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MR 64207

Charlie Auer  
Director  
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U.S. Environmental Protection Agency  
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Dear Mr. Auer:

The American Chemistry Council makes available to the public and appropriate government agencies final reports of environmental, health, and safety research that it manages. In keeping with this policy, the following report that the American Chemistry Council Carbon Disulfide Panel recently conducted is enclosed:

Carbon Disulfide Exposure and Ischemic Heart Disease: A Reanalysis of the Sweetnam (1987) and Price (1997) Data

The report does not include confidential information.

If you have any questions, please call F.J. "Sonny" Maher of my staff at (703) 741-5605.

Sincerely yours,

*Susan A Lewis*

Susan A. Lewis  
Managing Director, CHEMSTAR



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**CARBON DISULFIDE EXPOSURE AND ISCHEMIC HEART DISEASE:  
A REANALYSIS OF THE SWEETNAM (1987) AND PRICE (1997) DATA**

Prepared for

American Chemistry Council  
Carbon Disulfide Panel

Prepared by

Casey Crump, M.D., Ph.D.  
Kenny S. Crump, Ph.D.

The K.S. Crump Group  
ICF Consulting, Inc.  
602 East Georgia Avenue  
Ruston, Louisiana 71270

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August 21, 2002

**CARBON DISULFIDE AND ISCHEMIC HEART DISEASE:  
A REANALYSIS OF THE SWEETNAM (1987) AND PRICE (1997) DATA**

**Summary**

We reanalyzed data from a published study to characterize the dose-response relationship between carbon disulfide (CS<sub>2</sub>) exposure and ischemic heart disease (IHD) mortality. Among the studies identified by OSHA for its carbon disulfide assessment, only that by Sweetnam et al (1987) reported the cross-classification of a cohort by CS<sub>2</sub> exposure scores and IHD mortality necessary for dose-response modeling. This cohort consisted of 1,664 men with at least 10 years of work experience in the viscose rayon industry who were occupationally exposed to CS<sub>2</sub> for at least one year between 1945 and 1949 and followed for IHD mortality through 1982. Average CS<sub>2</sub> exposures for this cohort were reconstructed by Price et al (1997) using external data, because direct air sampling measurements were not available. Although these appeared to be the best available exposure data, the fact that they were obtained from other cohorts added additional uncertainty to the estimates of exposure for the Sweetnam et al cohort. This uncertainty carried over into our estimates of the dose-response relationship and attributable risk of IHD mortality for CS<sub>2</sub>.

Using standard statistical methods, the dose-response relationship for the relative risk of death due to IHD was characterized using three exposure measures: cumulative CS<sub>2</sub> exposure, cumulative CS<sub>2</sub> exposure during the most recent 2 years, and average CS<sub>2</sub> exposure during the most recent 2 years. A stronger dose-response trend was observed for recent CS<sub>2</sub> exposure (both cumulative and average exposure during the most recent 2 years) than for cumulative CS<sub>2</sub>

exposure. A significant linear trend was found for average exposure during the most recent 2 years as high as 61 ppm or 43 ppm, but not for 26 ppm or less. The association between CS<sub>2</sub> exposure and IHD mortality was much diminished after 65 years of age compared to individuals younger than 65.

The data were consistent with an exposure threshold at an occupational (time-weighted 8-hour average) exposure to CS<sub>2</sub> of 26 ppm, a higher level than the current legal permissible exposure level (PEL) of 20 ppm. The data were also consistent with an approximately linear ( $e^{b \cdot d}$ ) relationship between CS<sub>2</sub> exposure and the relative risk of IHD mortality. Assuming a linear relationship, we estimated the additional risk of IHD mortality attributable to constant lifetime occupational CS<sub>2</sub> exposure. Given that the actual lifetime probability of dying from IHD in the United States is approximately 30%, this analysis suggested that constant lifetime occupational exposure to CS<sub>2</sub> at 5, 10, or 20 ppm theoretically could increase this probability to 30.1%, 30.3%, or 30.6%, respectively. The corresponding risks attributable to CS<sub>2</sub> exposure are equal to or less than risks associated with other PELs recently issued by OSHA.

## **Introduction**

On behalf of the American Chemistry Council Carbon Disulfide Panel, the K.S. Crump Group conducted an assessment of potential risk of cardiovascular disease associated with occupational exposure to carbon disulfide (CS<sub>2</sub>). OSHA identified the key studies<sup>1-6</sup> for its carbon disulfide assessment at a meeting with the Chemical Manufacturers Association Carbon Disulfide Panel (now the American Chemistry Council Carbon Disulfide Panel) on April 5, 2000. The K.S. Crump Group was directed to conduct its assessment using the same studies

identified by OSHA and using models consistent with the mechanism of action suggested by those studies.

Among the studies identified by OSHA, only that by Sweetnam et al<sup>1</sup> met the minimum criteria necessary for dose-response modeling: cross-classification of a cohort by quantitative CS<sub>2</sub> exposure and disease occurrence. Sweetnam et al (1987) conducted a retrospective cohort analysis of 1,664 men with at least 10 years of work experience in the viscose rayon industry. These men were occupationally exposed to carbon disulfide for at least one year during 1945-49, and were followed through 1982 for mortality due to ischemic heart disease (IHD).<sup>1</sup> We reanalyzed the results published by Sweetnam et al to characterize the dose-response relationship between CS<sub>2</sub> and IHD mortality.

### **Statistical Methods**

Sweetnam et al assigned CS<sub>2</sub> exposure scores to workers based on an ordinal rating of CS<sub>2</sub> exposure intensity (0="no exposure" to 4="highest exposure"), multiplied by the number of months spent on a particular job, and summed over all jobs.<sup>1</sup> These scores reflect both intensity and duration of exposure. Price et al (1997) used these exposure scores and the CS<sub>2</sub> air concentrations reported in 15 other published studies to estimate upper and lower bounds for average CS<sub>2</sub> exposure (in ppm) for this cohort. The reader can refer to Price et al for more details of the exposure assessment methods.<sup>7</sup>

Standard statistical methods were used to characterize the relationship between occupational CS<sub>2</sub> exposure and death from ischemic heart disease. Poisson regression is the method of choice for quantitatively characterizing the association between categories of an observed exposure and counted outcomes such as the number of cause-specific deaths. Poisson

regression results based on the Sweetnam data were combined with U.S. mortality rates for IHD to estimate the additional risk of IHD mortality attributable to constant lifetime occupational CS<sub>2</sub> exposure at specified levels (5, 10, 20 ppm). These methods will be explained in more detail below.

The Poisson regression model was used to estimate the relative risk of IHD mortality, as approximated by the standardized mortality ratio (SMR), associated with average CS<sub>2</sub> exposure in this occupational cohort. The number of observed deaths due to IHD was modeled as the outcome variable. CS<sub>2</sub> exposure was modeled in three alternative ways: 1) cumulative exposure (ppm-years), 2) cumulative exposure during most recent 2 years (ppm-years), and 3) average exposure during most recent 2 years (ppm). These exposure measures were dictated by the data presented in Sweetnam et al.<sup>1</sup> Each of these measures was modeled as a grouped linear variable in separate models.<sup>1</sup>

The observed number of IHD deaths was modeled as a Poisson variable with expected value equal to the expected number of IHD deaths based on population rates multiplied by  $e^{(b*d)}$ , where  $b$  is the regression coefficient and  $d$  is the CS<sub>2</sub> exposure variable included in the model. The model assumes that the numbers of observed deaths in different exposure categories are independent and Poisson distributed. The intercept was assumed to be zero, which is equivalent to fixing the SMR equal to 1 among non-exposed. The adequacy of the dose-response regression model was evaluated by applying the Poisson goodness-of-fit chi-squared test to each fitted model. All regressions were performed using the Stata statistical software.<sup>8</sup>

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<sup>1</sup> The analysis conducted by Sweetnam et al presumably utilized a categorization of person-years rather than persons. For example, to categorize data according to cumulative exposure during the most recent two years, each person-year of observation of each subject was assigned an exposure equal to the cumulative exposure to CS<sub>2</sub> during the most recent two years prior to that person-year of observation. These exposures were then used to categorize each worker's person-years of observation and his resulting mortality experience. For example, if a worker retired at age 65 his person-year of observation between the age of 70 and 71 would be assigned zero cumulative exposure

Additional risks of IHD mortality from various posited theoretical exposures were estimated using a life table approach based on 1997 rates for IHD mortality in the U.S. general population. Rates for 1997 were used in order to make the estimates more applicable to current and future workers. Additional risk attributable to constant lifetime occupational CS<sub>2</sub> exposure (age 20 to age 65) was estimated by  $P(1) - P(0)$ , where  $P(1)$  is the lifetime probability of dying from IHD while exposed to a specified constant level of CS<sub>2</sub>, and  $P(0)$  is the lifetime baseline probability of dying from IHD in the general population. CS<sub>2</sub> exposure was evaluated at levels of 5 ppm, 10 ppm, and 20 ppm. Using the life table approach,  $P(0)$  is computed recursively as the probability of dying at a particular age conditional on surviving up to that age, summed over all age strata (in 5-year categories).  $P(1)$  is a modification of this probability in which the age-specific IHD mortality rates are multiplied by  $e^{(b*d)}$ , where  $b$  is the regression coefficient from the Poisson analysis of the Sweetnam et al data and  $d$  is the appropriate exposure measure, taking into account the exposure measure used in the Poisson regression, the age category, and the assumed occupational exposure pattern. For example, if the age category was 45-50 years, the exposure measure used in the Poisson regression was cumulative exposure during the most recent two years, and the exposure pattern was 10 ppm beginning at age 20, then  $d = 20$  ppm-years. Because the exposure of interest is occupational, the life table was constrained so that exposure is 0 before age 20 and after age 65. The life table approach models the attrition from other causes of death; thus it was not necessary to assume a typical value for a human lifespan (e.g., 70 years) in this analysis. The 95% confidence intervals for additional risk were computed using the 95% confidence limits for the Poisson regression coefficients in the same life table method.

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during the most recent two years. Note that the term "recent" is relative to the person-year of followup under consideration, and does not refer to absolute calendar time.

## Results

Table 1 summarizes the SMRs for ischemic heart disease associated with the maximum and minimum estimates of average CS<sub>2</sub> exposure reported by Price et al.<sup>7</sup> A dose-response trend appeared more pronounced for more recent CS<sub>2</sub> exposures. These trends are depicted in Figures 1-3 for cumulative exposure, cumulative exposure in the most recent two years, and average exposure during the most recent two years, respectively.

Table 2 presents the Poisson regression results for association between each CS<sub>2</sub> exposure metric and IHD mortality. The reported coefficients are statistically significant if the 95% confidence intervals exclude zero, which was the case for each exposure metric. The regression coefficients for association between cumulative CS<sub>2</sub> exposure in the last 2 years and IHD mortality ranged from 0.0039 (for estimated maximum exposure) to 0.012 (for estimated minimum exposure), both of which were statistically significant. The coefficient 0.0039 may be interpreted as follows: a group of workers with cumulative CS<sub>2</sub> exposure during the most recent two years that was 10 ppm-years higher on average than a comparison group of workers had a relative risk of death due to ischemic heart disease of  $e^{(10)(0.0039)} = 1.04$ , or a 4% increased risk of this outcome.

The goodness-of-fit chi-squared tests were non-significant for each fitted model, indicating that the data did not depart significantly from the assumed linear dose-response,  $e^{(b*d)}$ . However, as Figures 2 and 3 suggest, the data were also consistent with other dose-response relationships, including a threshold response. We tested for a threshold relationship, or a no observed effect level (NOEL), using the following procedure: We tested for a linear dose-response trend after removing the highest average current (average over the most recent two

years) exposure level (61 ppm) from the Poisson regression model. If a significant result was obtained, we removed the next-highest average current exposure level (43 ppm) and again tested for a linear dose-response trend. We repeated this process until we found the highest exposure level at which there was no significant linear trend. We found a significant linear trend for average exposures during the most recent two years as high as 61 ppm or 43 ppm, but not for 26 ppm or less. Thus no effect was observed for occupational exposure to CS<sub>2</sub> as high as 26 ppm. The results of this formal statistical analysis are confirmed by Figure 3 which clearly shows that the observed SMR did not begin to increase until average exposure during the most recent two years reached approximately 43 ppm.

Table 3 presents the additional risks and 95% confidence intervals that were estimated using the linear model. A geometric average of the additional risks for maximum and minimum exposure was computed as a summary result. Statistical significance of additional risk necessarily corresponds to that of the corresponding regression coefficient. The estimated excess risk of IHD mortality from continuous occupational CS<sub>2</sub> exposure between the ages of 20 and 65 to 5 ppm, 10 ppm, or 20 ppm was 1.4 per thousand, 2.9 per thousand, or 6.3 per thousand, respectively.

### **Discussion**

The methods used in this analysis assume that the risk of IHD mortality is proportional to CS<sub>2</sub> exposure and higher in persons with higher background risks. Goodness-of-fit tests (Table 2) indicated that the data were consistent with these assumptions. However, these data were also consistent with other dose-response relationships, including a threshold response. As indicated

in Figure 3, no effect was evident whenever CS<sub>2</sub> exposures during the most recent two years were below 26 ppm.

Although the data from Sweetnam et al<sup>1</sup> and Price et al<sup>7</sup> appeared to be the best available for dose-response modeling of CS<sub>2</sub> exposure and IHD mortality, they also had considerable limitations. Sweetnam's assignment of ordinal exposure scores according to job descriptions was admittedly crude; although it was based on area monitoring data, no CS<sub>2</sub> air sampling concentrations were reported.<sup>1</sup> Price reconstructed CS<sub>2</sub> air concentration estimates using air sampling data from 15 other studies conducted from 1941 to 1995.<sup>7</sup> The coupling of these external measurements to Sweetnam's exposure scores introduced additional uncertainty to the estimates of CS<sub>2</sub> exposure on which the present analysis is based.

Nevertheless, these data do suggest some insights into the biologic mechanism by which CS<sub>2</sub> may be involved in cardiovascular disease. If CS<sub>2</sub> promotes atherosclerosis through impaired lipid metabolism and increased blood pressure, one would expect mortality from IHD to remain high even when exposure has ceased. In these data, the association between CS<sub>2</sub> exposure and IHD mortality was much diminished after age 65 years compared to individuals younger than 65 (data not shown).<sup>1</sup> This is consistent with the hypothesis that the cardiovascular effect of CS<sub>2</sub> is direct and reversible, such as thrombosis or arrhythmia, and may subside after exposure ceases. This hypothesis was further supported by the fact that IHD mortality was more strongly associated with CS<sub>2</sub> exposure during the most recent two years than with total cumulative exposure. If the predominant biologic effect of CS<sub>2</sub> is direct and reversible, then more recent exposures are the most important for risk assessment. The present analysis found a dose-response relationship between recent CS<sub>2</sub> exposures (both cumulative exposure during the most recent two years, and average exposure during the most recent two years) and IHD

mortality that was consistent both with a linear response ( $e^{b*d}$ ) and with a no-observed-effect-level (threshold) of 26 ppm.

If a linear dose-response relationship is assumed, our risk assessment based on cumulative exposure during the most recent two years resulted in best estimate risks ranging from 1.1 to 3.6 per thousand from lifetime occupational exposure to 5 ppm CS<sub>2</sub>, from 1.9 to 6.4 per thousand from lifetime occupational exposure to 10 ppm CS<sub>2</sub>, and from 3.6 to 13 per thousand from lifetime occupational exposure to 20 ppm CS<sub>2</sub> (Table 3). Risk estimates based on average exposure during the most recent two years were very similar. To put these risks into perspective we searched the literature for estimated mortality risks from lifetime occupational exposure to other chemicals at permissible exposure levels (PELs) promulgated by OSHA. We found the following examples:

Chemical	Date	PEL	Risk at PEL (per thousand)
1,3-butadiene <sup>9</sup>	1997	1 ppm	1.3 to 8.1
cadmium <sup>10</sup>	1992	5 µg/m <sup>3</sup>	3.9 to 9.0
carbon tetrachloride <sup>11</sup>		2 ppm	3.7
vinyl bromide <sup>12</sup>		5 ppm	40

Thus, our estimates of risk from exposure to the current CS<sub>2</sub> PEL of 20 ppm (based on a linear model applied to cumulative exposure during the most recent two years) were similar to risks estimated at these PELs previously promulgated by OSHA.

## References

1. Sweetnam PM, Taylor SWC, Elwood PC. Exposure to carbon disulphide and ischaemic heart disease in a viscose rayon factory. *Brit J Ind Med*. 1987; 44:220-227.
2. MacMahon B, Monson RR. Mortality in the US rayon industry. *J Occ Med*. 1988; 30:698-705.
3. Swaen GMH, Braun C, Slangen JJM. Mortality of Dutch workers exposed to carbon disulfide. *Int Arch Occup Environ Health*. 1994; 66:103-110.
4. Hernberg S, Partanen T, Nordman C-H, Sumari P. Coronary heart disease among workers exposed to carbon disulphide. *Brit J Industr Med*. 1970; 27:313-325.
5. Hernberg S, Tolonen M, Nurminen M. Eight-year follow-up of viscose rayon workers exposed to carbon disulfide. *Scand J Work Environ Health* 1976; 2:27-30.
6. Hernberg S, Tolonen M. Epidemiology of coronary heart disease among viscose rayon workers. *G Ital Med Lav*. 1981; 3:49-52.
7. Price B, Bergman TS, Rodríguez M, Henrich RT, Moran EJ. A review of carbon disulfide exposure data and the association between carbon disulfide exposure and ischemic heart disease mortality. *Regul Toxicol Pharmacol*. 1997; 26:119-128.
8. StataCorp. *Stata Statistical Software: Release 6.0*. College Station, TX: Stata Corporation, 1999.
9. [http://www.osha-slc.gov/Preamble/13Butadiene\\_data/1\\_3\\_BUTADIENE0.html](http://www.osha-slc.gov/Preamble/13Butadiene_data/1_3_BUTADIENE0.html)
10. [http://www.osha-slc.gov/Preamble/Cadmium\\_data/CADMIUM9.html](http://www.osha-slc.gov/Preamble/Cadmium_data/CADMIUM9.html)
11. Documentation of the Threshold Limit Values and Biological Exposure Indices. Sixth Edition. American Conference of Governmental Industrial Hygienists, Inc. pp. 233-236. Cincinnati, Ohio (1991).

12. Documentation of the Threshold Limit Values and Biological Exposure Indices. Sixth Edition. American Conference of Governmental Industrial Hygienists, Inc. pp. 1690-1692. Cincinnati, Ohio (1991)

**Table 1.** SMRs for association between carbon disulfide (CS<sub>2</sub>) exposure and mortality due to ischemic heart disease (IHD).

Exposure	CS <sub>2</sub> exposure score range <sup>a</sup>	Cumulative CS <sub>2</sub> exposure <sup>b</sup> (ppm-years)		Average CS <sub>2</sub> exposure <sup>b</sup> (ppm)		Observed IHD deaths <sup>a</sup>	SMR for IHD <sup>a</sup>
		Minimum	Maximum	Minimum	Maximum		
All previous	0-99	69.3	217.0	--	--	28	1.00
	100-199	206.0	646.0	--	--	79	1.16
	200-299	379.0	1080.0	--	--	80	1.38
	≥300	1140.0	1550.0	--	--	80	1.44
Most recent 2 years only	0	0.0	0.0	0.0	0.0	149	1.15
	1-23	8.4	26.3	4.2	13.2	12	1.06
	24-47	24.9	77.8	12.5	38.9	30	1.04
	48-71	41.7	130.4	20.9	65.2	49	1.69
	72-96	58.8	184.1	29.4	92.1	27	2.36

<sup>a</sup> Sweetnam et al 1987 [Tables 6, 7].

<sup>b</sup> Adapted from Price et al 1997 [Table 2].

**Table 2.** Poisson regression results for association between carbon disulfide (CS<sub>2</sub>) exposure and mortality due to ischemic heart disease.

Surrogate	CS <sub>2</sub> Exposure		Poisson Regression Results		
	Estimates		Coef. <sup>a</sup>	95% CI	GOF <sup>b</sup> P value
<b>Cumulative</b> All previous	Max.		2.5×10 <sup>-4</sup>	1.4×10 <sup>-4</sup> , 3.6×10 <sup>-4</sup>	0.84
	Min.		3.7×10 <sup>-4</sup>	2.0×10 <sup>-4</sup> , 5.5×10 <sup>-4</sup>	0.21
Most recent two years only	Max.		3.9×10 <sup>-3</sup>	2.5×10 <sup>-3</sup> , 5.4×10 <sup>-3</sup>	0.13
	Min.		1.2×10 <sup>-2</sup>	7.8×10 <sup>-3</sup> , 1.7×10 <sup>-2</sup>	0.13
<b>Average</b> Most recent two years only	Max.		7.8×10 <sup>-3</sup>	5.0×10 <sup>-3</sup> , 1.1×10 <sup>-2</sup>	0.13
	Min.		2.5×10 <sup>-2</sup>	1.6×10 <sup>-2</sup> , 3.4×10 <sup>-2</sup>	0.13

<sup>a</sup> Model assumes that intercept = 0 (i.e., relative risk among unexposed is 1).

<sup>b</sup> GOF = Goodness of Fit  $\chi^2$  test

**Table 3. Additional risk of ischemic heart disease mortality attributable to carbon disulfide (CS<sub>2</sub>) exposure.**

CS <sub>2</sub> Exposure		Risks based on Max. Exposure (best case scenario)		Risks based on Min. Exposure (worst case scenario)		Geometric Average *
Surrogate	Level (ppm)	Additional risk	95% CI	Additional risk	95% CI	Additional risk
<b>Cumulative</b> All previous	5	1.1×10 <sup>-2</sup>	5.9×10 <sup>-3</sup> , 1.5×10 <sup>-2</sup>	1.6×10 <sup>-2</sup>	8.4×10 <sup>-3</sup> , 2.4×10 <sup>-2</sup>	1.3×10 <sup>-2</sup>
	10	2.1×10 <sup>-2</sup>	1.2×10 <sup>-2</sup> , 3.1×10 <sup>-2</sup>	3.2×10 <sup>-2</sup>	1.7×10 <sup>-2</sup> , 4.9×10 <sup>-2</sup>	2.6×10 <sup>-2</sup>
	20	4.4×10 <sup>-2</sup>	2.4×10 <sup>-2</sup> , 6.6×10 <sup>-2</sup>	6.8×10 <sup>-2</sup>	3.5×10 <sup>-2</sup> , 1.1×10 <sup>-1</sup>	5.5×10 <sup>-2</sup>
Most recent two years only	5	1.1×10 <sup>-3</sup>	7.2×10 <sup>-4</sup> , 1.6×10 <sup>-3</sup>	3.6×10 <sup>-3</sup>	2.3×10 <sup>-3</sup> , 5.3×10 <sup>-3</sup>	2.0×10 <sup>-3</sup>
	10	1.9×10 <sup>-3</sup>	1.2×10 <sup>-3</sup> , 2.7×10 <sup>-3</sup>	6.4×10 <sup>-3</sup>	4.0×10 <sup>-3</sup> , 9.4×10 <sup>-3</sup>	3.5×10 <sup>-3</sup>
	20	3.6×10 <sup>-3</sup>	2.2×10 <sup>-3</sup> , 5.1×10 <sup>-3</sup>	1.3×10 <sup>-2</sup>	7.7×10 <sup>-3</sup> , 2.0×10 <sup>-2</sup>	6.8×10 <sup>-3</sup>
<b>Average</b> Most recent two years only	5	7.6×10 <sup>-4</sup>	4.8×10 <sup>-4</sup> , 1.1×10 <sup>-3</sup>	2.5×10 <sup>-3</sup>	1.6×10 <sup>-3</sup> , 3.5×10 <sup>-3</sup>	1.4×10 <sup>-3</sup>
	10	1.6×10 <sup>-3</sup>	9.8×10 <sup>-4</sup> , 2.2×10 <sup>-3</sup>	5.4×10 <sup>-3</sup>	3.3×10 <sup>-3</sup> , 7.7×10 <sup>-3</sup>	2.9×10 <sup>-3</sup>
	20	3.2×10 <sup>-3</sup>	2.0×10 <sup>-3</sup> , 4.7×10 <sup>-3</sup>	1.2×10 <sup>-2</sup>	7.2×10 <sup>-3</sup> , 1.8×10 <sup>-2</sup>	6.3×10 <sup>-3</sup>

\* Geometric average of additional risk point estimates based on maximum and minimum exposure.

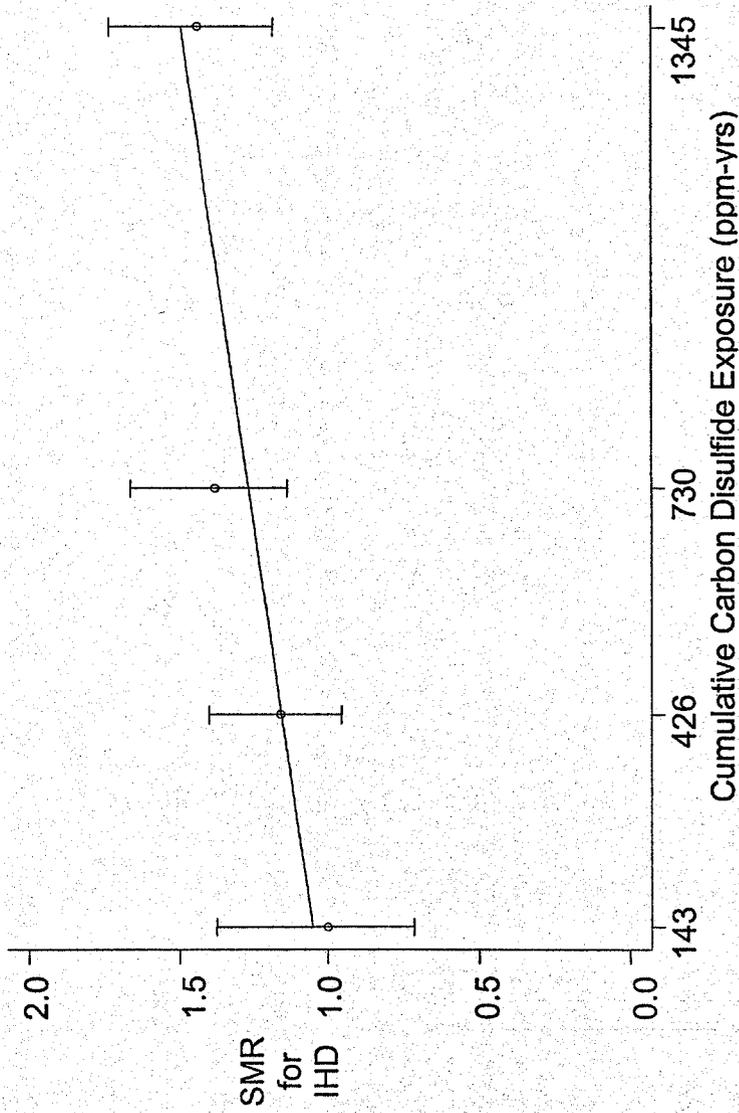
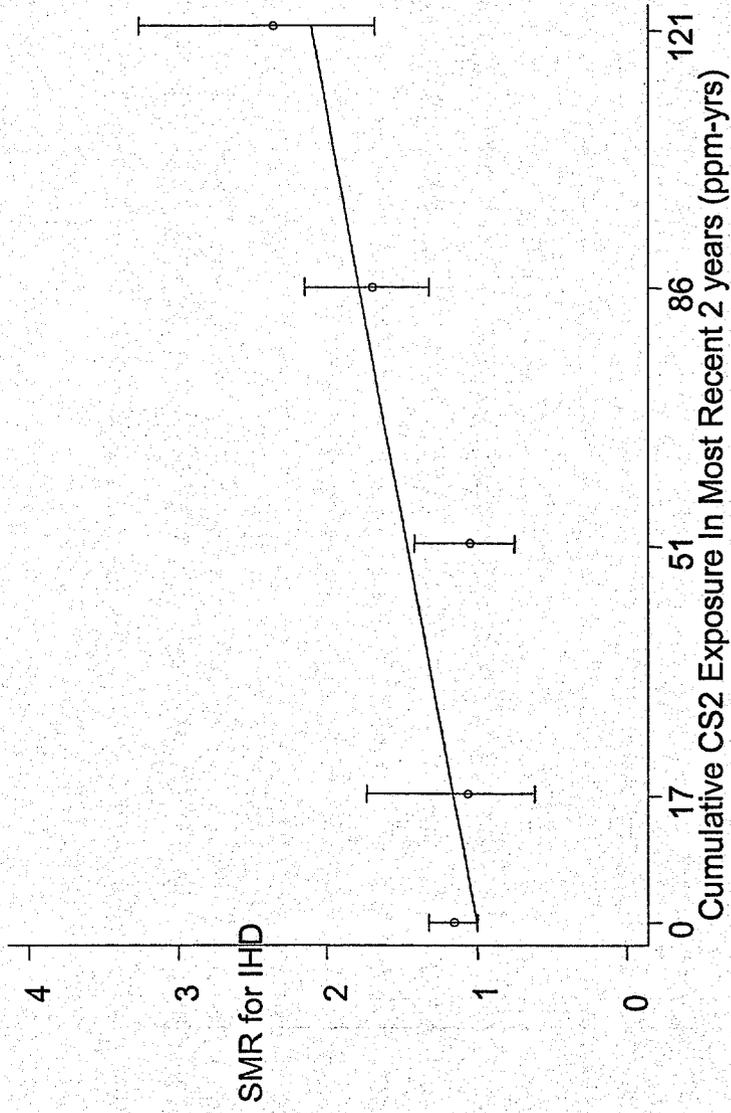
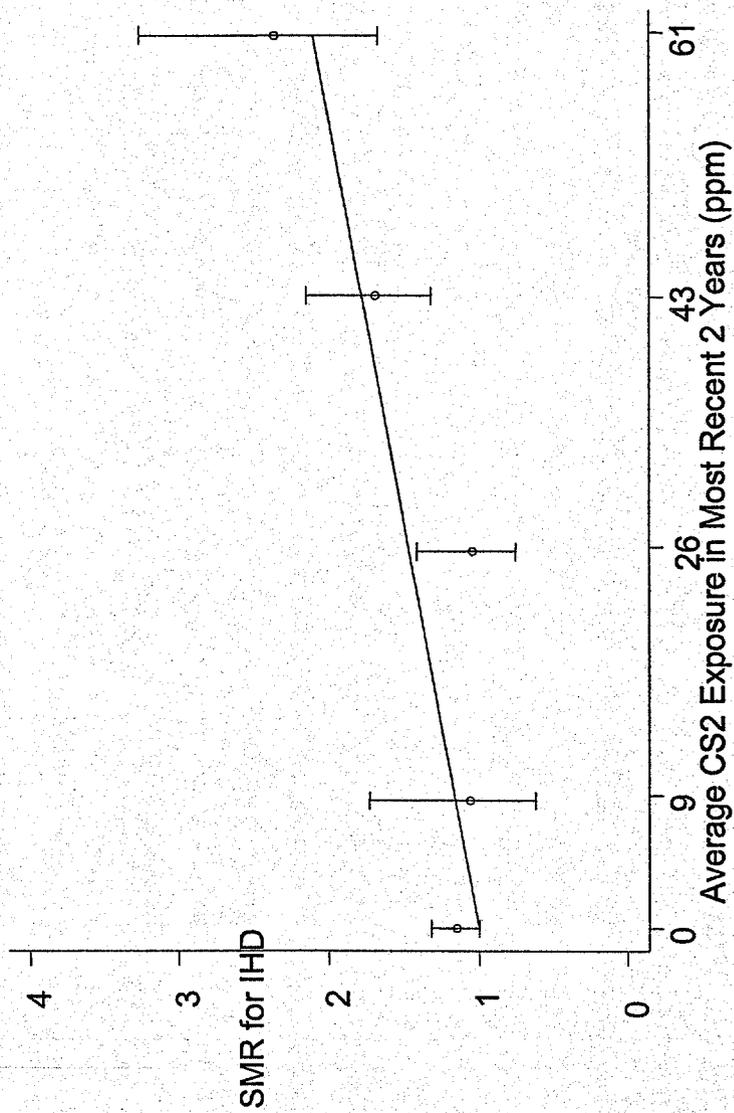


Figure 1. Cumulative CS<sub>2</sub> exposure (ppm-years) and SMR for ischemic heart disease (IHD), with Poisson regression line. The upper and lower brackets for each point represent upper and lower 95% confidence intervals for SMR.



**Figure 2.** Cumulative CS<sub>2</sub> exposure during most recent two years (ppm-years) and SMR for ischemic heart disease (IHD), with Poisson regression line. The upper and lower brackets for each point represent upper and lower 95% confidence intervals for SMR.



**Figure 3.** Average CS<sub>2</sub> exposure during the two most recent years (ppm) and SMR for ischemic heart disease (IHD), with Poisson regression line. The upper and lower brackets for each point represent upper and lower 95% confidence intervals for SMR.