	95.3	98
48–71	49	29.0	169	7	15.1	46	99	95.1	104
72–96	27	11.4	236	9	5.9	153	54	37.9	142

Test for trend: IHD χ^2 (1 df) = 10.5; $p < 0.01$.

Table 8 Observed and expected deaths and SMRs by interval since last employment and exposure score; all ages. Period of follow up 1950-82

Interval since last employment	Exposure score	IHD			Other circulatory			All causes		
		Obs	Exp	SMR	Obs	Exp	SMR	Obs	Exp	SMR
Current workers	0-99	9	10.0	90	3	6.0	50	26	33.9	77
	100-199	21	26.9	78	19	14.3	133	74	88.4	84
	200-299	48	26.6	180	9	13.7	66	102	86.4	118
	≥ 300	45	21.4	210	15	11.7	128	89	72.4	123
	All	123	84.9	145	46	45.7	101	291	281.1	104
1 to 9 years after leaving	0-99	12	10.6	113	12	7.7	156	37	35.3	105
	100-199	34	26.7	127	34	17.6	193	115	86.7	133
	200-299	20	20.6	97	27	13.0	208	94	65.6	143
	≥ 300	24	19.5	123	30	12.5	240	96	63.2	152
	All	90	77.4	116	103	50.8	203	342	250.8	136
10 or more years after leaving	0-99	7	7.5	93	13	6.3	206	31	26.2	118
	100-199	24	14.4	167	15	10.5	143	72	48.0	150
	200-299	12	10.8	111	12	7.8	154	40	36.4	110
	≥ 300	11	14.8	74	12	11.7	103	42	51.1	82
	All	54	47.5	114	52	36.3	143	185	161.7	114

Test for trend: All causes—current workers χ^2 (1 df) = 8.8, $p < 0.01$.
 —1 to 9 years after leaving χ^2 (1 df) = 3.6, NS.
 IHD—current workers χ^2 (1 df) = 15.8, $p < 0.001$.
 Other circulatory—1 to 9 years after leaving χ^2 (1 df) = 1.7, NS.
 ≥ 10 years after leaving χ^2 (1 df) = 2.6, NS.

after leaving the factory but this does not reach the conventional 5% level of statistical significance. There is no such trend 10 or more years after leaving.

Mortality from IHD is highest (SMR = 145) among the current workers but the difference between the three employment groups is not significant. Within the current workers, however, there is a powerful trend (χ^2 (1 df) = 15.8, $p < 0.001$) for IHD mortality to increase with exposure. There is no such trend after operatives have left the factory. Conversely, mortality from other circulatory diseases is higher after leaving the factory (χ^2 (2 df) = 16.6, $p < 0.001$). Mortality from other circulatory diseases increases with exposure in men one to nine years after leaving the factory, but there is a similar trend in the opposite direction 10 or more years after leaving the factory. Neither of these trends, however, even approaches the conventional 5% level of statistical significance.

Discussion

The original cohort of men followed up by Tiller *et al*³ from 1950 to 1964 has been successfully reconstructed and the follow up extended to 1982. Among men who had worked for at least 10 years in the viscose rayon industry, Tiller *et al* found that between ages 45 and 64 mortality from ischaemic heart disease was high in those who had worked in the spinning departments.³ When this analysis is extended to 1982 the same group of men are found to have higher mortality than

expected from all causes. The excess deaths are almost entirely accounted for by an excess of circulatory system deaths, the main component of which is an excess of deaths from IHD. The spinning operatives have a SMR for IHD of 172. There was no evidence of any excess mortality among the viscose process workers. In general, the pattern of mortality in the period 1965-82 is similar to that seen in 1950-64.

Men in the spinning departments are exposed to much higher levels of carbon disulphide (CS₂) than men in the viscose making department. But, as several workers^{3,9} have pointed out, some men in the spinning departments of viscose rayon factories are exposed to both CS₂ and hydrogen sulphide (H₂S). The excess mortality in the spinning departments could be explained either by the higher levels of CS₂ or by the exposure to H₂S. Tiller *et al* concluded that H₂S was unlikely to be the causative agent.³ One reason for this was that in their proportional mortality study they found an excess of 13 observed against 4.6 expected deaths from IHD among the viscose workers in the two older factories. Viscose workers have no exposure to H₂S and in those two older factories had much higher exposures to CS₂ than viscose workers in the modern factory on which the cohort study is based.

Within the spinning department are three sections: spinning, wash, and drying. In the spinning section men are exposed to the highest levels of CS₂ and also to H₂S. In the wash section they are exposed to levels of CS₂ that are nearly as high as in the spinning

section but to considerably lower levels of H_2S . Men in the drying section are exposed to little CS_2 and no H_2S . A comparison of those men who had worked as spinners with those who had worked as washers but not as spinners should give some indication of the effect of exposure to H_2S . Unfortunately, the number of men whom we were sure had been pure washers was small, only 66. Between the ages of 45 and 64 there were, among the washers, seven observed deaths from ischaemic heart disease as opposed to 3.7 expected (SMR = 188). Among the men who had worked in the spinning section there were 29 observed deaths against 15.6 expected (SMR = 186). These numbers are small but they give no support to the thesis that H_2S is the causative agent.

The trends that we have shown for ischaemic heart disease mortality to increase with increasing exposure to CS_2 also point to CS_2 as the causative agent. It has to be admitted that the exposure score is crude. We rated each job on a scale from 0 to 4. We then summed the product of that rating with the months spent in the job for each job that the man had done in the period under consideration. This assumes that the exposure rating score is on an interval scale, which it is not. Nevertheless, we would argue that it is a better index of exposure to CS_2 than the occupational group. The classification into occupational group makes no allowance for the period spent in the job and it combines together jobs which may have widely differing exposures to CS_2 . For example, the group of spinning operatives comprises spinners, washers, and dryers whose different exposures to CS_2 and H_2S have already been described. It is also true that many of the men with the highest exposure scores are the men who are additionally exposed to H_2S . We thus cannot rule out the possibility that H_2S is involved. On balance, however, it seems to us more likely that CS_2 is the causative agent.

The main hypothesis previously put forward to explain the association between exposure to carbon disulphide and ischaemic heart disease is that exposure to carbon disulphide promotes atherosclerosis.¹⁻³ Occupational group is a measure of the worst ever exposure to carbon disulphide but takes no account of the duration of that exposure. If CS_2 promotes atherosclerosis then it may well be that total exposure to CS_2 is more important than worst exposure. An exposure score was derived for each man. Between ages 45 and 64 both total mortality and IHD mortality rose with increasing exposure score, the latter considerably.

If CS_2 promotes atherosclerosis, however, then we would expect mortality from IHD, and perhaps from other circulatory diseases, to remain high even when exposure has ceased. In particular there is no reason to exclude experience over the age of 65. When the

analyses are repeated using all ages, the trends for total and IHD mortality to increase with exposure are much decreased. This happens because at age 65 and above there is no increase in mortality with increasing exposure which suggests that the effect of CS_2 is reversible and that the risk disappears after exposure ceases. The fact that mortality from other circulatory causes, while generally high, shows no sign of any increase with exposure also argues against the hypothesis that CS_2 promotes atherosclerosis.

If the effect is a reversible, direct effect then mortality should be more strongly related to recent exposure than to total exposure, and there is some evidence (table 7) that this is so. IHD mortality shows a strong trend to increase with exposure to CS_2 in the immediately previous two years. Further evidence to support the hypothesis of a reversible effect is found in the fact that mortality from IHD is higher among current workers (SMR = 145) than among those who had left who had an SMR of 116 one to nine years after leaving and of 114, ten or more years after. Among the current workers there is a pronounced increase in death from IHD with previous exposure, the SMR rising from 90 in the lowest exposed group to 210 in the highest. There were no such trends after leaving the factory. Mortality from other circulatory causes was much higher after leaving the factory but there was no evidence that this was related to past exposure.

All these results are based on the 1664 men who had spent at least 10 years in the viscose rayon industry. This is why the results reported here show no evidence of a healthy worker effect.¹⁰ The major component of the healthy worker effect is the initial selection of a healthy population for employment. This will have largely disappeared after 10 years. It could be argued that if the effect of CS_2 is direct then it might also be seen in the 1184 men with less than 10 years experience in the industry. In fact there is no suggestion that mortality from ischaemic heart disease is related to occupation group among these men. Analysis by exposure score also shows no evidence of any hazard. It does show, however, that most of these men had no exposure to carbon disulphide and those that were exposed only have very short exposures. Ninety per cent of these men had left the industry for the last time before 1955, at which point the average age of the group was only 41. Thus they are a group of men who have had at most short exposures at a young age. It is generally agreed that the risk of IHD varies according to the total burden of risk factors present. Perhaps exposure to higher levels of carbon disulphide only triggers an ischaemic event in a man who is already at high risk of the disease.

The hypothesis of a reversible direct effect of carbon disulphide is supported by Nurminen and Hern

berg.¹¹ The mortality of a cohort of 343 Finnish rayon workers exposed to carbon disulphide for at least five years was monitored from 1967 to 1982. In 1972 a preventive programme was introduced which included removing from exposure all workers with coronary risk factors, and reducing exposure levels below 10 ppm. Before the intervention mortality from ischaemic and other heart diseases showed a 4.7-fold excess compared with a control cohort of paper mill workers. After the intervention the mortality rates were similar in the two groups. They concluded that the "cardiotoxic effect of CS₂ is reversible."

Tiller *et al* expressed the hope that further work might throw light on mechanisms concerned in coronary heart disease.³ This hope has not been borne out. Tolonen *et al* found higher blood pressures among their cohort exposed to CS₂ than among the comparison group of paper mill workers.⁴ There were, however, no differences in lipids, glucose tolerance, or exercise ECG. Tolonen *et al* also found a slightly higher prevalence of angina among their Finnish workers exposed to CS₂ than among their paper mill controls. There were, however, no differences in the prevalence of ischaemic changes on either resting or exercise ECG. Two groups of Japanese workers, one exposed to CS₂ and the other not, showed no difference in blood pressure or in the prevalence of angina or ischaemic changes on ECG. Oliver and Weber were unable to find any association between exposure to CS₂ and blood pressure.¹³ Few morbidity studies have been done and they provide little convincing evidence either that IHD is more prevalent among workers exposed to CS₂ or that levels of coronary risk factors are higher. These negative findings are consistent with the hypothesis that CS₂ may act to trigger a clinical event in a man who is at high risk. Perhaps morbidity studies should instead be

looking at the effect of CS₂ on factors that are related to thrombosis, on the autonomic innervation of the cardiovascular system, and on cardiac muscle and enzymes.

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