Effects of intervention on the cardiovascular mortality of workers exposed to carbon disulphide: a 15 year follow up

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ABSTRACT The cardiovascular mortality of a cohort of 343 Finnish men exposed for at least five years to carbon disulphide (CS_2) in a viscose rayon plant has been monitored prospectively from 1967 to 1982. The results from the first five years of follow up in 1972 showed a 4.7-fold excess mortality for ischaemic and other heart diseases (ICD A83-A84) compared with a comparable reference cohort of paper mill workers. After 1972 a preventive intervention programme instituted at the rayon plant included removing all workers with coronary risk factors from exposure. Thus only 19% of the exposed cohort continued to be exposed in 1977 compared with 53% in 1972. Moreover, exposure levels were reduced after 1972 in compliance with the set hygienic standard of 10 ppm. These measures were reflected in a normalisation of the risk of cardiovascular death; the relative risk was 1.0 in the period after the intervention (1 July 1974 to 30 June 1982), whereas it had previously been 3.2 (from 1 July 1972 to 30 June 1974). The risk of a fatal heart attack remained at 11.6% throughout the 15 year follow up period (95% confidence limits 8.5%–15.4%) among the exposed compared with 7.8% (5.3%–11.2%) among the unexposed. The entire risk difference of 3.8% was accumulated during the first seven years of follow up. Thus we can estimate that 59 CS_2 -related cardiovascular deaths would have occurred during the next eight years (instead of the actual 19 deaths) had there been no preventive action. Calculations yielded a preventive fraction of 68%.

The pathological effects of exposure to carbon disulphide (CS_2) on the heart have been investigated epidemiologically in our department since 1967.¹ After finding an excess of coronary heart disease over a five year period among workers exposed to CS_2 in a viscose rayon plant,² we began a vigorous intervention programme. The programme comprised, inter alia, such preventive measures as the transfer of workers with symptoms and signs of coronary heart disease to exposure free work areas. Thereafter, we decided to monitor mortality among the established cohort to investigate the trend in the risk of death from cardiovascular diseases. A reanalysis of the first five year data yielded a significant exposure-response relation (as measured by the Mantel extension test, one sided $p = 0.003$; see ref 8). With the non-exposed referent group as

the standard (and no exposure level being scored as zero), the age standardised mortality rate ratio estimates in the low exposure (average level score 1.2), medium exposure (score 2.9), and high exposure (score 5.3) categories were 4.5, 6.8, and 7.4, respectively. If the non-exposed category were excluded from the analysis of a trend, however, the pattern of the exposure-response relation was flat. The follow up mortality studies³⁻⁵ indicated that the higher risk of the rayon plant workers was levelling off when compared with the risk among a reference cohort of unexposed paper mill workers. This paper presents a 15 year update of the impact of cardiovascular disease on the risk of death, with an allowance for deaths due to other causes.

Design of study

As a review of the project has been published elsewhere,⁶ only an outline of the essential features will be given.

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STUDY POPULATIONS

The index cohort comprised 343 men with five or more years of exposure to CS₂ at any time (median duration of exposure 11 years) at the onset of the prospective follow up in 1967. In all, 62% of the cohort continued to be exposed at work, the remainder having changed to jobs in which they were no longer exposed to CS₂. A reference cohort of equal size was selected from a nearby paper mill. The referents had had no or insignificant (less than six months) exposure to CS₂ or other industrial intoxicants. The two cohorts were matched with respect to the most influential confounders—namely, age, district of birth, and type of job. Their smoking habits, physical fitness, and use of medicines proved to be almost the same.

EXPOSURE

The concentrations of CS₂ have varied greatly over time. In most departments the exposure concentrations have been decreasing since 1945. (The company was founded in 1942.) A notable decline in the average concentrations took place after 1972–3 (fig 1). Furthermore, in 1972 only half (53%) and in 1977 only one fifth (19%) of the members of the original index cohort continued to be exposed at work, as those with indications of incipient coronary disease (electrocardiographic changes, angina, hypertension or hyperlipidaemia) had been systematically removed from exposure.

METHODS OF MORTALITY ANALYSIS

At the end of the 15 year period in 1982 there were no losses to follow up. Copies of the death certificates were obtained for all the dead subjects

and coded uniformly according to the 1965 revision of the International Classification of Disease, Injuries, and Causes of Death.⁷ Ischaemic heart disease (category numbers 410–414 or A83), other heart diseases (420–429 or A84), and cerebrovascular diseases (430–438 or A85) were tabulated as separate disease entities and grouped hierarchically.

The statistical problem of competing causes of death was handled by the actuarial or density method, which collects the man-years of follow up contributed by each subject during a set calendar time and age subinterval. Estimation of the mortality rate ratio was based on a large sample test statistic with an assumption of a binomial model (see reference 8 for details). A log-linear model (log (rate ratio) = a + b (years)) was fitted to the annual data (grouped into five strata) to describe the relationship. The maximum likelihood estimates of the model parameters were then used, firstly, to evaluate the hypothesis that no functional trend existed—that is, that b = 0 or the rate ratio was constant over the study period and, secondly, to test the tenability of the model. Finally, the relative mortality rates of the cohorts were expressed with the corresponding Finnish national death rates for 1975 (the median year of death) as the standard.⁹ As the sampling errors associated with the standard population are negligible, the statistical testing was based on a Poisson distribution.⁸

Results

As the compared cohorts were equal in size when the follow up began, the absolute numbers of death for the entire 15 year period are informative in themselves; see table 1. Vascular diseases caused more deaths in the exposed cohort (63%) than in the unexposed cohort (48%), but this was counterbalanced by a higher number of deaths due to cancer among the paper mill workers (34%) than the rayon plant workers (21%). The preponderance of cardiovascular and cerebrovascular deaths was 1.6 times greater in the exposed cohort than in the

Fig 1 Median value and interquartile range ($Q_3 - Q_1$) of average concentrations of carbon disulphide (mg/m^3) in air of rayon stable fibre factory from 1965 to 1980; Q_1 , Q_2 , Q_3 = 1st, 2nd (median), 3rd quartile. Finnish hygienic standards ($60 \text{ mg}/\text{m}^3$ (22 ppm) before 1972 and $30 \text{ mg}/\text{m}^3$ (10 ppm) after 1972) are also shown.

Table 1 Number of deaths between 1967 and 1982 according to selected causes of death (ICD).

Cause of death	Cohort	
	Rayon plant workers (n = 343)	Paper mill workers (n = 343)
Ischaemic heart disease (A83)	32	24
Other forms of heart disease (A84)	6	1
Cerebrovascular disease (A85)	4	2
Neoplasms (A45–A61)	14	19
All other causes	12	10
All causes	67	56

Table 2 Mortality rates* (per 1500 man-years) and rate ratios for vascular diseases and neoplasms in the 15 year prospective follow up

Cause of death	Cohort		Rate ratio	Confidence limits (95%)	p value (two-sided)
	Rayon plant workers (4685 man-years)	Paper mill workers (4830 man-years)			
Cardiovascular and cerebrovascular disease (A83-A85)	13.4	8.4	1.6	1.0-2.6	0.05
Cardiovascular disease (A83-A84)	12.2	7.8	1.6	0.9-2.6	0.08
Ischaemic heart disease (A83)	10.2	7.5	1.4	0.8-2.3	0.24
Neoplasms (A51-A61)	4.5	5.8	0.76	0.4-1.5	0.44
All causes	21.5	17.4	1.2	0.9-1.8	0.24

*Incidence densities.

unexposed cohort, and the rate ratio was almost significant (table 2). The more than twofold excess of deaths due to lung cancer among the paper mill workers failed to reach statistical significance, however.

The estimated overall mortality rate ratio for ischaemic heart diseases in the rayon plant workers was affected by changes in exposure. Figure 2 shows how the raised mortality of the exposed cohort in the period preceding the intervention (carried out in 1973 to 1974) descended to the level of the referents. The test for the trend was significant ($X^2_{(1)} = 7.0$, $p < 0.01$) and the exponential model did not deviate appreciably from the period specific estimates of the rate ratio ($X^2_{(3)} = 3.2$).

When national rates were used as the standard (equal to 100), the exposed cohort still had an unfavourable mortality rate for ischaemic heart diseases (relative mortality rate 130), whereas the unexposed cohort was relatively better off (rate 79).

Discussion

We have provided epidemiological evidence that indicates that the levelling off of the cardiovascular risk among a group of workers exposed to CS_2 was

Fig 2 Mortality rate ratio (RR) of ischaemic heart disease among workers exposed to carbon disulphide relative to unexposed workers during 15 year follow up period.

brought about by the measures taken to exclude the toxic substance from the environment. The striking parallelism between the course of the average level of exposure (fig 1) and the estimated mortality rate (fig 2) supports the contention that the cardiotoxic effect of CS_2 is reversible. Perhaps the strongest decisive factor, however, was the gradual withdrawal of cohort members from work where exposure occurred.

If we contrast, somewhat arbitrarily, the incidence figures for cardiovascular deaths during the first seven years of follow up with the figures for the latter eight year period we find that the relative death rates were 3.2 and 1.0, respectively. To evaluate the impact of the intervention measures, we can compute the (hypothetical) number of deaths from ischaemic heart disease that would have occurred among the index cohort had the same rate of mortality that prevailed before 1975 continued after 1975. On the basis of the rates for the referents, this number was estimated to be 59 instead of 19, the number observed. Thus the fraction of prevented or postponed cardiovascular deaths among the formerly exposed workers becomes $(59-19)/59 = 68\%$.

The rate ratio function approached unity, a result perhaps slightly affected by the aging of the cohorts, as the natural incidence of cardiac arrest increases with age. It is also possible that exposure to CS_2 hastens death in people prone to coronary heart disease. If so the survivors at the fifteenth year of follow up are those with a lower risk of coronary death than either the reference cohort or the general population of the same age structure.

In conclusion, our results suggest that the cardiotoxic effects of CS_2 are reversible in the sense that the cessation of, or a radical decrease in, exposure reduces the risk of cardiovascular mortality to background levels. Because the exposure of most cohort members had ceased our results cannot be used to specify a safe level of exposure; this would require follow up studies of workers with steady, low level exposure.

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