ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR CARBON DISULFIDE

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ADDENDUM FOR CARBON DISULFIDE
Supplement to the 1996 Toxicological Profile for Carbon Disulfide

Background Statement

This addendum to the Toxicological Profile for Carbon Disulfide supplements the profile that was released in 1996.

Toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). CERCLA mandates that the Administrator of ATSDR prepare toxicological profiles on substances on the CERCLA Priority List of Hazardous Substances and that the profiles be revised "no less often than once every three years". CERCLA further states that the Administrator will "establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" [Title 42, Chapter 103, Subchapter I, § 9604 (i)(1)(B)].

The purpose of this addendum is to provide, to the public and other federal, state, and local agencies a non-peer reviewed supplement of the scientific data that were published in the open peer-reviewed literature since the release of the profile in 1996.

Chapter numbers in this addendum coincide with the Toxicological Profile for Carbon Disulfide (1996). This document should be used in conjunction with the profile. It does not replace it.

2. HEALTH EFFECTS

2.1 INTRODUCTION

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

2.2.1 Inhalation Exposure

2.2.1.2 Systemic Effects

Cardiovascular Effects

Researchers have documented extensively an increased risk of cardiovascular abnormalities arising from chronic inhalation of workplace-related carbon disulfide. Adverse cardiovascular effects include increased serum low-density lipoprotein (LDL) cholesterol, and decreased serum high-density lipoprotein (HDL) cholesterol concentrations (Stanosz et al. 1994). Other effects include increased triglyceride plasma levels, development of atherosclerosis, and increased risk of coronary heart disease (CHD) (Wronska-Nofer et al. 2002).

Atherosclerosis and CHD

Wronska-Nofer et al. (2002) investigated the mechanisms of premature atherosclerosis development and CHD resulting from occupational exposure to carbon disulfide. They also investigated the role of oxidative stress, known to increase atherosclerosis risk. Wronska-Nofer et al. determined oxidative stress by measuring plasma concentrations of thiobarbituric reactive substances (TBARS) in 29 men occupationally exposed to carbon disulfide for 25to 30 years and in another group of 24 patients diagnosed with peripheral atherosclerosis. They then compared this cohort with 30 healthy, unexposed volunteers. The results showed that in comparison with the control volunteers, TBARS plasma concentrations were elevated significantly in the carbon disulfide exposed group and in the patients with atherosclerosis. The plasma TBARS which reflect plasma lipid peroxidation could be associated with increased mortality of workers exposed to carbon disulfide in the viscose rayon rubber industry due to cardiovascular disease and cerebrovascular disease. Results revealed decreased levels of the plasma antioxidant α-tocopherol and decreased activities in enzymatic antioxidants (i.e., glutathione peroxidase and catalase) in both the carbon

disulfide exposed group and the atherosclerotic patients. In an *in-vitro* assay, low-density levels of serum lipoprotein cholesterol isolated from the carbon-disulfide-exposed and atherosclerotic groups also showed increased susceptibility to metal-induced oxidation (Wronska-Nofer et al. 2002). The results also supported the contention that chronic carbon disulfide exposure depletes anti-oxidative defense mechanisms in plasma, which ultimately result in increased lipoprotein oxidation, and the results supported the contention that long-term carbon disulfide exposure might result in oxidative stress in plasma, which can then lead to atherosclerosis and increased CHD risk. Furthermore, some have suggested that free radical, mediated lipid peroxidation is an early effect of LDL cholesterol oxidation caused by many oxidants, that it could indicate long-term inhalation exposure to carbon disulfide results in oxidative modifications of LDL cholesterol, and that it plays a role in the pathogenesis of atherosclerosis. Wronska-Nofer and colleagues indicated that a causal relationship between carbon disulfide-induced oxidative stress in plasma may favor atherosclerosis development and increase CHD risk. They also concluded that several complimentary mechanisms could be associated in the pathogenesis of atherosclerosis in workers exposed chronically to carbon disulfide (Wronsa-Nofer et al. 2002).

Kotseva (2001) collected total serum cholesterol levels, measured blood pressures, and evaluated CHD of 141 workers (64 men) exposed to carbon disulfide at levels below the threshold limit value (TLV) in a Bulgarian viscose rayon industry and compared those data with 141 age-and-sex-matched controls. During the study period the TLV was 31 mg/m^3 [10 parts per million (ppm)].[1] The workers were between 20–60 years of age and had worked in the industry for at least 1 year. Kotseva estimated inhalation exposures to carbon disulfide by establishing a cumulative exposure index. She multiplied the number of years in a particular job by the average air level of carbon disulfide for exposed workers in that job. She determined average air levels using personal air samplers that detected carbon disulfide in air from 1-30 mg/m^3.

Kotseva divided the carbon disulfide exposed workers into two groups. Group 1 consisted of 70 workers (CS_2 cumulative exposure index of < 100). Group 2 consisted of 71 workers (CS_2 cumulative exposure index > 100). Although the results showed no increase in CHD nor any

[1] Given that prevailing opinion regards changes in these cardiovascular parameters as risk factors for cardiovascular disease, we discuss them here as adverse cardiovascular outcomes.

significant increases in blood pressures in workers exposed to carbon disulfide, the differences in total cholesterol serum levels only reached significance in Group 2 (i.e., CS_2 index group >100), but not in Group 1 (i.e., the CS_2 index group <100). The cholesterol-level increase in exposed persons was observed after adjusting for age, smoking, and body mass index ($p<0.001$). The odds ratio (OR) among workers in the carbon disulfide exposed index Group 2 of >100 was 5.52 (95% CI of 2.81–10.83).

Kotseva also observed an increased prevalence of hypercholesterolemia, defined as cholesterol levels of >5.17 mmol/L (millimole/liter). The prevalence of OR qualitative cardiovascular effects for all carbon disulfide exposed workers vs. all non-exposed controls was 2.56 (95% CI 1.47–4.46). Kotseva concluded that chronic occupational inhalation exposure to carbon disulfide below the TLV of 31 mg/m^3 (10 ppm) could increase total cholesterol serum levels, but provided no evidence of elevated risk for arterial hypertension or CHD (Kotseva 2001).

LDL and HDL Cholesterol

Tan et al. (2004) conducted a cross-sectional study that investigated the effects of chronic inhalation exposure to carbon disulfide on the cardiovascular system of 367 workers (252 males and 115 females) in a Chinese viscose rayon factory. The workers were exposed to carbon disulfide at levels below the American Conference of Governmental Industrial Hygienists (ACGIH) TLV of 31 mg/m^3 for a minimum of 4 years. The results, when compared with 125 non-exposed workers, revealed no significant differences in clinical complaints, electrocardiography (ECG) abnormalities, blood pressures, LDL and HDL cholesterol levels, or changes in triglyceride levels in the exposed workers. In general, the readings from the worker's personal air samplers showed that the carbon disulfide exposure levels were normally between 13.7-20.1 mg/m^3 below the ACGIH TLV but above the Chinese Maximum Allowable Concentration of10 mg/m^3. When the workers reported no clinical or cardiovascular complaints, the workplace exposure levels were reported as between 4.13–15.47 mg/m^3. Tan and colleagues suggested more studies regarding carbon disulfide-induced cardiovascular effects to determine any differences in sex response; in this study, due to the small number of women who participated, the sex effects might have been limited (Tan et al. 2004).

In Poland, Stanosz et a1. (1994) investigated the serum lipid fraction in 237 women chronically exposed from 11 to 20 years to 5–7 ppm carbon disulfide in the viscose rayon industry and compared the results with 70 non-exposed control women. Ages ranged from 25 to 55 years, with a mean of 42.9 ± 5.1 for the carbon disulfide exposed group and a mean of 42.1 ± 3.5 for the non-exposed control group. The results showed no differences in total cholesterol plasma levels, LDL-cholesterol, or HDL-cholesterol plasma levels in women exposed for fewer than 10 years to carbon disulfide and between 25 to 39 years of age, but women exposed to carbon disulfide from 11 to 20 years and were between 40 to 49 years of age had significantly higher levels of total cholesterol, LDL-cholesterol, and significant decreases in HDL-cholesterol plasma levels when compared with the controls. Between the groups, however, no differences appeared in serum fatty acid levels. Stanosz and colleagues pointed out that previous studies suggested that chronic exposure to carbon disulfide could result in inhibition of lipoprotein lipase an enzyme that causes serum lipoprotein turnover. Previous studies also suggested that chronic carbon disulfide exposure caused reduced ACTH (adrenocorticotrophic hormone), TSH (thyroid stimulating hormone), and thyroxin neurohormones directly involved in lipid metabolism and could activate the enzyme lipoprotein lipase. Stanosz and colleagues concluded that because of compromised endocrine activity of the ovaries, abnormalities in lipid biotransformation can occur in women who are over 39 years of age and who are chronically exposed to carbon disulfide.

In Taiwan, almost a decade later, Luo et al. (2003) conducted an occupational exposure study that investigated a dose-response relationship between carbon disulfide inhalation exposure and increased lipid profiles in 132 workers from two Taiwan viscose rayon industries. This was an intermediate exposure study, with personal air monitoring performed on an 8-hour, full shift every 2 weeks for 5 months. Health examinations occurred 5 months after the personal air monitoring. Luo and colleagues found in the viscose rayon factory workers an association between carbon disulfide exposure and a dose-dependent increase in triglyceride levels, as well as a decrease in HDL levels. Luo and colleagues divided the 132 carbon disulfide exposed workers into three groups based on exposure levels: the high-exposure group (24–127 ppm), middle-exposure group (5.2–22.3 ppm), and the low-exposure group (0.97–5.2 ppm), with mean exposures of 50.6 ppm, 12.9 ppm, and 3.5 ppm, respectively. Triglyceride levels were increased

in 63.7%, 42.2%, and 40%, of workers in the high, middle, and low carbon disulfide exposed groups, respectively. Study results showed a lower prevalence of elevated HDL plasma levels in the carbon disulfide high-exposed group when compared with the low-exposed group (15.2% vs. 31.4%). The results indicated that moderate exposure to carbon disulfide might increase triglyceride serum concentrations and total cholesterol concentrations. Although this study indicates that exposure to carbon disulfide at indoor air levels exceeding 20 ppm might be linked to increased risk and decreased protective effects for coronary heart disease, the results were inconclusive; more studies are needed to clarify further the observed-association mechanisms found in this study (Luo et al. 2003).

ECG Findings

In 1999–2000, Chang et al. (2006) conducted a chronic inhalation exposure study of carbon disulfide at three Taiwan viscose rayon facilities that used carbon disulfide in their manufacturing processes. The study examined 251 men who reported significant increases of ECG abnormalities (OR 12.8; 95% CI: 5.4–30.2) when compared with a non-exposed reference group (n=226). The reference group consisted of male clerical workers who were not exposed to carbon disulfide except at background levels. The duration of employment was associated with ECG abnormalities in older men, but not for younger men when grouped by age (<40, 40 to 49, and ≥50 years) and duration (1 to 9, 10 to 19, ≥20 years).

The investigators measured breathing zone exposures among 127 workers from three 8-hour work shifts and collected 29 environmental air samples over 24 hours on an average day of operation. About 73% of the employees in the study were exposed to an average air concentration of carbon disulfide at 14.5 ppm, which manifested an ECG abnormality prevalence of 25.9%. The reference group, which consisted primarily of administrative clerks, showed a prevalence of 2.7% of ECG abnormalities. The lowest carbon disulfide air level (i.e., 1.6 ppm) measured in the viscose rayon facility was detected in the supervisors' offices, but the supervisors' category had the highest risk (OR 20.6 %95 CI = 6.5–65.2) of abnormal ECG, followed by workers in the filament spinning area with an OR (14.2 CI=5.7–35.3). The increased risk for ECG abnormalities for the supervisors probably indicated that they had been

exposed in other work areas besides their offices (Chang et al. 2006). “The foremen were in all departments supervising and handling many situations and making mechanical repairs and probably being exposed more than other workers, because they wore less protective gear to avoid exposures (Chang et al. 2006).” The average air level of carbon disulfide was 20.1 ppm in the filament spinning area of the plant, where the second highest risk of abnormal ECG was observed. Chang and colleagues concluded that because carbon disulfide breath-zone samples and environmental air sample concentrations were similar, the exposures measured were representative. The results of this study provided evidence of a need to educate workers on issues of environmental exposures to carbon disulfide and to provide environmental intervention of carbon disulfide inhalation exposures in the workplace (Chang et al. 2006).

Korinth et al. (2003) conducted a cross-sectional epidemiological study in Germany between (1) 325 workers exposed via inhalation to carbon sulfide in a rayon producing industry, and (2) 179 control subjects from the same industry who were never exposed. The study objective was to determine whether carbon disulfide-induced negative-inotropic effects on the heart muscle caused an increase in the human heart chamber diameter. Negative-inotropic cardiovascular or heart muscle functions are those effects that weaken the contractility of the heart muscle. These effects are in contrast to positive-inotropic effects, which strengthen the heart muscles’ contractile function. In this study, the mean external exposure of carbon disulfide was 6.04 ppm (determined by personal air sampling) and did not result in significant differences of the diameters of the left heart chamber when compared with the un-exposed control group. The workers and control group examinations consisted of a standardized questionnaire, physical examination, assessment of body fat mass, an ergonomic test with measurements of heart rate variability of 100, 130, 150, and 170, beats/minute, and an ECG. A team of heart specialists performed the ergonomic tests. Statistical analysis did not reveal a correlation in heart chamber diameters in ECG between the exposed workers and the control group, but the results did show a trend albeit an insignificant trend toward an increase in the heart chamber diameters of the carbon disulfide exposed workers when compared with controls. Higher levels of physical activity in the exposed persons might explain this trend, given that the exposed persons in all likelihood had higher physical demands in the workplace than did the control group. The echocardiography registered the trend toward an increase in heart chamber diameters in the

carbon disulfide-exposed workers, and the workers' BMI positively correlated with that trend. Nevertheless, this study could not substantiate the hypothesis that carbon disulfide-induced, negative inotropic effect caused increased heart chamber diameters in humans (Korinth et al. 2003).

Heart-Rate Variability

Jhun et al. (2003) examined heart-rate variability (HRV) in 171 retired workers to determine possible persistent effects from a diagnosis of carbon disulfide poisoning. Before retirement, the subjects worked in a Korean viscose-rayon factory. Jhun and colleagues also examined a control group of 127 un-exposed public officials. Seven years after the viscose-rayon factory closed, the subjects in both groups received follow-up medical examinations and ECGs, including time and frequency domain measures. Juhn and colleagues indicated that the primary determinations of HRV were age, sex, and heart rate. No cardiovascular risk factors such as increased cholesterol and lipoprotein were used in this study, the information was not available. The results showed no significant differences in time measures of heart rate including maximum, average, and minimum relative risk interval. Although Jhun and colleagues observed a trend towards an inverse relationship between carbon disulfide exposure and low and high frequency domain measures, the results revealed a significant decrease only in low frequency measurements in comparison with controls. The investigators concluded that workers previously exposed to carbon disulfide might have impaired HRV, which might also manifest long after cessation of carbon disulfide exposure (Jhun et al. 2003).

Bortkiewicz et al. (1997) also examined the HRV associated with disturbances of the autonomic nervous systems of 152 workers from a Polish chemical fiber plant, all of whom were continuously exposed to carbon disulfide in the workplace. The carbon disulfide-exposed workers ranged from 24 to 66 years of age, with an exposure period from 5 to 38 years. The control group consisted of 93 age-matched control subjects with a body mass similar (25.4 ± 4.0) to the carbon disulfide-exposed case group (26.0 ± 3), and similar periods of employment (14.7 ± 10.8), (14 ± 8.9), respectively. The average daily carbon disulfide exposure level for the 152 male workers was 18.1 mg/m^3 (5.8 ppm) (range of 1.75–109.1 mg/m^3; 0.56–35 ppm), and no

carbon disulfide exposure for the control group. The general baseline medical examination for both groups consisted of an interview including cardiovascular and family history, 24-hour ECG monitoring, late ventricular potentials (LVP), and ambulatory blood pressures measured during a walk.

2.2.1.4 Neurological Effects

Godderis et al. (2006) reported neurobehavioral effects such as psychomotor slowing, positional tremors, peripheral polyneuropathy (PNP), and Parkinsonism in workers from a Belgium viscose rayon factory that were exposed to carbon disulfide at concentrations at levels ≤ 10 mg/m^3 (3.2 ppm) . Kotseva et al (2001) conducted a cross sectional occupational study to determine if exposure to carbon disulfilde below 31 mg/ m^3 (10 ppm) (i.e. TLV) would affect total cholesterol, blood pressure and coronary heart disease of 141 viscose rayon workers (64 men) and 141 age-and gender matched controls who were exposed to other noxious chemicals. The workers were divided into two exposed groups based on mean carbon disulfide exposures of < 31 mg/m^3 (60 subjects) or > 31 mg/m^3 (25 subjects) and an unexposed control group (66 subjects). Carbon disulfide exposure levels were collected from workers by personal air monitoring samplers. The sampling consisted of 169 valid personal air samples obtained over 16 days. Kotseva et al. (2001) describe the methods used to measure the carbon disulfide levels in the personal samplers. The examination consisted of

- Neurotoxic symptom checklists,
- A clinical neurological examination,
- Computer-assisted neurobehavioral tests, and
- Neurophysiological examinations (peripheral nerve conduction velocities and electromyography).

When compared with the control group, both exposed groups reported increased sensorimotor complaints and exhibited positional tremors and decreased finger tapping in the dominant and non-dominant hands of the carbon disulfide-exposed workers. In peripheral nerve conduction tests, Godderis and colleagues observed significant decreases in sural sensory nerve response amplitude and duration and sural sensory nerve conduction velocity. They observed an increase in sympathetic skin response amplitude in both carbon disulfide-exposed groups, but no changes

in motor nerve conduction velocities or response amplitude or durations. Godderis and colleagues concluded that carbon disulfide inhalation exposures at levels ≤ 10 mg/m^3 (3.2 ppm) could have effects on positional tremors, sural nerve amplitudes, electromyography, sympathetic skin response, and finger tapping in exposed workers' dominant and non-dominant hands (Godderis et al. 2006).

Chang et al. (2003) found that carbon disulfide exposure in combination with a noisy environment increased the incidence of hearing impairment, especially at lower frequencies. Chang and colleagues studied 131 males from a Taiwan viscose rayon plant and compared them with 105 men in a carbon disulfide un-exposed, noise-only group, and with an administrative group of 110 males exposed to low noise and no carbon disulfide. The noise levels were 80–91, 83–90, 72-82 dB (A) for the carbon disulfide, noise-only, and control groups, respectively. The prevalence of hearing loss (defined as >25 dB hearing loss) in the carbon disulfide workers was 67.9% compared with 34 and 26% in the noise-only and control groups, respectively. When the carbon disulfide exposed workers were divided into groups based on carbon disulfide exposure levels and noise exposure levels, the prevalence of hearing loss among workers exposed to ≥14.6 ppm (45 mg/m^3) was 22% in workers exposed to noise levels ≤85 dB(A) and 52% in workers exposed to >85 dB(A). By comparison, the prevalence of hearing loss among carbon disulfide workers exposed to <14.6 ppm was 22.6% in workers with noise levels of ≤85 dB (A) and 22.4% in workers exposed to >85 dB (A). The data suggest that co-exposure to carbon disulfide and noise is a greater hearing impairment than noise-only exposure at 85 dB. Chang and colleagues indicated that one study limitation was that the mean age of the carbon disulfide workers was 6 years higher than in the other two groups. Yet after controlling for age, smoking, drinking, and the use of noise-proof equipment, a concentration-response association did in fact appear between hearing loss and cumulative carbon disulfide exposure (Chang et al. 2003).

Herr et al. (1998) investigated nerve conduction velocity and performance on neurobehavioral tests in male and female Fisher 344 rats exposed to carbon disulfide at concentrations of 0, 50 (155 mg/m^3), 500 (1,557 mg/m^3), or 800 ppm (2,491 mg/m^3) (6 hours/day, 5 days/week) for 2,

4, 8, or 13 weeks. Exposure to carbon disulfide at 800 ppm for 8 weeks resulted in increased ventral caudal nerve conduction velocity in comparison with the control and in comparison with the 500 ppm carbon disulfide-exposed group. Exposure to carbon disulfide at 500 ppm (1,557 mg/m^3) or 800 ppm (2,491 mg/m^3) for 13 weeks resulted in lower ventral caudal nerve conduction velocity than for the 50 ppm (155 mg/m^3) exposed group. Herr and colleagues also observed increased caudal tail nerve action potential amplitude and decreased peak P_1P_2 interpeak latency in rats exposed for 13 weeks to 500 (1,557 mg/m^3) or 800 ppm (2,491 mg/m^3).

Moser et al. (1998) has detailed information regarding functional observational battery tests used to evaluate significant alterations in neurobehavioral performance as compared with pre-exposure baseline measurements. In the Moser et al. (1998) study, postural abnormalities were observed in the 800 ppm exposed group at all of the measured time points. The abnormalities progressed with increasing durations from hunched-back posture to diminished postural control. Changes in hind-limb gait activity were observed in the 800 ppm (2,491 mg/m^3) exposed group for all exposure durations, at 500 ppm (1,557 mg/m^3) at 4, 8, and 13 weeks, and at 50 ppm (155 mg/m^3) at 13 weeks. The severity of these changes increased with duration and exposure concentrations. The effects at 50 ppm carbon disulfide were rated as slight impairment to "somewhat" impaired. Decreases in hind limb and forelimb grip strength were also observed at 500 ppm and 800 ppm carbon disulfide exposure at durations of 4 weeks and longer. The hind limbs were more affected than were the forelimbs. Ataxia aside from gait alterations was observed in animals exposed to carbon disulfide at 500 ppm (1,557 mg/m^3) and 800 ppm (2,491 mg/m^3). Other observed effects included increased handling reactivity and mild tremors (Moser et al. 1998).

2.2.1.5 Reproductive Effects

Vanhoorne et al. (1994) used a questionnaire study to assess the effects of carbon disulfide exposure on male sexuality and reproduction of 116 viscose rayon workers (median age=33.3). A higher rate of complaints of decreased libido were reported in men with a high exposure or a high cumulative exposure (exposure x duration) to carbon disulfide. Exposure to carbon disulfide was considered high when exposure was greater than 30 mg/m^3 (9.6 ppm). A cumulative index of 300 mg/m^3 (96 ppm) was used as the cut-off for cumulative exposures. For

the carbon disulfide-exposed groups, Vanhoorne and colleagues did not report mean exposures or duration of employment. Nevertheless, a mean cumulative index for all exposed men was reported at 224 mg/m^3(71.7 ppm). The carbon disulfide-exposed men in both high-and low-exposure groups also had higher rates of complaints of impotence when compared with a group of 35 un-exposed men serving as the control. Vanhoorne and colleagues observed no significant fertility differences. Forty-three men from the exposed group and 35 un-exposed men also provided semen samples to determine semen quality in relation to carbon disulfide exposure. No significant differences in the quality of semen appeared from the carbon disulfide-exposed men when compared with the un-exposed men (Vanhoorne et al. 1994).

2.2.1.6 Developmental Effects

No updated data.

2.2.1.7 Genotoxic Effects

Bao et al. (1996) reported an increased incidence of chromosomal aberrations in the pronuclei of zygotes in adult female mice exposed to 10 or 100 mg/m^3 (3.2 or 32 ppm) of carbon disulfide for 3 weeks and mated with un-exposed male mice.

Genotoxicity. *In-vitro* exposure of human sperm to carbon disulfide concentrations of 10 micromole/Liter (μmol/L) resulted in increased occurrences of chromosomal aberrations (Le and Fu 1996).

2.4 RELEVANCE TO PUBLIC HEALTH

2.6 BIOMARKER OF EXPOSURE AND EFFECT

2.6.1 Biomarkers Used to Identify or Quantify Carbon Disulfide Exposure

An epidemiological study showed a strong correlation between carbon disulfide urinary concentrations from 407 male workers who worked in an Italian viscose rayon factory and carbon disulfide factory indoor air concentrations up to 64 mg/m^3 (20.5 ppm). Ghittori et al. (1998) used personal passive samplers installed in the breathing zones to measure the airborne

carbon disulfide levels for 4 hours. The survey was conducted four times per year during the second half of the workweek. Urine samples were provided by the workers for analysis during the mid-shift between at 2 p.m. and at 6 p.m. given that the shift was from 2 p.m. to 10 p.m. The urinary carbon disulfide background levels were determined by measuring the urinary levels from 50 male workers who worked in other areas of the facility. The carbon disulfide exposed workers were between 23 to 59 years of age and the mean age was 35. The non-exposed control group was 25 to 68 years of age. Most of the indoor air samples revealed carbon disulfide at levels below the TLV of 31 mg/m^3. The authors concluded that urinary carbon disulfide may be a good indicator to estimate the levels of exposure to carbon disulfide in the workplace. A positive correlation or urinary concentrations and indoor air levels indicated that a mean level of 15.5 µg/carbon disulfide/L (95% CI 13.8–17.1 µg) was excreted following exposure to carbon disulfide at 31 mg/m^3, the then-current occupational exposure limit in Italy (Ghittori et al. 1998).

Cox et al. (1998) investigated 2-thiothiazolidine-4-carboxylic acid (TTCA) concentrations as a biomarker of carbon disulfide exposure. The authors collected urine samples from six workers in a Virginia viscose rayon plant and from 19 workers in a Tennessee rubber product facility. The workers provided a total of 80 pre-and post-shift urine samples. This study included no control group. The post-shift TTCA urine levels were compared against pre-shift urine levels. The workers in the Virginia viscose rayon plant provided 36 urine samples, and the workers in the Tennessee rubber product facility provided 44 urine samples. Increased TTCA levels were detected in urine samples from 5/6 male workers from the Virginia viscose rayon plant despite wearing half-mask cartridge respirators. The TTCA levels detected in those urinary samples may have indicated that carbon disulfide exposures were greater than the National Institute of Occupational Safety and Health (NIOSH) recommended exposure limit (REL) of 1 ppm (3.1 mg/m^3). Still, in samples from the 19 male workers from the rubber product facility in Tennessee, Cox and colleagues only found TTCA urinary concentrations below the instrument limit of detection The workers with higher exposures to carbon disulfide had correspondingly higher urinary levels of TTCA. The insignificant TTCA concentrations measured in urinary samples from the workers at the Tennessee rubber plant indicated that dermal absorption of carbon disulfide was not important protective gloves and garments worn by the workers probably provided adequate protection against carbon disulfide dermal absorption. Although the results

of this study provided evidence that post-shift urinary TTCA concentrations can predict whether inhaled carbon disulfide exceeds recommended workplace standards, the current ACGIH's TLV has changed from 10 ppm (31mg/m^3) to 1 ppm (3.1 mg/m^3). The authors suggested that more emphasis should be placed on workplace protection factors rather than just addressing the indoor air carbon disulfide concentrations. They also suggested that TTCA urinary concentrations allow determinations of the workplace protection factor afforded workers using respirators and assist in determining who are not wearing respirators and not adhering to safety precautions in the workplace (Cox et al. 1998).

2.6.2 Biomarkers Used to Characterize Effects Caused by Carbon Disulfide

Jian and Hu (2000) investigated the mechanism of action of carbon disulfide exposure on the antioxidative stress mechanisms. The authors measured enzymes linked to oxidative stress, including cuprozinc-superoxide dismutase (CuZnSOD) and malonyldialdehyde (MDA) levels in the serum of 67 viscose rayon factory workers and in 88 non-exposed control subjects. The workers were between 20 to 41 years of age and had been exposed to carbon disulfide from 2 to 14 years, with an average exposure of 8 years. The carbon disulfide exposed workers were divided into 2 groups (i.e., $\leq$10 mg/m^3 and >10 mg/m^3 time weighted average) and compared with the control group. In comparison to control subjects, serum CuZnSOD levels were statistically, significantly increased in both groups of workers exposed to carbon disulfide at levels below and above 10 mg/m^3 (3.2 ppm) ($p<0.001$). This effect showed a dose-response relationship. Serum MDA levels were also increased in carbon disulfide exposed workers in both a concentration and in an exposure duration-dependent manner. The enzymes (i.e., CuZnSOD and MDA) may serve as biomarkers for inclusion in worker's health surveillances to determine early stages of impairment of the anti-oxidative stress response resulting from carbon disulfide exposure (Jian and Hu 2000).

3. CHEMICAL AND PHYSICAL INFORMATION

No updated data.

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

No updated data.

5. POTENTIAL FOR HUMAN EXPOSURE

5.2 Releases to the Environment

Carbon disulfide was one of seven sulfur-gas emission rates assessed from problem drywall installed in U.S. homes. The test aimed to determine whether the drywall contained the source of odorous and potentially corrosive indoor pollutants. The test of two phases, but a summary of the results reported here are from phase two of the project, which characterized chemical emissions from problem drywall. The tests were conducted on 30 drywall samples provided by the Consumer Product Safety Commission to the Lawrence Berkeley National Laboratory and reported standard emission factors for certain volatile organic compounds, aldehydes, and reactive sulfur gases. The tests investigated the effects of temperature, relative humidity, and paint coating on the emission factors for sulfur compounds. The results showed a robust positive correlation between emission factors of sulfur compounds and both temperature and relative humidity, but the effect of temperature had a greater influence on emission rates. In other words, from the drywall samples provided for evaluation, as the temperature and humidity increased so did the emission rates of carbon disulfide and other sulfur compounds. Sulfur compound emission factors appeared unaffected by the paint coating that was applied to the drywall (Lawrence Berkeley National Laboratory 2011).

6. ANALYTICAL METHODS

No Updated Data.

7. REGULATIONS AND ADVISORIES

Table 7-1. Regulations and Guidelines Applicable to Carbon Disulfide

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No	IARC 2009
WHO	Air quality guidelines		WHO 2000
	TWA based on effects other than cancer or odor/annoyance using an averaging time of 24 hours	100 µg/m^3	
	Using sensory effects or annoyance reactions, using an averaging time of 30 minutes		
	Detection threshold	200 µg/m^3	
	Guideline value	20 µg/m^3	
	Drinking water quality guidelines	No	WHO 2006
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)[a]	1 ppm	ACGIH 2008
	TLV-basis (critical effect)	Peripheral nervous system impairment	
NIOSH	REL (10-hour TWA)[b]	1 ppm	NIOSH 2005
	IDLH	500 ppm	
	Target organs	Central and peripheral nervous systems, cardiovascular system, eyes, kidneys, liver, skin, reproductive system	
OSHA	PEL (8-hour TWA) for general industry	20 ppm	OSHA 2009
	Acceptable ceiling concentration	30 ppm	
	Acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift for a maximum duration of 30 minutes	100 ppm	
b. Water			
EPA	Drinking water standards and health advisories	No	EPA 2006
	National primary drinking water standards	No	EPA 2009

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
c. Other			
ACGIH	Carcinogenicity classification	A4[c]	ACGIH 2008
	BEI (end of shift)		
	2-Thiothiazolidine-4-carboxylic acid (TTCA) in urine	5 mg/g creatinine	
	Notice of Intended Changes (NIC BEI)[d]	0.5 mg/g creatinine	
EPA	Carcinogenicity classification	No	IRIS 2009
	RfC	$7.0x10^{-1}$ mg/m^3	
	RfD	$1.0x10^{-1}$ mg/kg/day	
NTP	Carcinogenicity classification	No	NTP 2005

[a]Skin notation: refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, by contact with vapors, liquids, and solids.
[b]Skin designation
[c]A4: not classifiable as a human carcinogen.
[d]2008 Notice of Intended Changes: These substances, with their corresponding indices, comprise those for which (1) a BEI is proposed for the first time, (2) a change in the Adopted index is proposed, (3) retention as an NIC is proposed, (4) withdrawal of the Documentation and adopted BEI us proposed. In each case, the proposals should be considered trial indices during the period they are on the NIC.

ACGIH = American Conference of Governmental Industrial Hygienists; BEI = Biological Exposure Indices; CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; WHO = World Health Organization

8. REFERENCES

[ACGIH] American Conference of Governmental Industrial Hygienists. 2008. TLVs and BEIs: Based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH; p 18, 74–79, 100, 103, 110–111.

Bao YS, Zheng Q, Jiang H, et al. 1996. Toxic effects of carbon disulfide on mouse oocytes (Abstract). Teratology 53(2):101–02.

Bortkiewicz A, Gadzicka E, Szymczak W. 1997. Heart rate variability in workers exposed to carbon disulfide. J Auton Nerv Syst 66(1-2):62–68. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9334994.

Chang SJ, Shih TS, Chou TC, et al. 2006. Electrocardiographic abnormality for workers exposed to carbon disulfide at a viscose rayon plant. J Occup Environ Med 48(4):394–99. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16607194.

Chang SJ, Shih TS, Chou TC, et al. 2003. Hearing loss in workers exposed to carbon disulfide and noise. Environ Health Perspect 111(13):1620–24. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14527841.

Cox C, Hee SS, Tolos WP. 1998. Biological monitoring of workers exposed to carbon disulfide. Am J Ind Med 33(1):48–54. Availble at: http://www.ncbi.nlm.nih.gov/pubmed/9408528.

Drexler H, Goen T, Angerer J. 1995. Carbon disulphide. II. Investigations on the uptake of CS_2 and the excretion of its metabolite 2-thiothiazolidine-4-carboxylic acid after occupational exposure. Int Arch Occup Environ Health 67(1):5–10. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7622280.

Ghittori S, Maestri L, Contardi I, et al. 1998. Biological monitoring of workers exposed to carbon disulfide (CS_2) in a viscose rayon fibers factory. Am J Ind Med 33(5):478–84. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9557171.

Godderis L, Braeckman L, Vanhoorne M, et al. 2006. Neurobehavioral and clinical effects in workers exposed to CS_2. Int J Hyg Environ Health 209(2):139–50. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16503300.

Herr DW, Vo KT, Morgan DL, et al. 1998. Carbon disulfide neurotoxicity in rats: VI. Electrophysiological examination of caudal tail nerve compound action potentials and nerve conduction velocity. Neurotoxicology 19(1):129–46. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9498229.

Huang CC, Chu CC, Wu TN, et al. 2002. Clinical course in patients with chronic carbon disulfide polyneuropathy. Clin Neurol Neurosurg 104(2):115–20. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11932040.

[IARC] International Agency for Research on Cancer. 2009. Agents reviewed by the IARC Monographs. Volumes 1-100A. Lyon, France: Available at: http://monographs.iarc.fr/ENG/Classification/ListagentsCASnos.pdf. 2009May 19.

[IRIS] International Agency for Research on Cancer. 2009. Carbon disulfide. Integrated Risk Information System. Washington DC: Available at: http://www.epa.gov/ncea/iris/subst/0217.htm. 2009August 6.

Jhun HJ, Yim SH, Kim R, et al. 2003. Heart-rate variability of carbon disulfide-poisoned subjects in Korea. Int Arch Occup Environ Health 76(2):156-160. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12733089.

Jian L, Hu D. 2000. Antioxidative stress response in workers exposed to carbon disulfide. Int Arch Occup Environ Health 73(7):503–06. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11057420.

Korinth G, Goen T, Ulm K, et al. 2003. Cardiovascular function of workers exposed to carbon disulphide. Int Arch Occup Environ Health 76(1):81–85. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12592587.

Kotseva K. 2001. Occupational exposure to low concentrations of carbon disulfide as a risk factor for hypercholesterolaemia. Int Arch Occup Environ Health 74(1):38–42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11196079.

Le JY, Fu XM. 1996. Human sperm chromosome analysis—study on human sperm chromosome mutagenesis induced by carbon disulfide. Biomed Environ Sci 9(1):37–40. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8721625.

Luo JC, Chang HY, Chang SJ, et al. 2003. Elevated triglyceride and decreased high density lipoprotein level in carbon disulfide workers in Taiwan. J Occup Environ Med 45(1):73–78. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12553181.

Moser VC, Phillips PM, Morgan DL, et al. 1998. Carbon disulfide neurotoxicity in rats: VII. Behavioral evaluations using a functional observational battery. Neurotoxicology 19(1):147–57. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9498230.

NIOSH. 2005. Carbon disulfide. NIOSH pocket guide to chemical hazards. Atlanta, GA: National Institute for Occupational Safety and Health. Centers for Disease Control and Prevention. NIOSH Publication 2005-149. Available at: http://www.cdc.gov/niosh/npg/npgd0104.html. 2009August 6.

NTP. 2005. Report on carcinogens, eleventh edition. Research Triangle Park, NC: U.S. Department of Health and Human Services. Public Health Service. National Toxicology Program. Available at: http://ntp-server.niehs.nih.gov/ntp/roc/toc11.html. 2008 January 11.

OSHA. 2009. Table Z-2. Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000 Subpart Z. Available at: http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9993. 2009 August 6.

Stanosz S, Kuligowski D, Zuk E, et al. 1994. The pattern of some lipid fractions in the serum of women chronically exposed to carbon disulfide. Ind Health 32(3):183–86. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7698906.

Tan Xiaodong, Guanmin Chen et al. 2004. Cross-Sectional Study of Cardiovascular Effects of Carbon Disulfide Among Chinese Workers of a Viscose Factory. International Journal of Hygiene Environmental Health 206 (2004) 217–25.

[USEPA] US Environmental Protection Agency. 2009. National primary drinking water regulations. Washington, DC: Office of Ground Water and Drinking Water. EPA816F09004. Available at: http://www.epa.gov/safewater/consumer/pdf/mcl.pdf. 2009 August 7.

[USEPA] US Environmental Protection Agency. 2006. 2006 Edition: Drinking water standards and health advisories. Washington, DC: Office of Water. EPA822R04005. Available at: http://hero.epa.gov/index.cfm?action=reference.download&reference_id=91193; 2009 May 19.

Valentine WM, Valentine HL, Amarnath K, et al. 1999. Toluene-3,4-dithiol analysis of blood for assessing carbon disulfide exposure. Toxicol Sci 50(2):155–63. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10478851.

Vanhoorne M, Comhaire F, De Bacquer D. 1994. Epidemiological study of the effects of carbon disulfide on male sexuality and reproduction. Arch Environ Health 49(4):273–78. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8031184.

WHO. 2000. Summary of the guidelines. In: WHO air quality guidelines for Europe. 2nd ed. Geneva, Switzerland: World Health Organization. Available at: http://www.euro.who.int/document/aiq/3summary.pdf. 2009 May 19.

WHO. 2006. Annex 4 - Chemical summary tables. In: Guidelines for drinking-water quality, third edition, incorporating first and second addenda. Geneva, Switzerland: World Health Organization, 488-492. Available at: http://www.who.int/water_sanitation_health/dwq/GDWAN4rev1and2.pdf. 2009 May 19.

Wronska-Nofer T, Chojnowska-Jezierska J, Nofer JR, et al. 2002. Increased oxidative stress in subjects exposed to carbon disulfide (CS_2)--an occupational coronary risk factor. Arch Toxicol 76(3):152-157. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11967620.